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[†]Jackson LL, Gourin CG, Thomas DS, et al. Use of the Harmonic Scalpel in superficial and total parotidectomy for benign and malignant disease. Laryngoscope. 2005; 115:1070-1073.

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JOURNAL OF ENT MASTERCLASS®

Volume 3 Issue 1 December 2010

Contents

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JOURNAL OF ENT MASTERCLASS®

Welcome to Volume 3 Issue 1 of Journal of ENT Masterclass® 2010

The ENT Masterclass is now "of age" and is firmly established itself into the annual calendar of post-graduate education for all medical residents, nurses and many related to the practice of Oto-Rhino-Laryngology, Head and Neck Surgery (ORL-HNS) in the United Kingdom.

This year 2010 has been another very successful period for ENT Masterclass, continuing with the 6th Annual ENT, 3rd Tracheostomy and 3rd Thyroid and Salivary Masterclass's. In true "Q" style, during previous Masterclass sessions he became aware for the additional needs of the medical residents the need for a National ENT Radiology Masterclass which was held in June 2010. Also the 6th Annual ENT Masterclass, January 2010, the proceedings was transmitted Free Live International Webcast to the World of ENT audience on http://www.dbh.nhs.uk/entmasterclass receiving over 2000 hits from 31 countries. It was supported by the Doncaster Royal Infirmary and their IT staff and can still be viewed as a recording. A similar programme for next year has been planned and will be repeated.

The Journal of ENT Masterclass, now in its third year, continues to be a success. On this occasion the Editorial Board has contributed and with 24 articles from National and International experts across the breadth and depth of ORL-HNS. Five International ORL-HNS have provided us with their views on important topics on which they are truly "experts", and also included is a comprehensive review by a London based consultant in OMFS on the aetiology and surgical treatment of ranulae, which has been a "life's -work". To all we must be ever grateful.

This year we are adding Professor Alok Thakar, India to our Editorial Board. The Board will remain stable otherwise this year and will help to formulate and commission articles for future issues of the Journal.

Sadly during this year Doncaster Royal Infirmary lost Mr Nigel Clifton OBE, who was their Chief Executive for many years and a great supporter to ENT Masterclass. He will be sadly missed for his encouragement and provision of the hospital facilities whenever desired or required. Luckily, the present and current management of Doncaster Royal Infirmary continues to give their support for ENT Masterclass, during the current financial constraints and NHS "trying times".

As usual, The Journal welcomes suggestions and comments on how to better the Masterclass concept! The web site www.entmasterclass.com remains open and available to all! If direct contact is more desirable then please make contact directly with either the Editor or Chairman.

The Journal of ENT Masterclass, and the many Annual Masterclasses, thanks each and everybody who have helped organise and supported these projects over the past few years, and we hope that with your continued support that the venture will continue to thrive and attract large audiences for future years!

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November 2010.

Editorial:

Case Reports, Clinical and Personal Audit and Evidence Based Medicine – Is it all necessary?

Introduction:

In the modern world of post-graduate medical education and training, writing has become a compulsory, as a "rite of passage" to being accredited and certified, and to progress within one's chosen career Otolaryngology-Head and Neck Surgery (ORL-HNS).

Important for the medical graduate to proceed, it is essential to submit an application for career advancement which demonstrates a minimal evidence and understanding of research and audit. As a ST1-2, it is currently compulsory that "audit evidence of active participation" has been undertaken when applying for ST3. Then, over the subsequent 6 years of HST (Higher Surgical Training) there must be evidence of having partaken of 3 audit projects (not completion!) and been involved in one research project which has been presented at least at one National or International Specialist meeting and has been submitted or accepted (written up!) for publication at the time of submission of the application for Certificate of Completion of Specialist Training (CCST).

One question that our employer and sometimes patients continues to seek is "How good are our clinical service providers?". Most ORL-HNS clinicians express a personal prowess regarding some facet of their professional service – but so few ever can actually quote their own facts and figures when challenged? Patients have a right to seek reassurance that "their clinician" is "at least as good as the best"? So analysis and review of one's own clinical practice (or even the special bits!) could and should be embraced into a personal annual audit of activity! After all, patients have a self-adhesive address label, which can be collected during clinic, stuck onto a card with a diagnosis written and date, the case notes can then be retrieved at a later time for a more detailed retrieval of information of patient's outcome! If clinicians do not perform such analysis of one's own practice – then sadly somebody else will "police the system"!

"The Case Report":

The traditional teaching method in medical education has been by case presentation and this is reflected in published work by the case report [1]. The case report has been considered a valuable research and educational resource but has been

described as a most misunderstood tool. Today, MEDLINE lists more than one million case reports, and this number increases at a rate of 40,000 per year[2]. In January, 2007 the first peer-reviewed journal dedicated specifically to case reports, The Journal of Medical Case Reports was introduced[3]. Editors have considered that the publication of "case reports" lowers the impact factor of the publishing journal[4]. However he admits that the priority of the publisher and editor is quite different from that taken of the submitting author. The author aim is to "publish or perish" and that if there has not been quality, then at least quantity will be evident in their curriculum vitae. Occasionally the author(s) will embellish a "case report", with the addition of "Case report; and a Review of the Literature". When a "youth" I was informed that to report in such a format, one had to have included 10% or more new cases than was previous reported. It has been recorded that between 1975 and 1995, that there was increasing pressure to publish, and gave rise to the "gift authorship"[5]. If such publications are to be of any value, there needs to be an "academic policing" with the limited number of person authorship, otherwise there will be a devaluation of our specialty journals[6,7]. While meta-analysis and randomised controlled trials can provide a large data base of evidence, towards improvement and opportunities, it is suggested that case reports can still provide valuable clinical information[8]. In a review of the literature, specifically to compile a series of "rare harm case reports" in ORL-HNS not previously described in other forms of evidence-based medicine[9], the authors concluded that "case reports form the basis of progress in clinical science independent of basic subjects or epidemiological insight. They have a high degree of sensitivity to detect novelty and provide new ideas to explore and investigate."

Clinical Audit:

Clinical audit is a process that has been defined as "a quality improvement process that seeks to improve patient care and outcomes through systemic review against explicit criteria and the implementation of change[10]. The key component of clinical audit is that performance is reviewed (or audited) to ensure that what should be done is being done, and if not it provides a frame work to enable improvements to be made. Clinical audit

comes under the Clinical Governance umbrella and forms part of the system for improving the standard of clinical practice. As the process continues, each cycle aspires to a higher level of quality. After an agreed period, the audit should be repeated. The re-audit should demonstrate that changes have been implemented and that improvements have been made. Further changes may then be required, leading to additional re-audits. It is the re-audit or recycle of the audit process which is crucial to seek successful outcome of an audit, and is the most difficult to perform and complete as a trainee, unless such a project is commenced early in ones training and also one requires employment stability during that time period. The General Medical Council (GMC)[11] states that as part of good medical practice, maintaining and improving performance, doctors are required to; 1) take part in regular and systematic audit, 2) take part of quality assurance and quality improvement, and 3) respond constructively to the outcome of audit, appraisals and performance reviews, undertaking further training where necessary.

Evidence Based Medicine:
Evidence-based medicine (EBM) or evidence-based practice (EBP) aims to apply the best available evidence gained from the scientific method to clinical decision making[12]. The process seeks to assess the strength of evidence of the risks and benefits of treatments (including lack of treatment) and diagnostic tests[13]. One of the methods proposed for EBP is the evidence-based guidelines (EBG) in the practice of EBM at the organisational or institution level. This includes the production of guidelines, policy and regulations. This approach has also been called evidence-based healthcare. The evidence produced is stratified by quality, and the one most commonly known and quoted is the U.S. Prevention Services Task Force[14] for ranking evidence about the effectiveness of treatments or screening (Level 1 – evidence from Randomised Controlled Trials). Thus, using evidence from RCT is considered the "gold standard" and should be where available in daily clinical practice. Evidence used in evidence-based medicine that is only based on meta-analysis, RCT and clinical trials ignores other types of useful evidence and is flawed in that many clues towards insight of many medical diseases and management will be missed[15].

Conclusion:
The "case report" is an exercise describing the diagnosis and/or outcome of an individual patient, and a "case series" is a usually a "retrospective" reporting of a "group of patients" with the same disease or condition or who have been treated in a similar way, over a defined period of time. Audit is obligatory by the General Medical Council and all doctors, trainees and consultants must partake, and seeks to maximise

health care provision and efficiencies. Evidence –based medicine is a process employing agreed standards of care (Guidelines) – treatments or investigations for similar groups of patients and having the ability to predict patient's outcome. All of the processes described remain valid and are essential within the modern NHS and must be embraced during "life-long" clinical practice.

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Branchial anomalies

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Abstract
Branchial anomalies are rare congenital abnormalities of the head and neck, usually presenting in childhood. Their embryology, clinical presentation and treatment is discussed.

Key Words
Branchial arches, Embryology, Cutaneous fistula, Congenital.

Introduction
In order to appreciate branchial arch anomalies, it is vital to have a clear understanding of human embryology and developmental anatomy. Branchial arch anomalies may present in a number of ways, and frequently pose a diagnostic challenge. With a detailed history and careful examination, and by understanding the anatomy and mode of presentation, it should possible to make the diagnosis on clinical grounds, and to confirm this with appropriate tests.

Embryology
The structures of the human lateral face and neck are formed from paired branchial arches, pouches and clefts. The branchial apparatus forms between weeks four and five of fetal development, and consists of six paired branchial arches separated by branchial clefts externally and branchial pouches internally[1].

Of the six paired arches, the fifth arch only exists transiently during embryological growth and development. The arches in humans are therefore I, II, III, IV, and VI. The first three contribute to structures above the larynx, while the last two contribute to the larynx and trachea. Each arch contains a cartilaginous skeleton, a muscular component, a nerve and an artery[2]. (Table 1)

During the 5th week of gestation, the ventral aspect of the second arch grows caudally to overlap the third and fourth arches, forming the cervical sinus. This sinus disappears by the 7th week. The first pouch and cleft become closely related and ultimately form much of the middle ear, mastoid and Eustachian tube. The second pouch remains in part as the tonsillar fossa. The third pouch contributes to the thyroid gland and inferior parathyroid glands; and the fourth pouch contributes to the superior parathyroid glands. During week 6 of gestation, the external ear begins to develop, as three otic folds form on the first arch, and three on the second arch. These fuse to become the auricle. The thyroid gland develops from the foramen caecum of the tongue, in the floor of the pharynx, and descends to its final position, anterior to the trachea, by week seven of gestation. During its migration, the thyroid gland remains connected to the tongue by the thyroglossal duct. This duct then involutes. The thyroid begins to function after approximately 12 weeks gestation[3].

Terminology
Persistence of remnants of the branchial apparatus gives rise to a number of recognized branchial arch anomalies in the head and neck. A persistent cleft gives rise to an external sinus – a blind ending opening onto the skin. A persistent pouch causes an internal sinus, typically opening into the pharynx. Persistence of both cleft and pouch may therefore cause a fistula with both an internal pharyngeal and external cutaneous opening. The pharyngeal orifice is often tiny and difficult to identify. Clinically, almost all of these fistulas are lateral cervical fistulas, originating from the second pouch and cleft. Anomalies which cause a single sinus or the persistence of a tissue remnant are much more common than fistulae. The former group includes pre-auricular sinuses, cysts and skin tags[1].

Arch	Muscles	Skeleton	Nerve	Artery
Table 1: The branchial arches				
1st	Muscles of mastication, anterior belly of digastric, mylohyoid, tensor tympani, tensor veli palatini	Muscles of mastication, anterior belly of digastric, mylohyoid, tensor tympani, tensor veli palatini	Trigeminal (V2 and V3)	Maxillary artery
2nd	Muscles of facial expression, buccinator, platysma, stapedius, stylohyoid, posterior belly of digastric	Stapes, styloid process, hyoid (lesser horn and upper part of body), Reichert's cartilage	Facial nerve	Stapedial artery
3rd	Stylopharyngeus	Hyoid (greater horn and lower part of body), thymus	Glossopharyngeal nerve	Internal carotid, common carotid
4th	Cricothyroid muscle, all intrinsic muscles of soft palate	Thyroid cartilage, epiglottic cartilage	Vagus nerve, superior laryngeal nerve	Right: subclavian artery Left: aortic arch
6th	All intrinsic muscles of larynx except the cricothyroid muscle	Cricoid cartilage, arytenoid cartilages, corniculate cartilage	Vagus nerve Recurrent laryngeal nerve	Right: pulmonary artery Left: Pulmonary artery and ductus arteriosus

First Branchial Arch, Cleft and Pouch

Maldevelopment of the first branchial arch can result in various congenital malformations of facial and related structures. Those familiar to paediatric otolaryngologists typically involved underdevelopment of the mandible and structures relating to the external and/or middle ear. This constellation of abnormalities is a result of insufficient migration of cranial neural crest cells into the first branchial arch during the fourth week of gestation.

Treacher Collins syndrome is characterised by failure of development of first arch structures. There is micrognathia and underdeveloped zygomata along with auricular and middle ear abnormalities.

Failure of adequate mandibular development may lead to the Pierre Robin sequence where the resulting glossoptosis causes failure of midline palatal fusion and resultant cleft palate. This may be features of other recognised syndromes such as Stickler's and it may occur in association with Treacher Collin's.

Pre-auricular sinuses arise from abnormal development of the otic hillocks of the first and also second branchial arches.

Other anomalies related to maldevelopment of the first branchial arch include: agnathia and micrognathia associated with abnormal development of the mandibular process; anotia, microtia, macrotia, synotia and accessory auricles caused by failure of normal development of auricular structures; abnormal or absent malleus; anodontia, polydontia and supernumary teeth.

First branchial cleft anomalies are rare, accounting for less than 5% of branchial cleft anomalies. The classically described branchial cleft sinuses are often best thought of as duplication anomalies of the external auditory meatus. They may arise from the external auditory canal (Work Type I) or parallel to it (Work Type II) and lead to a cystic cavity which becomes recurrently infected and may drain in or near the ear. These tracts are often intimately associated with the facial nerve[4].

Other anomalies of first cleft development include: pits of the lower lip; clefts of the middle chin and ear lobe; cervical tags and dermoid cysts; atretic, stenosed or malformed external auditory canals; and double or congenitally perforated tympanic membranes.

Anomalous development of the first branchial pouch is rare but may produce atretic eustachian tubes, absence of tympanic cavity or mastoid antrum and cells, double or perforated tympanic membrane, and branchiogenic nasopharyngeal cysts.

Second Branchial Arch, Cleft and pouch

Anomalies of the second arch consist of absent or malformed auricle or ossicles, and muscular asymmetry of the face. Preauricular sinuses may arise from abnormal development of the second, and first, branchial arches.

Second branchial cleft cysts, sinuses and fistulae result from failure to obliterate the second cleft by the inferior extension of the second arch, creating a temporary structure, the cervical sinus of His.

It is likely that the classically described 'branchial cyst' is a misnomer. These typically appear in early adulthood and are not associated with congenital sinuses or fistulae. They are lined with squamous material, unlike a second cleft sinus which had a mucosal lining, and more likely result from ectopic squamous material within lymph nodes.

Incomplete obliteration of the second branchial clefts result in a sinus opening onto the skin in the anterior neck, usually at the anterior border of sternomastoid in the lower third of the neck. A complete congenital fistula may exist as a result of a combined second cleft and pouch anomaly. Fistulae of the second cleft and pouch are the most common branchial fistulae, and traverse along the carotid sheath between the bifurcation, to the tonsillar area, entering the pharynx in the region of the posterior faucal pillar.

Third Branchial Arch, Cleft and Pouch
Anomalies of third branchial arch development include hyoid bone deformities and aneurysms of the carotid artery system.

Abnormal development of the third branchial cleft manifests as thymic stalk, accessory thymus, thymic cyst, cervical cyst, and cervical fistula. Cervical cyst remnants of this origin typically lie deep to the internal carotid in intimate association with the vagus nerve.

Anomalies of third branchial pouch development can result in undescended or accessory parathyroid glands, thymic cysts, and diverticulum or sinus tract of the pyriform fossa. A sinus tract from the pyriform fossa can lead to the region of the left lobe of the thyroid gland. A complete congenital fistula, an anomaly of the third cleft and pouch, would route caudal to the glossopharyngeal nerve, over the superior laryngeal nerve, posterior to the internal carotid artery, opening through the thyrohyoid membrane into the pharynx near the pyriform sinus

Fourth Branchial, Cleft and Pouch
Recognised anomalies of the fourth arch are very rare and may include asymmetric or stenotic larynx, chondromalacia, and double arch aorta.

Fourth branchial cleft ectoderm gives rise only to the neural elements of the vagus nerve, abnormal development manifesting as a cyst which may produce a cough.

Failure of development of the third and fourth branchial pouches and their derivatives results in DiGeorge's Syndrome. This syndrome is characterized by absence of the thymus and parathyroid glands resulting in neonatal tetany and impaired cellular immunity. A complete fistula of the 4th pouch has not yet been described in humans, although cysts of the hypopharynx, larynx and thyroid are not uncommon. In addition, laryngocoele, posterior mediastinal thyroid and internal sinuses of the 4th branchial pouch have been reported.

The Branchio-Oto-Renal Syndrome
This is a rare genetic syndrome, inherited by as autosomal dominant with variable penetrance. It is characterised by branchial cysts, sinuses and fistulae, abnormalities of the inner ear with attendant sensorineural hearing loss and renal abnormalities[5]. Children presenting with branchial abnormalities should therefore have and audiological assessment and those with a hearing loss should go on to have a renal assessment.

Clinical Approach to Branchial Abnormalities
When treating these anomalies, techniques such as incision and drainage, sclerosis and radiation therapy should be avoided. Definitive management entails complete surgical excision, often involving removal of a small amount of normal tissue. Incomplete excision carries a high risk of recurrence. In the face of acute infection, the patient should be stabilized and any infection treated completely before undertaking a definitive procedure. On occasion this may necessitate drainage of a collection but it is important to recognize the possibility of an underlying anomaly especially in the case of unexplained recurrent infective problems such as recurrent abscess formation in the neck.

Sinus and fistulous tracts can be delineated preoperatively with radiological contrast studies although these are often unnecessary and not part of the senior author's routine practice.

Pre-auricular sinuses
These are common and arise from an abnormality of development of the otic hillocks which are derived from the first and second arches. They present as a punctum in the area immediately anterior to the anterior helix of the pinna. There may be acute infection or abscess formation. The sinus is lined by squamous epithelium and extends to the cartilage of the helix.

Asymptomatic pre-auricular sinuses are common and treatment is only necessary where there are complications such as infection or discharge. Treatment is by surgery. The best surgical option, in order to minimize recurrence,

Figure 1: *First branchial cleft fistula. There had been previous attempts to excise a recurrent cyst.*

is wide local excision of a wedge of tissue down to the cartilage of the pinna along with the involved segment of cartilage. The sinuses often branch and consequently attempting to dissect out the sinus is associated with a high rate of recurrence.

First Branchial Cleft Fistula

First branchial cleft fistula is rare. The largest published series of first branchial cleft anomalies[6] reported eighteen cases, eleven of whom had undergone incomplete surgery prior to referral. The opening at either end of the track is present at birth, and may become apparent by the discharge of debris, or by subsequent infection. The clinical presentation is with an opening onto the skin which is typically described in the submandibular region but can be anywhere in the region of the auricle (Fig 1). There is often a clinically apparent abnormality in the ear. This may consist of a strand of tissue extending from the floor of the meatus to the umbo. A sinogram may confirm the position and extent of the track although this is often unnecessary.

The fistulous track has a variable and unpredictable relationship with the facial nerve. It may pass deep or superficial to the nerve or may pass between the branches. Surgical excision necessitates removal of the track in its entirety, taking care to expose and preserve the facial nerve via a modified parotidectomy incision. It is essential that surgical treatment in children is only undertaken by surgeons familiar with parotidectomy in young children and that consent is taken to expose the facial nerve.

Second Branchial Cleft Fistula

Second branchial cleft fistulae and sinuses make up 95% of branchial cleft anomalies (excluding pre-auricular sinuses), and may form part of the branchio-oto-renal syndrome[5]. They present as a congenital opening anterior to the sternomastoid muscle which often leaks mucoid fluid and may become infected, occasionally forming an abscess.

Surgical excision is advisable because of the risk of infection. This is carried out by making an elliptical incision around the external opening, and following the track, upwards (Fig 2). Instilling methylene blue in small quantities into the opening can greatly aid identification of the track intra-operatively. A second skin incision can be made in order to access the upper part of the track, although this is often unnecessary. It is the senior author's practice to operate on children with symptomatic second cleft anomalies at an early stage as it is technically easier to access the upper part of the track when the neck is still relatively short.

Third and Fourth Branchial Pouch Anomalies

Sinuses and fistulae of the third and fourth branchial pouches are rare. Presentation is usually as a left-sided neck abscess which may communicate with the pyriform fossa. There may be recurrent abscesses requiring incision and drainage before the diagnosis is considered. The diagnosis can be made either with a contrast swallow
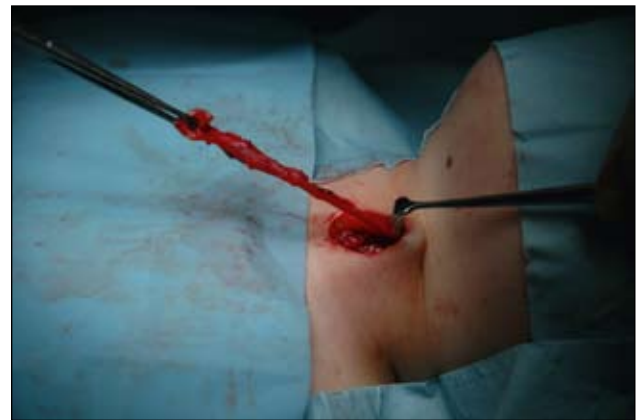
Figure 2: *Surgery to excise a second branchial cleft fistula.*

Figure 2: *Internal opening of a fourth branchial pouch sinus seen in the left pyriform fossa in a child who presented with a left sided neck abscess.*

X-ray, which will outline the sinus, or by laryngoscopes where the sinus opening can be visualized (Fig 3). The clinical appearance may mimic acute suppurative thyroiditis[7]. Treatment is by complete surgical excision of the track, which can be approached externally incorporating a left hemithyroidectomy to allow access or by endoscopic cautery of the track.[8]

CONCLUSIONS
Branchial abnormalities are, with the exception of pre-auricular sinuses, rare. However, their diagnosis is often delayed because of a failure to consider the possibility of an underlying congenital anomaly. They should be considered in cases of unusual or recurrent infection in the head and neck. A sound knowledge of the relevant embryology greatly aids the diagnosis and treatment of these lesions.

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Down's Syndrome – ORL H&N Manifestations

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Abstract

Patients with Down's syndrome, and in particular children may present to ENT surgeons with a variety of medical problems requiring specialist assessment and management. There are specific medical and anatomical issues relevant to surgery which should be considered. In the paediatric population, it may be desirable to see children in a specialist setting such as a dedicated clinic. Other members of the multidisciplinary team and parents/ carers should be actively involved in care decisions. Good communication is paramount, underpinned by sensitive use of language when speaking to parents and patients.

Key Words

Down's Syndrome, Obstructive Sleep Apnoea, Trisomy 21

Introduction

Down's syndrome or Down syndrome are synonyms for a chromosomal disorder affecting chromosome 21, and first described by John Langdon Down in the nineteenth century. It is the most common chromosomal abnormality, the specific gene abnormality having been identified in the 1960's.

Whilst there is an increase in the incidence of Down's syndrome with increasing maternal age, the majority of children are born to younger mothers due to the increased fertility of this age group.

Patients with Down's syndrome (PWDS) are able to lead healthy lives. Their life expectancy has increased to around 60 thanks to improved cardiac outcomes. Nonetheless, individuals have a higher risk of congenital heart defects, Alzheimer's disease, childhood leukaemias, thyroid conditions and respiratory and otological problems. Accordingly they may require input from many medical specialties, often from a young age. The otorhinolaryngologist plays an important role, in close conjunction with their audiology colleagues.

Specialist Paediatric ENT Clinics for Children with Down's Syndrome

Some centres (Manchester, Glasgow etc) have specialist clinics specifically for affected children. In this setting, a specific overview can be had of the child's general development outwith the constraints of the general clinic, and supported by educational and audiology colleagues. Problems such as glue ear, adenotonsillar hypertrophy and obstructive sleep apnoea syndrome may be addressed. As with any child with complex needs, care should be taken not to overburden parents and caregivers with excessive outpatient review as they will often have appointments with multiple specialists.

There is a philosophy in our clinic of optimising hearing and sleep quality/ oxygenation in the early years through an aggressive approach to ventilation tubes, hearing aids and adenotonsillar surgery. This approach is underpinned by the expectation that this may pay dividends in terms of both educational and cognitive function in later childhood.

Communication with parents

Pejorative terminology which may justifiably offend patients and their carers should be avoided. Parents will often feel strongly that their child is not defined by their Down's syndrome, and that instead they are a child who happens to have Down's syndrome. Phrases such as "child who has Down's syndrome" may be utilised effectively, whilst "Down's child" should be avoided. Particular care should be taken not to draw comparison with "normal" children,

but if comparisons are to be made, use the phrase "typically-developing child". Many children with Down's syndrome will attend mainstream school, at least in their early years.

There are a number of organisations (Down's Syndrome Association, National Down Syndrome Society) and educational resources available to both parents and health care professionals. As with many conditions and syndromes in childhood, a good basis to a relationship of mutual respect with the parent is an assumption from the outset that the parent may be better informed about their child's condition than their doctor!

Clinical Features relevant to the Otolaryngologist

Clinical features are variable and by no means ubiquitous. A subset of PWDS demonstrate what is known as mosaicism – not all cells are affected, permitting incomplete expression of the classical phenotypic features (Table 1).

Specialised growth charts are available for children with Downs' syndrome, and were commissioned by the UK

Down's Syndrome Medical Interest Group (DSMIG). These are based on analysis of healthy children with Down's syndrome, excluding those with major cardiac problems, for example.

Children with Down's syndrome may develop attention deficit hyperactivity disorders or features of autistic spectrum disorders and these necessitate appropriate involvement of psychologists and paediatricians. Interestingly, autistic features may appear at a much later age than usual and may therefore present to otolaryngologists with communication difficulties, possibly within the context of a hearing clinic. On a practical level, adequate time and patience are required in the ENT outpatient setting to reassure children and enlist their cooperation during clinical assessment. Table 2.

Otological

Anatomy

In Down's syndrome, the pinnae may be smaller, with a characteristic folding over of the superior portion of the helix. PWDS may also have small narrow ear canals precluding easy access to the tympanic membrane. The obvious sequelae are those of wax accumulation, problems with hearing aid moulding and fitting and difficulty in inserting tympanostomy tubes.

Glue Ear

Locally, we identified a 93% prevalence of otitis media with effusion at age 1 falling to 68% by age 5 (Scottish Medical Journal, In Press).

Specific consideration is given to the management of hearing loss in these children in the National Institute for Clinical Excellence Clinical Guideline published in 2008 – Surgical Management of Otitis Media With Effusion in Children1. It states that "hearing aids should normally be offered to children with Down's syndrome and OME with

Table 1: Clinical Features
Single palmar crease
Almond shaped eyes/ upward slanting
Epicanthal folds
Hypotonia
Short stature
Developmental delay
Macroglossia
Microgenia (+/- prominent tongue)
Increased space between great and second toe
Short neck
Brushfield spots (white spots on iris)
Immunodeficiency
Epilepsy
Thyroid problems
Leukaemias
Specific surgical and anaesthetic considerations
Cardiac Status
Cervical Spine
Thyroid Function
Macroglossia
Subglottic Stenosis – Downsize tube
(Immunological) – no evidence that wound healing compromised
Adjunctive procedures-
Dewaxing while under GA
ERA if behavioural testing unreliable

Table 2: Features of the ages of Down's Syndrome
Neonate Subglottic Stenosis
High Risk on UNHS – Repeated Testing
Laryngomalacia?
VC Palsy/ SGS after cardiac surgery
Preschool OSAS
Glue Ear / SNHL
Recurrent Croupy illnesses
School Remnants COM
Persistent nasal discharge
Progressive SNHL
Late onset autistic spectrum disorder

hearing loss." Furthermore, "Before ventilation tubes are offered as an alternative to hearing aids for treating OME in children with Down's syndrome, the following factors should be considered:

• the severity of hearing loss
• the age of the child
• the practicality of ventilation tube insertion
• the risks associated with ventilation tubes
• the likelihood of early extrusion of ventilation tubes."

This recommendation is made in the acknowledged context of a paucity of high quality research looking specifically at the management of hearing loss in this population.

Sensorineural hearing loss
Children are in a high risk category for congenital sensorineural hearing loss (SNHL). They should be identified as such during universal neonatal hearing screening.

In addition, late onset SNHL should be considered in children with a hearing loss not helped by tympanostomy tube insertion. Typically, SNHL is progressive and high tone in nature and can develop at any age.

The DSMIG recommend annual hearing screening of all preschool children and biennial screening thereafter.

Hearing aids
For the anatomical reasons mentioned above, hearing aids may be a less acceptable option for many children leading to poor compliance. Frequent mould changes and blocked tubing can require regular visits to local audiology services. For this reason, some surgeons have a more aggressive approach in offering ventilation tubes. The decision regarding surgery versus hearing aiding in otitis media with effusion should always be informed by audiology, parent and child preference.

Testing
Specific consideration should be given to the most appropriate means of testing hearing. A developmentally appropriate hearing assessment should be performed, and it can be helpful to have audiology colleagues well versed in techniques to keep children interested and co-operative. It may be helpful to complete audiometry at a further early review appointment.

Immunological
Children with Down's syndrome are up to 12 times (National Institute for Health[2]; National Health Service) more likely to develop a respiratory tract infection, due to immunological dysfunction. This included middle ear infections, tonsillitis and pneumonias – some of these can be fatal. The T-cell mediated pathways are often affected. Leukaemias are also more prevalent in these children.

Oropharyngeal
Up to 50% of children with Down's syndrome will have sleep disordered breathing[3456]. This is for a variety of reasons which include macroglossia, adentonsillar hypertrophy, midfacial hypoplasia, and generalised hypotonia of the upper airway. In reality, many of these problems may coexist and contribute to the problem.

Due to the high prevalence, clinicians should keep an open mind to the very real probability of OSAS. Clinical findings such as daytime somnolence, irritability and hyperactivity, snoring and witnessed apnoeas are important. Children with Down's syndrome and OSAS may develop pulmonary hypertension. The added negative impact of this in children with an underlying cardiac abnormality is unclear. In our clinic, by the age of 5 years 79% of children had undergone adenotonsillectomy or had ongoing obstructive symptoms (Scottish Medical Journal, In Press).

Interestingly, one study suggests that up to 40% of children with Down's syndrome with OSAS do not have habitual snoring[7]. For this and other reasons, some centres recommend formal sleep evaluation at 7 years of age in all children with Down's Syndrome, even going to the lengths of undertaking static and cine magnetic resonance imaging to assess the level of obstruction in recurrent OSAS following adentonsillar surgery[8].

The Royal College of Paediatricians working party on sleep physiology and respiratory control disorders in childhood[9] quote prevalence figures of between 70 and 100% of sleep related breathing disorders in children with Down's syndrome and argue that "All children with Down's syndrome should be offered screening for SRBD, using at least oximetry; suggested screening ages are at least once in infancy then annually until age 3-5 years."

Tonsillitis and pharyngitis may be more common due to the underlying immunological compromise present in many children.

Atlanto-axial instability
PWDS are known to have a higher chance of presenting with atlanto-axial instability. Unfortunately, the signs and symptoms are relatively non specific. Radiology suggests that up to 15% of asymptomatic individuals have features on X-Ray. Only 2% will need any intervention. This does not support the use of routine Xrays as these are not helpful in predicting subsequent injury[10].

Nonetheless, ENT surgeons intervening in theatre are likely to perform manoeuvres which may present risk to a susceptible C-Spine. These include hyperextension of the neck for tonsillar and adenoid surgery and rotation during otological procedures, including grommets. Care should be taken at all times when moving the anaesthetised patient[11]. The neck should be treated as potentially unstable in all children with Down's syndrome and excessive extension and rotation should be avoided.

Thyroid

1% of children born with Down's syndrome will have abnormal thyroid function, normally hypothyroidism. The remainder are at risk of developing thyroid problems and annual thyroid function tests are indicated. Children undergoing anaesthesia for ENT interventions such as grommets should have blood for TFT's withdrawn under anaesthesia to aid paediatricians and minimise traumatic interventions for the child.

Ophthalmological

Children with learning difficulties and sensory impairment such as hearing loss may be further compromised by visual problems such as squint and hypermetropia (up to 40% of preschool children). Referral to ophthalmological, orthoptic and optometric colleagues may be indicated.

Epiphora may present in children with Down's syndrome and it has been postulated that rather than mechanical blockage, the "lacrimal pump" is impaired due to the relative hypotonicity and anatomical differences of the eye region[12]. Conventional endonasal dacrocystorhinostomy is possible in these children with satisfactory results reported[13]– however some authors report lower success rates of ophthalmological surgery in these children and close liaison with ophthalmology colleagues is desirable.

ENT Surgical Interventions

Airway

The overlap and complex interplay between hypotonicity, laryngo and pharyngo malacia, and narrow nasopharynx should not be ignored. Children may require diagnostic micro-laryngo-bronchoscopic examination to evaluate the airway and assess several levels of obstruction. A recognition of the need for an individualised treatment plan is recommended[14].

Laryngomalacia has been reported to be more common in this population by some authors. The proposed explanation includes the relative hypotonicity in the upper airway. For the same reason, some authors suggest that supraglottoplasty is less successful and tracheostomy is warranted[15]. Nonetheless supraglottoplasty should not be discounted in

these children, although as with all children with laryngomalacia, parents and clinicians must be aware that a tracheostomy may be the eventual outcome.

There is a greater prevalence of congenital subglottic stenosis in Down's syndrome, much of which is asymptomatic. Acquired subglottic stenosis may result from repeated intubation, and inappropriate tube size. This may manifest itself as post extubation stridor (eg post cardiac surgery) in congenital undiagnosed SGS with inappropriate tube selection. Other causes of stridor including vocal cord palsy should of course be considered in this group.

Anaesthetic colleagues should be aware of the requirement for a smaller endotracheal tube when intubating these children[16]. The possibility of significant subglottic stenosis should be considered. Reference tables and guidance have been published based on "leak sizes" in a population of children with Down's syndrome[17]. In practice, many anaesthetists will automatically select a tube one or two sizes smaller than that required for typically-developing children.

Large series suggest a lower but still satisfactory success rate of laryngotracheal reconstruction in this population of children, and a higher incidence of posterior glottic stenosis [18].

Adenotonsillar Surgery

Many authors comment on the high "failure" rate in OSAS surgery in children with Down's syndrome[19]. Indeed, children with Down's syndrome undergoing adenotonsillectomy for OSAS may obtain less benefit than their peers in the general population[20]. However the benefit obtained may still be perceived significant to parents and children.

There is a relative paucity of data relating to the use of Continuous Positive Airways Pressure Ventilation (CPAP) in this patient group.

Many authors would maintain that any adenotonsillar surgery in children with Down's syndrome should not be done as a day case. With regard to surgery for OSAS, admission to the high dependency unit or intensive care may be required post operatively and surgery should be carried out in the appropriate setting. The UK consensus body[21] also identify Down's syndrome as a condition in which paediatric respiratory investigations are indicated – this may take the form of full polysomnography.

Ventilation Tubes

Grommet insertion in Down's syndrome should be informed by the NICE guidance referred to above. Surgeons should be prepared for a technically difficult procedure, the possibility of early and late post

tympanostomy tube otorrhoea, and early extrusion. Multiple sets of grommets may be required. Otorrhoea is more common[22] and when not controlled by topical therapy may necessitate grommet removal.

There is no high quality evidence to support the widespread adoption of any particular type of ventilation tube over another in Down's syndrome.

BAHA

Bone Anchored Hearing Aids (BAHA) and the Soft Band™ have helped many children with Down's syndrome. Benefits of the Soft Band are that it is temporary and allows some children to progress to glue resolution without permanent fitting of an abutment. Indeed many children continue with Soft Band and never undergo surgery for traditional BAHA.

There are no specific anatomical considerations in BAHA surgery for children with Down's syndrome when compared with other children. Brachycephaly and microcephaly may be apparent. The usual provisos apply with regard to depth of drilling in young children.

Tongue Reduction Surgery

Tongue reduction surgery has been recommended by some authors for perceived benefits of improved speech, and "oral competence". Reduction surgery remains controversial due to perceived crossover with cosmetic indications. It has some popularity in the United States, but is uncommon within the UK for children with Down's syndrome.

Cosmetic Surgery

Cosmetic surgery in this population is controversial. Procedures carries out worldwide include canthal fold surgery and other facial surgery. The Down's Syndrome Association in their position statement[23] support the right of adults with Down's Syndrome to seek a cosmetic surgical opinion. However they caution that such consultations may reflect an underlying societal issue with Down's syndrome, and that better education and acceptance may obviate the perceived requirement for such operations.

Conclusion

The prevalence of Down's syndrome and its related otolaryngological conditions mandates that ENT surgeons should be well versed in the management of such patients. In particular, paediatric otolaryngologists will have the opportunity to see and treat this rewarding group of children, and may wish to develop a subspecialty service together with paediatricians and professions allied to medicine.

Useful resource

The Down's Syndrome Medical Interest Group
www.dsmig.org.uk

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Assessment and surgical intervention of the paediatric laryngeal airway

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Abstract / Introduction

Obstruction of the paediatric airway can occur at many different anatomical levels. The aim of the clinical assessment is to establish the level of the obstruction and whether the obstruction is at a single or multiple levels. Obstruction in the neonate with obligate nasal breathing can occur within the nose due to anterior piriform aperture stenosis, choanal stenosis or atresia. Pharyngeal level obstruction may result commonly from adenotonsillar hypertrophy, less commonly from other obstructive lesions such as lymphatic malformations or from tongue and jaw anomalies such as in Pierre-Robin sequence or as a result of neurological deficits such as generalised hypotonia. The scope of this article is restricted to the assessment of the infant with stridor and the principles of the surgical correction of laryngeal airway obstruction.

Key words

Stridor, infant airway obstruction, laryngomalacia, subglottic stenosis, laryngotracheoplasty

Assessment

Clinical assessment

More than in many other conditions, history and inspection are the most important components of the clinical assessment of the infant with breathing difficulty. In situations of acute-onset stridor, obtaining a history can be very difficult due to the understandable distress of the parents. In elective situations, a carefully elicited history should be directed towards establishing the likely site of the obstruction, the likely pathology and the severity of the obstruction, in turn indicating the urgency of intervention. No symptom is absolutely pathognomonic of any particular pathology causing laryngotracheal obstruction, but the synthesis of antenatal and perinatal history, time of onset of stridor, history of neonatal intubation, history of cardiothoracic surgery, presence or absence of choking on feeding, exacerbating and relieving factors, timing of the noisy breathing as well as nature of the cry focuses the diagnostic process. The time of onset

of stridor gives some suggestion of the diagnosis, but is not a robust indicator. For example, while stridor associated with laryngomalacia is often described as having a delayed onset of 2-4 weeks after birth, a history of onset at birth is not uncommon and should not preclude laryngomalacia from the differential diagnosis. Subglottic haemangiomas also tend to present from a few weeks to months of age but in contrast to laryngomalacia, it is very uncommon for them to present at birth. Although it is the second most common congenital anomaly of the larynx, vocal fold paralysis lies a distant second behind laryngomalacia and is typically bilateral, presenting with a harsh biphasic stridor at birth. Unilateral vocal fold paralysis is most commonly associated with cardiothoracic surgery but while congenitally paralysed vocal folds tend to lie in the midline, acquired vocal fold paralysis tends to result in the vocal fold lying in a paramedian position. This is reflected in the usual finding of harsh stridor, a normal cry and absence of aspiration in congenital bilateral vocal fold paralysis but that of a soft stridor, a dysphonic cry and occasionally aspiration in the infant with acquired unilateral vocal fold paralysis. An aphonic cry with stridor should alert the clinician to the possible diagnosis of a congenital glottic web.

A history of "blue spells" (periods of apnoea with cyanosis) and failure to thrive are important aspects of the history to indicate severity increasing the urgency of formal laryngotracheobronchoscopy and possible surgical intervention. "Blue spells" are also associated with tracheomalacia.

Inspection, both acoustic and visual, is perhaps the most important component of the examination of a stridulous infant. The timing and quality of the stridor gives much information about the likely location and the nature of the obstruction. Inspiratory stridor suggests and extrathoracic or supraglottic obstruction while expiratory stridor suggests an intrathoracic obstruction. Biphasic stridor tends to indicate obstruction at the glottic or subglottic laryngeal level, such as in vocal fold paralysis, glottic

web, subglottic stenosis and subglottic haemagioma or cysts. Although attempts to 'test' experts' ability to diagnose pathology and assess severity of obstruction by listening to recordings of stridor have failed to show a correlation between the diagnosis made on listening to the actual diagnosis, the quality of the stridor can sometimes refine the differential diagnosis prior to endoscopic examination[1] The stridor associated with laryngomalacia, a dynamic obstruction, is often described as high pitched and musical; that associated with bilateral vocal fold paralysis, a hard, fixed obstruction tends to be harsh and monotone.

The volume of stridor is not a good indicator of the severity of the obstruction and this is particularly true for soft, fixed obstructions such as subglottic cysts and subglottic haemangiomas. Indeed, stridor becoming quieter in an infant may reflect tiring of the child and impending respiratory collapse. Visual observation of the infant gives a much better assessment of the severity of the airway obstruction. Pre-tracheal tug, intercostal and sternal recession, shallow respiration and tachypnoea are indicators of severity. In smaller babies, recruitment of the accessory muscles of respiration results in a characteristic "head-bobbing' and increased air hunger causes nasal flaring. Overt cyanosis is a very late occurrence.

Flexible fibreoptic laryngoscopy is a very useful adjunct to the clinical examination but one with limitations. The fibreoptic laryngoscope can either be introduced through the mouth or through the nose. It is possible to pass a 2.8mm fibreoptic endoscope through the nostril of most infants and it gives a good panoramic view of the glottis and supraglottic larynx. It is particularly useful in confirming the clinical suspicion of laryngomalacia, vocal fold paralysis and glottic webs as well as in excluding rarer lesions such as laryngocoeles, but is not useful in the evaluation of the subglottis.

Radiology
The role of radiology in the elective assessment of the paediatric airway is limited. Contrast swallow is perhaps the most useful radiological study as it can aid in the diagnosis of aspiration, laryngeal cleft, tracheomalacia, tracheo-oesophageal fistula, gastro-oesophageal reflux and extrinsic compression of the trachea from aberrant upper mediastinal vasculature. Infants who have already had vocal paralysis diagnosed by fibreoptic nasolaryngoscopy can have their vocal fold mobility monitored by ultrasonography. Infants with congenital bilateral vocal fold paralysis should have a brain MRI to exclude an Arnold-Chiari malformation as a cause of the vocal fold paralysis. 3D virtual endoscopy remains a research tool in development at this time.
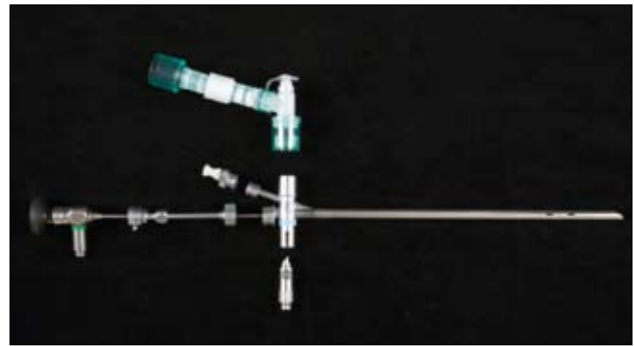

Figure 1: *An 'exploded' photo of a Storz ventilating bronchoscope indicating how the different components fit together.*

Endoscopy
The gold standard investigation for stridor remains formal laryngotracheobronchoscopy using the Storz ventilating bronchoscope under general anaesthesia (Figure 1). Laryngotracheobronchoscopy, together with microlaryngoscopy and endoscopic palpation of the cricoarytenoid joints if appropriate, is essential for the planning of any surgical intervention. This is particularly important when assessing the severity and position of fixed obstructions of the larynx as it will determine whether a cricotracheal resection or an augmentation laryngotracheoplasty is required. If the latter is required, accurate diagnosis will inform whether an anterior graft, a posterior graft or both are needed.

The safe execution of this procedure requires intimate teamwork between the anaesthetist, the laryngologist and the operating room nurse. As a lot of equipment is required, familiarity of the operating room nurse with the Storz ventilating bronchoscope, the circulating nurse with the adjunctive drugs required and the operating room orderly with the placement of the endoscopic camera system is absolutely essential. Furthermore, first inspection of the larynx by the anaesthetist occasionally reveals a rare and unexpected diagnosis which is alarming, such as a laryngocoele and a large pedunculated laryngeal papilloma (Figure 2a and 2b). In such situations, familiarity of the team members with the equipment is essential to a safe outcome in securing the airway. General anaesthesia is usually induced by inhalation of sevoflurane in oxygen and the larynx is anaesthetised with 2% plain lignocaine. The infant is allowed to breathe spontaneously and the anaesthesia is maintained by sevoflurane and oxygen delivered through a nasopharyngeal airway, permitting an endotracheal tube-free examination of the larynx, trachea and main bronchi. If subglottic stenosis is diagnosed, it is imperative to size the airway and grade the stenosis using an endotracheal tube. The largest tube which permits an air leak at a positive pressure of 30cmH20 is considered to
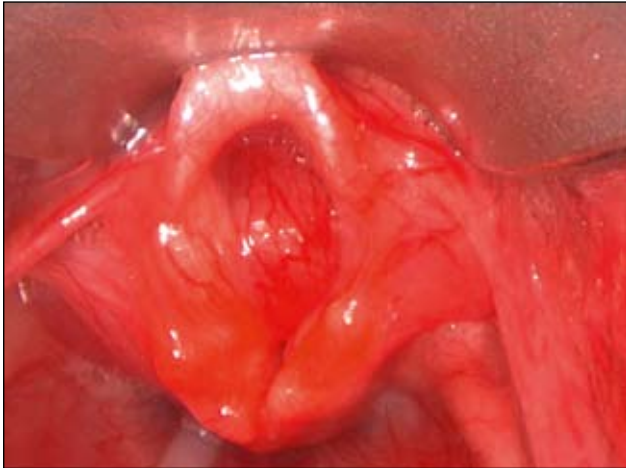
Figure 2a: *Laryngocoele completely obstructing the glottic larynx*

Figure 2b: *A pedunculated laryngeal papilloma popping up through the glottis, obstructing it completely.*

represent the size of the airway and the degree of obstruction estimated from that (Figure 3).

Surgical intervention

It cannot be emphasised enough that "it is not just about the operation". Many infants presenting to the otolaryngologist with stridor have multifactorial causes for their respiratory compromise. This may be due to co-existing pathologies such as congenital cardiac anomalies, pathologies arising as a result of prematurity such as lung disease of prematurity and prolonged endotracheal intubation and other factors rendering the laryngopharyngeal environment suboptimal such as gastro-oesophageal reflux. If these comorbidities are not carefully elucidated and managed, the success of surgical reconstruction is likely to be significantly compromised.

It is beyond the scope of this article to describe exhaustively all the surgical interventions in the paediatric larynx.

Figure 3: *Myer-Cotton classification for subglottic stenosis[2]*

Changes in practice and technology have greatly influenced the frequency, timing and type of paediatric laryngeal surgery offered to patients. Recognition that excessive endotracheal tube size, endotracheal tube instability and laryngopharyngeal reflux has resulted in a change in neonatal care, which has resulted in a reduction in the incidence of acquired subglottic stenosis. This has been balanced by the increased survival of severely premature babies who develop acquired subglottic stenosis even with the finest neonatal tube care. The administration of propranolol in the treatment of subglottic haemagiomas has dramatically reduced the need for open excision of subglottic haemangiomas[3] (Figure 4). Although open laryngeal framework surgery (augmentation laryngotracheoplasty or cricotracheal resection) remains the most effective management in many cases of subglottic stenosis, the evolution of endoscopic laryngeal surgery and balloon dilatation of early laryngeal stenoses has enhanced the repertoire of the paediatric laryngologist.

Figure 4: *Subglottic haemangioma before (left) and after (right) treatment with propranolol for two weeks*
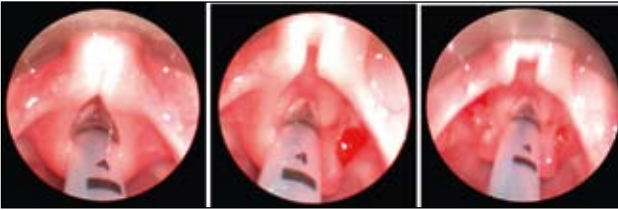
Figure 5: *Aryepiglottopasty using microlaryngeal scissors and 1:10,000 adrenaline on neuropatties for haemostasis*

Laryngomalacia

The surgical management of laryngomalacia has evolved over the years from tracheostomy, through amputation of the epiglottis to the current variations on the theme of supraglottoplasty. The principle of supraglottoplasty lies in the removal of redundant mucosa overlying the arytenoid cartilages and the release of a fore-shortened aryepiglottic fold with a view to increasing the aperture of the laryngeal inlet and reducing the propensity of the supraglottis to collapse (Figure 5). Overzealous tissue removal, especially posteriorly, can predispose to aspiration or, in the long term, supraglottic stenosis. Aryepiglottoplasty has been shown to be effective at improving stridor in 94.5% with a complication rate of under 10%[4].

Vocal fold paralysis

Perhaps surprisingly, not all infants with bilateral vocal fold paralysis fail to thrive or develop sufficient respiratory compromise to require surgical intervention. The nature of the surgical intervention should be informed by the natural history of congenital vocal fold paralysis, that being spontaneous recovery in over half the children, mostly by the age of five but reported as late as eleven years[5]. Therefore, a conservative approach should be adopted with respect to the larynx. However, the otolaryngologist often comes under pressure to achieve decannulation before the child starts school and the paediatric laryngologist must invest much time into the indications and consequences of suture lateralization of the vocal fold or cordotomy in terms of expectation, voice outcome and the risk of aspiration[6].

Pre-emptive intervention in laryngeal stenosis

Early intervention in infants with stridor, particularly infants in the paediatric intensive care unit who fail

Figure 6: *Evolving subglottic stenosis and balloon dilatation using a 5mm valvotomy balloon.*

Figure 7: *Subglottic cysts*

endotracheal extubation, has led to the recognition of early subglottic stenosis and the introduction of balloon dilatation of the stenosis (Figure 6). Dilatation should only be carried out with a balloon which exerts pressure circumferentially without the shearing injury associated with bougies. This may be done in isolation or together with an anterior laryngotracheal decompression ("cricoid split")[7]. The criteria for an anterior cricoid split are fairly stringent and include a weight above 1.5kg, no assisted ventilation for ten days preoperatively, supplemental oxygen requirement less than 35%, and no congestive heart failure for a month before evaluation. Although the anterior cricoid split was designed as a decompression procedure, an interposition graft can be placed in the split cricoid both as an augmentation of the cricoid as well as facilitating healing of the cricoid and therefore extubation. Thyroid alar cartilage has been used but the authors' preference is for the body of the hyoid. Early laryngotracheobronchoscopy also identifies subglottic cysts which can be deroofed endoscopically (Figure 7).

Figure 8: *: Congenital anterior glottic web*

Figure 9: *Anterior and posterior cartilage grafts in situ after removal of the endotracheal tube at day 7 post laryngotracheoplasty.*

Figure 10: *Anterior cartilage graft mucosalised 3 months post laryngotracheoplasty*

Management of glottic webs

Congenital glottic webs are rarely thin films but usually thicker webs associated with an underlying anterior subglottic stenosis (Figure 8). Therefore, a simple endoscopic division is doomed to failure with reforming of the web unless the anterior subglottis is augmented with a costal cartilage graft laryngotracheoplasty.

Subglottic stenosis

The overwhelming majority of subglottic stenoses are acquired. True congenital subglottic stenosis arises as a result of failure of complete canalisation of the cricoid cartilage leading to a small and circumferentially thickened cricoid. Costal cartilage graft augmentation laryngotracheoplasty remains the augmentation procedure of choice in subglottic stenoses up to Cotton-Myers Grade III in severity. First described by Cotton in 1978, it involves the interposition of one or two costal cartilage grafts to augment the anterior and/or posterior cricoid ring[8]. The graft is harvested from the right fifth and/or sixth costal cartilages, leaving the deep perichondrium intact to minimise risk of pneumothorax as well as promotion of neochondrogenesis, through a curvilinear incision approximating to the submammary line. Careful placement of this incision is particularly important in girls to prevent subsequent deformity of the right breast. The posterior graft is held in place by circumferential pressure from the cricoid ring while the anterior graft is secured with monofilament absorbable sutures. Technically, the flanged anterior graft should be sufficiently stable not to require stenting of the grafted airway, but the authors' practice is to use the nasotracheal tube as a stent in situ for 7 days using a single-stage reconstruction method[9]. The tube is removed in the operating room and an endoscopy performed before returning the child to the PICU unintubated (Figure 9). In two-stage laryngotracheal

reconstructions, the stent may be separate from the tracheostomy (such as a shaped, cut endotracheal tube or a silastic roll) or it may be integral with it (such as a Montgomery T-tube). Once the cartilage graft eventually becomes mucosalized and the airway is stable, the stent can be removed and decannulation attempted (Figure 10). Decannulation rates for single-stage and two-stage laryngotracheal reconstructions are similar and reach 93-96%[10,11].

Posterior glottic stenosis

Posterior glottic stenosis (or interarytenoid fixation) may occur in isolation or coexist with subglottic stenosis. This distinction is important to establish and it determines whether an attempt at endoscopic cordotomy, division of interarytenoid fibrosis with suture lateralisation of the vocal fold or arytenoidectomy is worthwhile (Figures 11 and 12). If these procedures fail to achieve the necessary airway improvement for tracheostomy decannulation or

Figure 11: *Division of the interarytenoid band in posterior glottic stenosis with suture lateralisation of the right vocal fold*
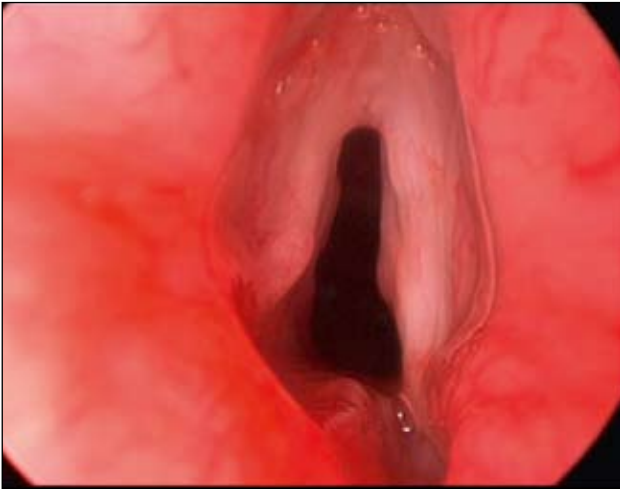
Figure 12: *Left vocal cordotomy in patient with posterior glottic stenosis*

adequate exercise tolerance, a posterior graft augmentation laryngotracheoplasty would be the reconstruction of choice. This is usually achieved through a laryngofissure approach, but can be achieved endoscopically after posterior cricoid split with a CO2 laser[12,13].

Resection

Despite universal acceptance of cartilage graft laryngotracheal reconstruction as the accepted surgical method for treating subglottic stenosis, results for severe grade III and grade IV subglottic stenoses remain suboptimal. Monnier proposed partial cricotracheal resection as an alternative to anterior and posterior graft LTR in these patients with thyro-tracheal anastomosis. The aim of the procedure is to resect the anterior segment of the cricoid and any stenotic tracheal rings with advancement and reanastomosis of the distal trachea to the thyroid and posterior cricoid remnent. Care should be taken to avoid damaging the recurrent laryngeal nerves, which can be safely achieved by remaining in the pre tracheal tissue plane during tracheal dissection. In the Lausanne series, 36 of 38 (94%) children undergoing cricotracheal resection for grade III/IV subglottic stenosis achieved decannulation with 31 out of 38 showing no exertional dyspnoea[14].

Summary

The elective assessment of the stridulous child relies upon a good history and observation to refine the diagnosis and to assess the severity of the airway obstruction.

Fibreoptic nasolaryngoscopy is an important adjunct to clinical examination but its diagnostic scope is limited to supraglottic structures. It is particularly useful for confirmation of clinical suspicion of laryngomalacia and evaluation of vocal fold movement.

Laryngotracheobronchoscopy under general anaesthesia with spontaneous ventilation remains the gold standard investigation for stridor.

A significant proportion of infants presenting with persistent stridor have co-existing pathology and comorbidities. Recognition and management of these pathologies is central to the success of any airway surgical intervention.

Laryngotracheal reconstruction needs to be tailored to the anatomy, severity and level of the laryngeal obstruction based on accurate microlaryngoscopic assessment. Successful decannulation rates over 95% have been reported, although sometimes after revision surgery.

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Aetiology and Treatment of Ranula

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Abstract

A scientific basis for the aetiology and treatment of ranula is now possible because of recent advances in knowledge of the local anatomy and the pathophysiology of the salivary glands and a recent detailed literature review of the different types of treatment. The oral and plunging ranulas are cystic extravasation mucoceles that arise from the sublingual gland and usually from a torn duct of Rivinus. The sublingual gland is a spontaneous secretor and the salivary flow is resistant to obstruction, which is caused by fibrosis induced by the extravasation. The submandibular gland is not a spontaneous secretor, is less resistant and does not give rise to ranulas. Removal of the involved unit of the sublingual gland or inducing sufficient fibrosis to seal the leak through which the mucus extravasates is the basis of effective treatment.

Key Words

Ranula; extravasation mucocele; sublingual gland; submandibular gland; salivary gland disease

Introduction

The origin of the ranula was discovered to be the sublingual gland in the nineteenth century[1,2], yet it was not until 1956 that it was discovered to be produced by extravasation of mucus from a damaged salivary duct and not to be lined by epithelium[3]. Hiatuses in the mylohyoid muscle through which parts of the sublingual gland herniated had also been discovered in the nineteenth century, and were considered to explain the origin of the plunging ranula from the sublingual gland[4]. Recent advances in knowledge of the local anatomy and the pathophysiology of the salivary glands and a detailed literature review of the different types of treatment of ranula[5] now enable the establishment of a scientific basis for the aetiology and treatment of ranula.

Local Anatomy

The sublingual gland[6] lacks a capsule and is in areolar tissue between the mucosa of the floor of the mouth and the mylohyoid muscle. A lesser sublingual gland is always present and consists of a mass of small glands, which number from 15 to 30, are elongated vertically and from every one of which a short duct of Rivinus passes to the plica sublingualis. A greater sublingual gland, which is situated between the lesser sublingual gland anterolaterally and Wharton's duct medially, is sometimes present and then usually unilaterally. Bartholin's duct passes from the greater sublingual gland either to join Wharton's duct or to run alongside it to open next to it at the caruncula sublingualis. The uncinate process of the submandibular gland is usually present and is superior to the mylohyoid muscle and may be separate from or in continuity with the main submandibular gland inferior to the mylohyoid muscle. The posterior part of the sublingual gland usually fuses with the uncinate process of the submandibular gland and can only be distinguished from it by histology.

One or more hiatuses in the anterior two thirds of the mylohyoid muscle through which a process of the sublingual gland usually herniates have been found in up to 45 % of cadavers and they may be unilateral or less often bilateral[4, 5].

Pathophysiology of sublingual and submandibular glands and ranula

The ranula is an extravasation mucocele that arises from the sublingual gland, either from a torn main duct, or from ruptured acini following obstruction[3,7,8]. The sublingual gland is a spontaneous secretor and produces a continuous flow of mucus even in the absence of stimulation. Extravasated mucus produces an inflammatory reaction in

which macrophages breakdown the organic component, which allows the water and inorganic component to drain away in the lymphatics, and granulation tissue forms fibrous tissue, which restricts the extravasation and sometimes seals the leak. However, the secretory activity of the sublingual gland is resistant and often persists in spite of the fibrosis, and a balance is then achieved between extravasation of mucus and its removal by macrophages and lymphatics. The secretory activity of the submandibular gland is much less resistant and extravasation of saliva is eventually stopped by fibrosis[9, 10].

Aetiology of ranula

A detailed histological investigation by McGurk et al[8]. found a torn duct of Rivinus in every one of 8 cases of oral ranula, which indicates an origin from part of the lesser sublingual gland following trauma to the floor of the mouth. Possibly there is unnoticed trauma during mastication. The plunging ranula could arise from a torn duct of Rivinus, and mucus pass through a hiatus in the mylohyoid muscle or pass posteriorly over the posterior border of the mylohyoid muscle to reach the submandibular and other regions.

Also, a plunging ranula could arise from part of the sublingual gland that is herniated through a hiatus in the mylohyoid muscle and constricted by the muscle. Such an obstructive constriction would either lead to atrophy or to persistent extravasation of mucus from acini ruptured by the secretory force of the sublingual gland. These various possibilities are illustrated in Figure 1.
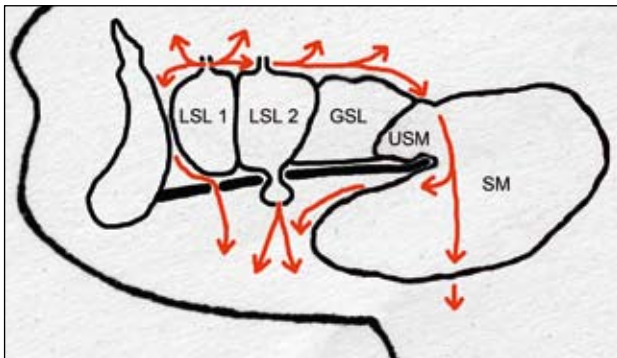

Figure 1. *Diagram of sources and spread of extravasated mucus in the ranula. Mucus extravasates from a torn duct of Rivinus of one of the lesser sublingual glands (LSL 1) and spreads above the sublingual gland to form an oral ranula, and sometimes passes through a hiatus in the mylohyoid muscle or around the posterior border of the mylohyoid muscle by the submandibular gland (SM) to form a plunging ranula. Part of the sublingual gland (LSL 2) has herniated through a hiatus in the mylohyoid muscle and mucus extravasates from acini ruptured because of obstruction and passes cervically to form a plunging ranula without an oral component. The greater sublingual gland (GSL) fuses with the uncinate process of the submandibular gland (USM).*

Treatment of ranula

Table 1 is a summary of treatments for ranula that have been used since 1957, and is the source of the following outcomes of treatment. Comprehensive details of the literary sources of Table 1 are published elsewhere[5].

The aim of treatment is to stop the extravasation of mucus from the sublingual gland. Once this happens, the ranula, which consists of inflamed granulation tissue, will eventually disappear. Successful treatment therefore depends upon either the removal of the unit of sublingual gland from which the extravasation occurs or the sealing of the leak from the gland.

Removal of the unit of sublingual gland from which the extravasation occurs

Excision of the sublingual gland is a successful treatment of ranula, and the recurrence in 2 % of 881 operations that involved excision of the sublingual gland is caused by incomplete excision, including persistence of sublingual gland in a hiatus of the mylohyoid muscle. However, McGurk et al.[8] developed a successful technique that involves the preparatory procedure of reducing the size of an oral ranula by paracentesis and then excising only the associated part of the sublingual gland, thereby ensuring that the part of the sublingual gland that is excised is the unit from which the ranula arises.

Sealing of the leak from the sublingual gland

Although ranulas do not arise from the submandibular gland, 18 % of 28 excisions of the submandibular gland without the sublingual gland were successful. These successes relate to postoperative fibrosis that fortuitously seals the leak from the sublingual gland, particularly as 4 out of the 5 successful excisions involved extensive dissection of the ranula in order to remove it, which would almost certainly have involved the origin from the sublingual gland.

Sealing of the leak from the sublingual gland by postoperative fibrosis accounts for the successes of dissection of the ranula alone, which are 63 % of 8 operations for oral ranula and 8 % of 26 operations for plunging ranula, and of simple marsupialization, which are 55 % of 53 operations for oral ranulas and 38 % of 8 operations for plunging ranulas. Marsupialization with packing the cavity was more successful, with a success rate of 82 % of 73 operations for oral ranulas and 100 % of 8 operations for plunging ranulas. The pack itself would induce fibrosis and also immediately obstruct extravasation from the sublingual gland, and such obstruction also accounts for the success of marsupialization with pressure. Marsupialization of oral ranulas by laser was successful in all 13 operations: the defocused lasering of the base of the

Table 1. Survey of treatment of ranula.			
Treatment	**Success**	**Fail**	**Success%**
Oral Ranula			
Removal of sublingual gland	11	0	100
Removal of sublingual gland and ranula	174	2	99
Removal of ranula alone	5	3	63
Marsupialization	29	24	55
Marsupialization by laser	13	0	100
Marsupialization with packing	60	13	82
Injection of OK-432	40	15	73
Micromarsupialization by seton	22	0	100
Incision and drainage	0	5	0
Incision and drainage perinatally	4	11	27
Injection of botulinum toxin	3	0	100
Homoeopathy in children	8	0	100
No treatment in children	2	0	100
Total of 444 Operations	**371**	**73**	**84**
Plunging Ranula			
Removal of sublingual gland	180	7	96
Removal of sublingual gland and ranula	38	2	95
Removal of sublingual and submandibular glands	9	0	100
Removal of sublingual and submandibular glands and ranula	17	2	89
Removal of submandibular gland	1	16	6
Removal of submandibular gland and ranula	4	7	36
Removal of ranula alone	2	24	8
Marsupialization	3	5	38
Marsupialization with packing	8	0	100
Injection of OK-432	58	40	59
Incision and drainage	1	31	3
Injection of botulinum toxin	1	0	100
Total of 456 Operations	**322**	**134**	**71**
Unspecified ranula			
Removal of sublingual gland	283	3	99
Removal of sublingual gland and ranula	151	2	99
Removal of ranula alone	26	18	59
Marsupialization	10	22	31
Marsupialization with packing	2	0	100
Injection of silver nitrate	3	4	43
Incision and drainage	0	4	0
Total of 528 Operations	475	53	90
Overall total of 1428 Operations	**1168**	**260**	**82**

ranula coagulates tissue and thereby seals the leak from the sublingual gland, and this is followed by fibrosis.

OK-432 produces inflammation and fibrosis, and injection into the lumen of the ranula was successful in 73 % of 55 oral ranulas and 59 % of 98 plunging ranulas.

Injection of silver nitrate into the lumen of the ranula owes its success in 43 % of 7 cases to its coagulative effect on tissues, which is followed by inflammation and fibrosis.

Micromarsupialization of oral ranulas by seton in which sutures are inserted into the roof of the ranula was successful in all 22 cases. The likely explanation for this is that the mucus in the ranula leaks away around the sutures, and mucosal epithelium grows along the sutures into the ranula to establish an epithelially lined tract. This would allow a flow of mucus from the ranula to persist, which would relieve the pressure on the wall, and the granulation tissue in the wall would reduce the size of the lumen until the epithelially lined tract fuses with the torn glandular end of a duct of Rivinus to create a regenerated duct.

Simple incision and drainage was unsuccessful except for perinatal oral ranulas, of which 27 % of 15 were successfully treated. The reason for this success is not apparent, although possibly the mucosal epithelium is more proliferative perinatally and sometimes establishes an epithelially lined tract before the wound closes.

The success of injection of botulinum toxin into the ranula and sublingual gland relates to inhibition of the parasympathetic secretory stimulation. Although the sublingual gland is a spontaneous secretor and sympathetic secretory stimulation continues, the balance between secretory activity that produces the extravasation and the opposing effect of the macrophages and granulation and fibrous tissue changes in favour of the opposition, which accounts for the success in all 4 cases so treated.

The reason for the success of homoeopathy in 8 cases of oral ranula in children is unclear, although spontaneous resolution of oral ranula was observed in 2 children, which emphasises the variable balance that exists between secretory output from the sublingual gland and the opposing macrophages and granulation and fibrous tissue.

This balance is the explanation for the persistent slight extravasation following therapy that is detected by imaging but is not detectable clinically[5]. This indicates that a slow turnover of extravasated mucus is likely to be present in many cases of clinically successfully treated ranulas, since postoperative monitoring by imaging has only been reported in a few publications. This also indicates that clinical recurrences may be a manifestation of a persistent extravasation mucocele with a movement of the balance between extravasation of mucus and its removal in favour of extravasation.

Conclusions

1. Ranulas arise from the sublingual gland.

2. Mechanical trauma to a duct of Rivinus is the usual cause of oral ranulas. A plunging ranula occurs: when extravasated mucus from a torn duct of Rivinus passes around the posterior border of the mylohyoid muscle or through a hiatus in the muscle to enter the submandibular region; or from extravasation from ruptured acini in part of the sublingual gland that has herniated through a hiatus in the mylohyoid muscle and become obstructed by the muscle.

3. Successful treatment of oral and plunging ranulas depends upon either the removal of the unit of the sublingual gland from which the extravasation occurs, the induction of fibrosis to seal the leak, or the inhibition of the secretory activity of the sublingual gland, which changes the balance between extravasation and the local opposition of macrophages and granulation and fibrous tissue in favour of the opposition.

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Complications of sinus surgery - prevention and management

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Abstract
Experience and expertise in surgical techniques within the confines of the paranasal sinuses has seen a decrease in the incidence of complications. Knowledge of potential complications and how they can be prevented is essential for all otolaryngologists. We present a regional/topical approach for the management of sinus surgery complications should they arise. Management algorithms aim to minimise both short and long term morbidity from infrequently occurring but significant complications.

Keywords
Surgery; Sinuses; Para-nasal Sinuses; Complications

Introduction
There are a many indications for surgery within the paranasal sinuses and nasal cavity (Table 1). Endoscopic surgical techniques described by Messerklinger and Wigand[1,2] complemented by open surgical techniques, remain the management choice for sino-nasal disorders refractory to medical therapy. Despite excellent visualisation of the relevant anatomical landmarks one must be aware that most risks from surgery are specific to the anatomical region and experience/training of the surgeon.

External and Endoscopic Surgery
External and endoscopic surgical techniques are complementary in approach with indications for each type of surgery dependant on the surgeons training and the pathology evident. With external approaches complications due to bleeding or damage to adjacent structures are similar to the problems that arise from endoscopic procedures, however damage to cutaneous or superficial nerves can also occur related to the approach.

The complications from sinus surgery can be examined in many different ways; we shall use a regional/topical approach to these problems.

Prevention of complications

Patient selection/preparation:
Knowledge of the possible procedures and their realistic outcomes assists in selecting patients that would benefit from sinus surgery and not be placed at unnecessary risk.

Table 1: Some Indications for Sino-nasal surgery both external and endoscopic
• Chronic rhinosinusitis
• Acute rhinosinusitis
• Peri orbital abscess
• Nasal polyps
• Mucocoeles
• Allergic fungal sinusitis and mycetoma
• Invasive fungal disease
• DCR
• Epistaxis
• Tumour
• CSF leak repair
• Pituitary surgery
• Orbital and optic nerve decompression

Table 2: Pre-operative checklist for reviewing CT images		
Region	**Considerations**	**Complication**
Uncinate	Variable attachment to either: Middle Turbinate Lamina Papyracea Skull base Avoid laterally directed incision into infundibulum	Orbital Emphysema CSF leak
Lamina Papyracea	Dehiscent	Slow onset venous bleeding Orbital emphysema Diplopia
Ethmoid Roof	Location of AEA and level or presence of fovea ethmoidalis cells. Asymmetry of ethmoid roof Thinnest aspect of skull base.	CSF leak (Meningitis, abscess, thrombosis) Rapid onset arterial bleeding (AEA), orbital haematoma Synechiae Anosmia
Cribriform Plate	KEROS classification [21] I 1-3mm II 4-7mm III 8-16mm	CSF leak (Meningitis, abscess, thrombosis) Rapid onset arterial bleeding- Anterior communicating artery Anosmia Frontal lobe injury Pneumocephalus
Posterior ethmoids	Height and presence of Onodi cells. Relationship to optic Nerve. 5 % optic nerve dehiscent [16]	CSF leak (Meningitis, abscess, thrombosis) Blindness Rapid onset arterial bleeding (ICA, PEA)
Middle Turbinate and middle meatus	Presence and stability. Concha bullosa. Relationship to skull base. Avoid excessive anterograde widening of natural osteum	CSF leak (Meningitis, abscess, thrombosis) Synechiae Naso-lacrimal duct damage
Sphenoid Sinus	Degree of septations. Septal relationship to ICA. Bony dehiscence of ICA canal. Relationship to optic nerve Integrity of skull base. Meningoencephalocoele	CSF leak (Meningitis, abscess, thrombosis) Blindness Rapid onset arterial bleeding (ICA, SPA)
Frontal Recess	Agger Nasi Cells Fronto-ethmoid Cells number and relation to uncinate Kuhn Type I, II, III, IV [22]	Iatrogenic frontal sinus mucocoele CSF Fistulae

Increased risk associated with operating in acutely inflamed mucosa, for example acute sinusitis can facilitate problematic bleeding[1]. Pre-operative courses of antibiotics and/or corticosteroids can reduce the vascularity in the surgical field where this opportunity is possible[3]. Good topical and infiltrative vasoconstrictive preparation of the nose should be routine for all nasal surgery to minimise the bleeding in the surgical field. Many different techniques are advocated by different authors, however this is beyond the scope of this article.

The patient should be screened in their case history for bleeding dyscrasias. Bleeding associated with anti-platelet therapy such as aspirin (inhibitor of thromboxane A2) or clopidogrel (inhibitor of adenosine diphosphate receptor preventing platelet aggregation) or anticoagulants such as warfarin that prolongs the 'Prothrombin Time' (inhibitor of vitamin K dependent clotting factors) can be avoided by temporarily stopping these medications. However this may be required 10-14 days before surgery to allow normalisation of the clotting time [3, 4, 5].

Once the decision has been made to operate, imaging with high resolution Computed Tomography (CT) scans of 1-3mm[5] axial slices with coronal reconstruction is fundamental to identifying potential intra-operative risks. Sagittal reconstructions are valuable for planning work in the frontal recess. CT aids the assessment of the disease as well as the underlying anatomy, the volume and position of the pathology correlates directly with the rate of complications. Table 2 provides a pre-operative check list that all surgeons should consider when evaluating the CT images before and during surgery. Revision surgery is more challenging due to the loss of anatomical landmarks that may predispose to complications.

The Surgeon:
A good working knowledge of sino-nasal anatomy is essential before undertaking any form of sino-nasal surgery. Stankiewicz noted a close relationship between experience and the incidence of complications with 5% and 29% major and minor complication rates respectively in his first 90 cases and 0.7% and 2.2% in the subsequent 90 cases[6]. This contrasts with Cumberworth's[7] findings that paradoxically correlate complications with experienced surgeons as a result of operating on a greater number of challenging cases. Trainee surgeons should use every opportunity for cadaveric dissection and close supervision by senior surgeons before they attempt surgery alone. Some authors suggest experience of a 100 diagnostic endoscopic procedures before performing endoscopic sinus surgery[8]. Orientation within the sino-nasal cavity is essential. If disorientation or loss of good vision within the operating field occurs, for example due to bleeding, then the surgery should be stopped and re-orientation undertaken. This may require a pause in the surgical proceedings to achieve both haemostasis and a review of the CT scans, or recourse to navigation strategies or the surgery may need to be suspended and further imaging undertaken at some later time.

Avoiding excessive mucosal trauma will reduce the incidence of osteitis, synechiae and stenosis particularly important in the osteomeatal complex and frontal recess[1]. Stammberger who encourages early post operative follow up with regular nasal toilet/douching, reports an 8% incidence of synechiae but only 20% of these patients are symptomatic as a result[1]. Both endoscopic and open approaches should be performed in an ordered stepwise fashion taking particular care in the ethmoids where the incidence of complications is highest.

Knowledge of not only the normal anatomy but also common anomalies associated with the sinuses and the related structures should be acquired by all sinus surgeons (table 3).

The use of power-tools can be a further source for complication especially in inexperienced hands. Power-tools aid the resection of pathology and reduce complications due to excessive mucosal excision, however equally, if used in an unguarded fashion power-tools may cause significant problems in the orbit and intra-cranial cavity often with little realisation by the surgeon [9].

In the event of a complication arising during or after surgery the surgeon should have a management algorithm in place to minimise both short and long-term morbidity.

Managing Complications

Bleeding:
Bleeding can have both an early and delayed onset and may be profuse/sudden or gradual. The vessels at most

Table 3: Anomalous anatomy to take into consideration pre-operatively
• Agger Nasi Cell
• Paradoxically turned Middle Turbinate
• Onodi Cell
• Haller Cell
• Pneumatisation of the frontal sinus/recess
• Dehiscence of the ICA
• Relation of naso-lacrimal duct from natural osteum 3-6mm (16)

risk are the anterior ethmoid artery (AEA) and internal carotid artery (ICA). Both can often be localised on CT imaging.

Smaller vessel bleeding can be treated by direct pressure with pledgets soaked in a vasoconstricting agent. If bleeding is refractory, then bipolar cautery may sometimes be considered.

Internal Carotid Artery

Experience and expertise have meant the incidence of all forms of peri-operative bleeding is decreasing with reports of 0.58% incidence [10]. The ICA is at risk when operating in the sphenoid sinus. The artery, which is dehiscent in up to 22% [3,11] of cases, is often closely related to the bony sphenoid septum and, disruption that should be avoided, may cause a sudden dramatic haemorrhage[1]. In such an event the area should be packed tightly and pressure placed upon the ipsilateral carotid artery in the neck. Once the bleeding is controlled, an angiogram may be used to confirm the site of the bleed and examine for collateral ICA and vertebral blood flow. If the bleeding is controlled the pack can be left in place for one week and is carefully removed in theatre. Re-bleeding would require re-packing and balloon occlusion[3].

Anterior Ethmoid Artery and the orbit

Trauma to the AEA occurs in conjunction with operating in the roof of the anterior ethmoid. The artery usually lies within the canalis orbitocranialis but may be dehiscent in 40% of cases[3]. If the bleeding vessel can be identified within the nasal cavity it may be clipped or cauterised. The main concern is retraction of the artery into the orbit causing an intra-orbital haematoma. Early signs of bleeding in the orbit include lid oedema, ecchymosis and proptosis. A significant arterial bleed in the orbit produces a rapid rise of intra-orbital pressure, thus causing optic nerve and retinal ischaemia. Delayed onset bleeding may produce a slower rise in the intra-orbital pressure and could be managed with Timolol Drops 0.5%, Dexamethasone 10mg IV, Acetazolomide 500mg and/or Mannitol 20% 2mg/kg IV over 20-30 minutes[1,12]. Regular observations must be made to document any deterioration of vision. If this occurs or if the bleeding is sudden and dramatic in theatre, a lateral canthotomy and inferior cantholysis should be performed to relieve the intra-orbital pressure (by up to 14mmHg) and avoid an orbital compartment syndrome. The optic nerve has only 60-90 minutes[13,14] before succumbing to ischaemia so decisions must be made promptly. In most cases the vessel goes into spasm and relief of pressure is all that is required. If however bleeding continues, further decompression of the orbit must be performed by way of either endoscopic removal of the lamina papyracea and incision of the periorbita to allow decompression of the orbital fat into the nasal cavity or an external Lynch-Howarth approach to similarly achieve decompression[13]. Exploring the orbit for a bleeding vessel should be avoided as this causes more intra-orbital damage.

Bleeding from other vessels

Other vessels are at risk of sinus surgery but their locations are not as exposed. The sphenopalatine artery (SPA) may be traumatised usually where it enters the nasal cavity with posterior widening of a middle meatal antrostomy or inferior extension of a sphenoidotomy where a branch lies inferiorly on the anterior sphenoid wall. The posterior ethmoidal artery (PEA) is rarely compromised due to its hidden location and small calibre on the supero-lateral aspect of the sphenoid.

Orbital Breach:

Breach of the bony medial wall of the orbit and periorbita most frequently causes exposure of the orbital fat. Intra–operatively this is seen as increased bleeding arising from the ethmoid/orbital region and post-operatively surgical emphysema and peri-orbital bruising are noted. No attempt should be made to manipulate the orbital fat, as this can further traumatise the extra-ocular muscles. The operation can be continued if the lamina papyracea is defined anteriorly and posteriorly to ensure no further breach occurs. The patient's vision should be formally assessed post-operatively[3].

Injury to the extra-ocular muscles can occur with the medial rectus being most at risk. In this event an ophthalmic opinion is required postoperatively to determine the eye movements and degree of diplopia that may occur. Direct surgery to the extra-ocular muscles may be required to prevent scarring and subsequent shortening of the muscles causing more permanent diplopia[15].

More severe disruption in the orbit with optic nerve damage may require decompression of the nerve surgically, steroids and ophthalmic support[16].

Naso-Lacrimal Duct Damage:

Extension of the middle meatal antrostomy anteriorly may cause removal of bone over the frontal process of the maxilla. The naso-lacrimal duct lies within this bony structure and may be damaged with dissection in this region. Symptoms consistent with epiphora may be seen early or late after surgery depending upon the degree of disruption or scarring of the duct. This is more usually seen with extensive endonasal resection of tumours and may require subsequent dacryocystorhinostomy to aid lacrimal drainage[16].

CSF fistulae:

CSF leaks most commonly occur whilst operating around the ethmoid, frontal or sphenoid sinus with a reported incidence of 0.5%[4]. CSF fistulae may be seen and managed intra-operatively and endoscopically with a reported 98% success[14], or managed conservatively. CSF fistulae can be located intra-operatively using intra-thecal 5% fluoroscein dye[17]. CT scanning with metrizamide or T2 weighted MRI[4] scanning is used to identify leaks in the post-operative phase. The specific surgical management will be influenced by the location of the leak. Most commonly the lateral cribriform lamellar or cribriform plate is disrupted due to deficient bone integrity at this site. A defect < 2mm can be grafted with any live tissue (septal or middle turbinate mucosa, tranversalis fascia, muscle or fat). Defects 2-6mm require more substantial composite grafting such as middle turbinate with bone and defects >6mm should be grafted with bone from the nasal septum or mastoid and mucosa[5]. The key to successful repair is to expose the defect, define its edges, undermine the surrounding mucosa, and graft the defect then place mucosa over the top. The use of fibrin glue to hold the graft in place should not be excessive as this may delay mucosalisation. It is important to place the non-epithelialised surface intra-cranially in order to prevent iatrogenic mucocoele formation[3]. Post operatively deep extubation is preferred and a conservative strategy of limited activity, head elevation when in bed and stool softeners are employed to decrease any rise in intracranial pressure. Superolateral and posterior wall defects of the frontal sinus may require an osteoplastic flap repair[5].

Intracranial complications:

Post-operative infection may take the form of meningitis, brain abscess or sinus thrombosis. Patients are at particular risk if the skull base has been breached leading to a CSF leak carrying a 10 - 19%/year risk of developing meningitis particularily in the first 12 months, if not repaired[18,19]. Infection can also spread along vascular and lymphatic channels. A high index of suspicion for meningitis symptoms prompts early antibiotic treatment for common pathogens (see table 4). It is important to utilise anti-microbials that cross the blood brain barrier particularly when managing an intracranial abscess. Clearly a neurosurgical and microbiological opinion would frequently be required as part of a multidisciplinary approach.

The rare occurrence of a tension pneumocephalus as a result of an iatrogenic communication of the sino-nasal cavity with the intracranium most likely occurs at the cribriform plate[20]. A CSF leak may or may not be present. Bed rest with the inhalation of 100% oxygen and avoidance of assisted ventilation may be all that is required, however,

Table 4: Pathogens associated with intra-cranial sepsis	
Meningitis	**Brain Abscess**
Streptococcus pneumoniae	Streptococcus milleri
Haemophilus influenzae	Staphyloccocus aureus
Neisseria meningitidis	Bacteroides spp.
Staphylococcus aureus	Peptostreptococcus spp.
Listeria monocytogenes	Fusobacterium spp.
	Haemophilus spp.

needle aspiration of the space and ventriculostomy could be employed if a tension pneumocephalus is suspected.

Encephalocoeles may be managed with identification, excision of herniated brain contents, haemostasis and repair techniques similar to those described above for CSF fistulae closure.

Conclusion

Surgery within the sinuses will always carry a degree of risk. However experience, advances in imaging and instrumentation will continue to reduce the incidence of major and minor complications. Sinus surgery should be approached in a stepwise manor to prevent serious complications occurring and if they do arise the surgeon must know how to manage them.

Abbreviations

AEA   Anterior Ethmoid Artery

CSF   Cerebrospinal Fluid

CT   Computed Tomography

DCR   Dacrocystorhinostomy

SPA   Sphenopalatine Artery

IV   Intravenous

mg   Milligrams

mm   Millimetres

PEA   Posterior Ethmoid Artery

ICA   Internal Carotid Artery

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Recurrent Nasal Polyposis

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Abstract
Recurrent nasal polyposis is a difficult disease to manage, with controversy surrounding current management. The aetiology remains uncertain but is thought to involve infective, local allergic and systemic factors. Disorders such as asthma, acetylsalicilic acid intolerance and atopy also have a strong association with chronic rhinosinusitis with nasal polyps (CRSwNP). Testing for allergies and mucociliary clearance disorders should be considered in addition to standard investigations when recurrent disease is suspected. Management includes a combination of medical therapy, such as antibiotics, systemic and topical steroids, nasal douching and surgery, typically functional endoscopic sinus surgery.

Key Words
Chronic rhinosinusitis, corticosteroids, inflammation, nasal polyposis, recurrence, sinus surgery.

Introduction
Nasal polyps have a prevalence of 2.1 to 4.3%, rising to 6.7% in asthmatic individuals[1]. Controversy surrounds the management of nasal polyposis, particularly recurrent disease; a chronic condition that often requires both medical and surgical interventions. This paper outlines the pathophysiology and treatment of recurrent nasal polyps.

What are polyps?

Definition
Nasal polyps are considered a subgroup of chronic rhinosinusitis (polyps – CRSwNP; no polyps - CRSsNP). The European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS3) definition of CRSwNP is: "inflammation of the nose and paranasal sinuses, associated with two or more of the following; blockage/congestion, discharge (anterior or post-nasal drip), facial pain/pressure, reduction of smell and endoscopic evidence of polyps[1]". A nasal polyp is an abnormal pedunculated lesion arising from the nasal cavity (Figure 1). Although polypoidal structures may turn out to be neoplastic, neither benign nor malignant lesions will be covered further in this paper. Histologically the majority of polyps appear to be the product of eosinophilic inflammation, with subepithelial eosinophils and pseudocyst formation. Raised albumin and raised levels of inflammatory mediators interleukin-5 (IL-5) and eotaxin are typical[2]. Neutrophil predominant polyps occur in some Asian populations[3] and in other disorders related to ciliary dysmotility, yet it is not clinically possible to distinguish this on clinical examination.

Aetiology
Nasal polyps represent a final common pathway of several disease processes (figure 2). There are four diseases

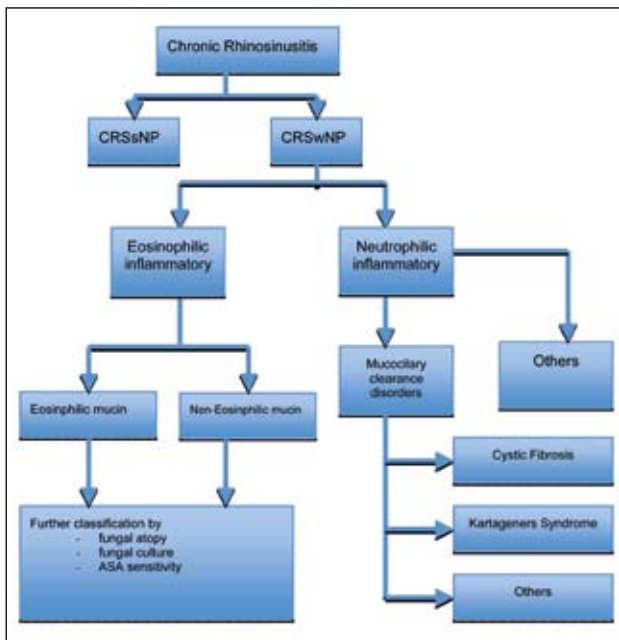**Figure 1:** *Clinical photograph of recurrent nasal polyps*

Figure 2: *Clinical classification of chronic rhinusitis with nasal polyps*

known to cause CRSwNP (aspirin insensitivity, allergic fungal rhinosinusitis, primary ciliary dyskinesia and cystic fibrosis). The vast majority of nasal polyps fall outside these diagnoses with proposed theories including hereditary, anatomical and systemic factors, local allergy, and infection/colonisation[4]. The following section summarizes the postulated causes of nasal polyposis:

Asthma
CRS is self-reported in 70% of patients suffering asthma[5], with 7% having nasal polyposis[6]. A dysfunction of leukotriene metabolism is associated with the well known Samter's triad[7] (aspirin-induced asthma associated with CRSwNP). Asthmatic patients with concomitant CRS have a higher disease burden and those with negative allergy tests have significantly more nasal polyps[6].

Acetylsalicilic acid intolerance and leukotriene metabolism
The prevalence of nasal polyposis in aspirin-sensitive asthmatics is 60-70%, as compared to less than 10% in other asthmatics[8]. The pathophysiology of aspirin intolerance is thought to be due to inhibition of cyclo-oxygenase-1 (COX-1) an enzyme responsible for prostaglandin synthesis. This inhibition switches arachidonic acid metabolism from the prostaglandin production pathway to the leukotriene pathway. Prostaglandins exhibit anti-inflammatory activity whereas leukotrienes are pro-inflammatory, creating an environment whereby IL-5 production, eosinophilic infiltration and polyp formation predominate.

Atopy
No conclusive link has yet been shown between nasal polyposis and the existence of atopy. 0.5-4.5% of subjects with allergic rhinitis have nasal polyposis[8] which is similar the normal population. Despite this, there is increasing evidence for the existence of local Ig-E production in patients with CRSwNP[9] and the term "Entopy" has been suggested as a suitable term for the presence of specific IgE at a tissue level, in the absence of systemic atopy[10].

Staphylococcus aureus
Evidence suggests that staphylococcus aureus plays a role in the development of CRSwNP, and this bacteria is found in the mucin of 60-70% of cases of massive nasal polyposis[11]. S.aureus is known to produce exotoxins which may act as superantigens, and cause the clonal expansion of lymphocytes with resulting cytokine production and polyp formation[11]. This may lead to up-regulation and increased survival of eosinophils in the nasal polyp[12]. IgE antibodies to exotoxins have been found in patients with nasal polyposis, lending further credence to the role of superantigens in nasal polyposis[13].

Allergic fungal rhinosinusitis:
The role of fungi in CRS remains controversial. Patients who fulfil the Bent and Kuhn criteria of type I (IgE mediated) hypersensitivity to fungi, nasal polyposis, characteristic radiographic findings of heterogeneous fungal lesions, eosinophilic mucin without fungal invasion into sinus tissue and positive fungal staining of sinus contents are classified as having allergic fungal rhinosinusitis[14]. These patients almost universally have CRSwNP.

Other forms of fungal rhinosinusitis:
The presence of fungi has been demonstrated in most, if not all patients with chronic rhinosinusitis. It has been hypothesised that non-IgE mediated mechanisms against fungi may be responsible for eosinophilic inflammation in some patients[15] and others have postulated an IgG rather than IgE mediated immunity to fungi as a possible disease pathway[16]. However many researchers believe the fungi are simply innocent bystanders in the process and that, with the exception of allergic fungal rhinosinusitis, conclusive evidence confirming fungi as a definitive aetiological factor in CRSwNP remains weak.

Biofilm
It is recognized that both S. aureus and fungi can form biofilms. These are defined as "….a microbially derived sessile community, characterized by cells that are irreversibly attached to a substratum … are embedded in a matrix of self produced extracellular polymeric substances

and exhibit an altered phenotype[17]". As a result of their protective matrix, bacteria in a biofilm are thought to be less susceptible to innate and adaptive host mechanisms as well as antibiotics. Bacterial biofilms are correlated with the persistence of post-operative symptoms and mucosal inflammation in patients with chronic rhinosinusitis[18]. There is now substantial evidence confirming the presence of biofilms in patients with CRSwNP[19]. Whether the biofilm is the causative factor or a secondary phenomenon has yet to be determined.

Mucociliary and immune disorders
Cystic fibrosis, primary ciliary dyskinesia and both acquired and congenital immune disorders can all be associated with CRSwNP. These polyps tend to be neutrophilic in nature and the diagnosis of CRSwNP in the paediatric population should always alert the clinician to the possibility of these conditions.

The management of recurrent CRSwNP

Investigation
It is important to ensure that patients presenting with recurrent disease are thoroughly investigated to ensure possible aetiological factors have been identified or definitively excluded. Allergy testing in the form of skin-prick testing and/or RAST is essential and ciliary function testing, cystic fibrosis phenotyping and immune function testing (e.g. Ig sub-classes) should be considered in selected cases. If aspirin sensitivity is suspected, an aspirin challenge should be performed in a suitable environment with full resuscitation facilities.

Medical treatment
Medical treatment aims to reduce patient symptoms by reducing or resolving the underlying inflammation. The evidence for medical treatment for adults with recurrent CRSwNP is shown in table 1.

Oral antibiotics
There is little evidence to support the use of broad-spectrum antibiotics in the management of recurrent CRSwNP. Macrolides are known to have significant anti-inflammatory effects in addition to their antibiotic properties. Macrolides inhibit protein biosynthesis and block the production of pro-inflammatory cytokines including interleukin-8 and tumor necrosis factor-a resulting in decreased neutrophil migration and adhesion. Macrolides have been demonstrated to produce remarkable benefit for some patients with CRSwNP but not others[20-22], yet many clinicians trial macrolides before considering revision surgery.

Table 1: Treatment evidence and recommendations for adults with chronic rhinosinusitis with nasal polyps			
Therapy	Level	Grade of Recommendation	Relevance
Oral antibiotics long term > 12 weeks	Ib	A	Yes (for late relapse)
Topical antibiotics	No data	D	No
Topical steroids	Ib	A	Yes
Oral steroids	Ib	A	Yes
Nasal douche	Ib		
(No data in single use)	A	For symptomatic relief	
Antimycotics – systemic	Ib	D	No
Antimycotics – topical	Ib	A	No
Oral antihistamine in allergic patients	Ib	A	No, in allergy
Anti-leukotrienes	III	C	No

Topical antibiotics and antimycotics
Although Richetti[23] found a 48% disappearance of polyps in patients treated with topical steroids and amphotericin B for four weeks, further randomized controlled trials have not shown amphotericin to be superior to placebo[24-27]. Anti-mycotics may also have a role in patients with allergic fungal rhinosinusitis and there is some evidence of itraconazole having benefit in other patients with CRSwNP. These medications have significant side effects and further evaluation of their efficacy is probably needed before their widespread use is recommended.

Intranasal corticosteroids
Topical nasal corticosteroids remain the mainstay of treatment for CRSwNP. There is good evidence that they are effective in the treatment of primary CRSwNP[28-30] and they have been shown to reduce the recurrence rates of polyps for up to five years following surgery[31]. Steroid drops (fluticasone nasules or pulmicort respules) may be more effective in controlling CRSwNP, especially in the frontal recess or in patients with recurrent disease but high level evidence to confirm their effect is currently lacking.

Oral corticosteroids
Systemic corticosteroids produce significant improvements in both nasal symptoms and radiological findings[32,33]. The optimal dosage and duration is not known (Hissaria et al used Prednisolone 50mg daily for two weeks[33]) and although steroids are undoubtedly beneficial in the treatment of recurrent nasal polyps, their anti-inflammatory effects cannot be separated from their metabolic effects and patients need to be adequately counseled of the risks including: osteoporosis, cataract formation, adrenal

suppression, insomnia and avascular necrosis of the hip. Recent evidence suggests that whilst a 2 week course of oral corticosteroids is associated with a significant reduction in polyp size and symptoms, there was total recurrence in nasal polyps after 3 months[34]. This casts doubt on the long-term benefit of this treatment approach.

Nasal douching

We routinely advocate the use of saline douches for our patients with recurrent nasal polyposis but whereas there is good evidence of their benefit in terms of alleviation of symptoms, endoscopic findings and improved quality of life indices in patients with chronic rhinosinusitis[35] no such evidence exists for patients with nasal polyposis[1].

Aspirin desensitization and leukotriene antagonism

In patients with Samter's triad, aspirin desensitization is considered an effective treatment for reducing the recurrence rates of polyps and is thought to act by reducing the number of leukotriene receptors[36]. Anti-leukotriene therapy, such as Montelukast, has been shown to improve sinonasal symptoms and reduce the severity of polyposis[37], and should be considered before further surgery. Patients with aspirin sensitivity are treated with increasing doses of oral aspirin or topical lysine-acetylsalicylate[38] and have been shown to have significant reductions in the need for surgery, sinus infections, hospitalizations for asthma and use of systemic corticosteroids[39,40].

Topical furosemide

Intranasal furosemide – an inhibitor of sodium chloride co-transporter channel at the basolateral surface of the respiratory epithelial cell has surfaced as a possible therapeutic intervention from this patient group. The basis of this treatment is to interfere with the early phase of nasal polyp development, particularly the oedematous infiltrate which may be the result of an alteration of the sodium chloride net flux[41]. Protection against nasal polyp recurrence following surgery with up to nine years follow-up has been demonstrated[41]. Relapse rates were recorded as 17.5% in the furosemide group, 24.5% in the mometasone group and 30% in the no treatment group.

Surgical and post-surgical treatment

The primary goal of surgical treatment is to remove nasal polyps from the nasal airway in order to restore airflow. Surgery also removes irreversibly diseased mucosa, aerates the sinuses and facilitates entry of topical medical treatment to the nose and sinuses. Functional endoscopic sinus surgery is now recognized as the gold standard for the management of CRSwNP that is resistant to medical management1. The success rates of FESS have improved significantly with better surgical and optical equipment and the development of advanced surgical techniques. It is recognized that FESS success rate in CRSsNP lies in range of 76% to 97.5%[42], however the in CRSwNP the surgical success rate falls to 50% - 70%[2,43,44]. Our practice is to eliminate any underlying causes of nasal polyposis and maintain maximal medical therapy for 3 months prior to offering surgery for most patients with recurrent nasal polyposis. We do offer earlier surgical intervention for patients with allergic fungal rhinosinusitis as we subscribe to the theory that their polyps are unlikely to resolve until the underlying fungal load has been eradicated.

Surgical technique

Our surgical approach involves completely removing nasal polyps and bony septations as well as opening up any of the sinuses that are involved. Mucosal preservation is achieved wherever possible. Recent CT imaging is mandatory prior to revision surgery as traditional landmarks can be distorted by the disease or previous surgery and may be absent. We find image guidance useful in selected revision cases but do not regard it as essential for 'standard of care'.

We routinely use powered instrumentation and find that the microdebrider allows rapid removal of polyps with mucosal preservation and reduced bleeding. The tip should be visualised at all times and it is important to note that a slow rotation speed allows more tissue to be sucked into the cage on each rotation and allows for faster debridement of polyps. The use of a trans-axillary approach to the frontal recess aids dissection of the agger nasi and frontal recess cells. Angled telescopes and microdebrider blades are essential to achieve optimal outcomes.

At the end of surgery we place fluticasone impregnated Nasopore absorbable dressings in the middle meati and routinely medialise the middle turbinates by "Bolgerisation" and a conchopexy suture through the nasal septum. This reduces the risks of adhesion formation, increases access for medication and helps to create well-aerated accessible cavities that can be easily visualised and toileted in the outpatient clinic.

Saline douching and debridement

Chemical surfactants cause cell membrane disruption, and microbial cell death, as well as acting as a biocide with action against biofilms. Baby shampoo has been recognised as a cost-effective, well tolerated and readily available surfactant with active ingredients of PEG_80 sorbitan laurate, cocamidopropyl betaine and sodium tridceth sulfate. A recent study of CRS patients who were symptomatic despite sinus surgery and conventional medical therapy were trialled with baby shampoo nasal

irrigations. The concentration was determined through in vitro testing on Pseudomonas aeruginosa and P. aeruginosa biofilms, finding that 1% solution inhibited formation of biofilms compared with normal saline, and was effective in eradicating planktonic P. aeruginosa[45]. Although limited by small clinical numbers there were subjective improvements in symptoms in over 50% of patients, which is noteworthy given 80% were asthmatic, and the average number of surgeries per patient pre-trial was nearly [3]. Consequently this is certainly worthy of further long-term studies, however its validity in CRSwNP is still to be determined but is likely to be most useful in those with thick mucus secretions and post nasal discharge[45].

Minimally Invasive Sinus Technique

The minimally invasive sinus technique (MIST) is a method first described in 1996[46] as a "targeted intervention,[47]" addressing the transition spaces surrounding the sinus ostia without changing the ostia themselves. There is less mucosal disruption, less required debridement, and also consequently less discomfort. The premise behind this technique is that mucociliary transport is disrupted in the anterior group of paranasal sinuses by mucosal oedema of the four transition spaces that these sinuses drain to. These space are the infundibulum, the medial wall of the ethmoid bulla, posteromedial wall of the agger nasi, and basal lamella and retrobulbar space. There are few outcome based studies in this technique, however recent research suggested that for patients with CRSwNP, whilst short term results were impressive, this improvement faded in the long-term[48].

Balloon sinuplasty

Balloon catheter dilation was first described by Brown and Bolger with the intent of enlarging stenotic sinus ostia[49,50]. Currently ideal patient selection for balloon sinuplasty remains controversial, however it has been suggested that patients requiring revision surgery, or with extensive polyposis will benefit more from conventional sinus surgery[51] which is our routine practice.

Conclusions

Recurrent CRSwNP remains a difficult disease to treat. It is essential the clinician goes back to first principles and performs revision history, examination and thorough investigation of these patients. Aggressive medical management in the form of both topical and systemic therapies needs to be offered prior to revision surgery in patients who fail medical management. Meticulous surgical technique, an optimal surgical field, adequate instrumentation and attention to detail are required to achieve good results. Post-operative management should involve frequent ENT review, aggressive topical and systemic therapies and long-term follow up. Even with

this approach, many patients will continue to present with recurrent polyps and their fate may depend on future research advances.

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Sinonasal Inverted Papilloma

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Abstract
Inverted papillomas are the most common benign sinonasal tumour. They typically present with unilateral obstructive symptoms. Little is known about their aetiology. They have the potential to undergo malignant change and are also associated with metachranous carcinomas. This review discusses the presentation, investigation and surgical management of these tumours with reference to the current literature.

Key words:
Inverted papilloma, papilloma, sinus, nose, endoscopic, surgery.

Definition
Inverted papillomas are benign epithelial tumours of the sinonasal tract.

Introduction
Inverted papillomas are the most common benign tumour of the nose and paranasal sinuses. In the past they have been called Schneiderian papillomas because they arise from the primitive mouth ectoderm (stomodeum), which forms the sinonasal mucosa or Schneiderian mucosa. This is distinct from the mucosa of the rest of the aero-digestive tract and hence inverted papillomas are localised to the sinonasal mucosa. The term 'inverted' is used as the neoplastic epithelium grows into the underlying stroma as opposed to the typical exophytic outward proliferation of papillomas elsewhere.

Inverted papillomas usually arise from the lateral nasal wall around the middle meatus and may extend into ethmoid and maxillary sinuses. With time they can fill all the sinuses on the side of origin but typically do not grow intracranially. Unlike a carcinoma they do not breech the mucosal basement membrane. However, unlike inflammatory polyps they can cause destruction of surrounding tissue including bone.

The two main features of inverted papillomas are their tendency to recur and association or transformation into carcinoma, usually squamous cell carcinoma. Carcinoma may arise in the inverted papilloma itself or be a separate lesion[1]. The incidence of associated carcinoma is variable but an analysis of 3058 reported cases showed the prevalence of malignancy to be 2.1% rising to up to 11% in recurrent cases. The prevalence of metachronous carcinoma was 3.6% (in 2047 patients with a mean interval of 52 months)[2]. This may be an over-estimate due to recurrent or malignant cases being referred to the reporting tertiary centres. Most cases are squamous cell carcinomas but transitional cell carcinoma, adenocarcinoma, mucoepidermoid carcinoma and verrucous carcinoma can also occur. Most so-called 'recurrences' occurring within the first few years after treatment are cases of residual disease. This will be discussed in the management section.

Incidence
Inverted papillomas have an incidence of 0.43 – 1.5 per 100,000 per year[2-4]. Men are affected 3 times more than women[5]. They can occur in almost all age groups but are rare in children and young adults[6].

Aetiology
The aetiology of inverted papillomas is poorly understood. They are often associated with rhinosinusitis but this is probably an effect of the tumour mass obstructing the sinus drainage pathways rather than a true causative factor. Human papilloma virus (HPV) is a DNA virus implicated in papilloma formation elsewhere in the body.

HPV-6, 11, 16 and 18 have been isolated within inverted papillomas and the surrounding mucosa but are by no means present in all cases of inverted papilloma[7,8].

Clinical presentation

The most common presentation is a unilateral nasal polyp causing nasal obstruction. This may be associated with rhinorrhea, epistaxis and, if it presses on the nasolacrimal system, epiphora. It can also lead to orbital displacement by direct pressure or due to a mucocele. Although typically unilateral, bilateral cases have been reported in approximately 1-9% of cases[9,10]. Inverted papillomas have even been found mixed with ostensibly normal bilateral inflammatory polyps. They usually have a slow growth pattern so patients may present many years after symptoms first became manifest.

Endoscopic examination usually shows a unilateral polypoid lesion, which may appear more 'fleshy' in colour and have a 'papillomatous' surface in contrast to the typically translucent, oedematous inflammatory polyps or an antrochoanal polyp (figure 1).

Investigation

On computerised tomography (CT) 75% of inverted papillomas show bone destruction or remodelling, suggesting the diagnosis but the potential of a malignant lesion must always be considered. They commonly originate on the lateral nasal wall in the region of the middle meatus and expand through the maxillary ostium. The inverted papilloma itself may contain calcified areas which appear as areas of hyperdensity. There may also be hyperostosis or sclerotic changes at the interface between the lesion and the adjacent bone (figure 2)[11]. Other diagnoses to consider are antrochoanal polyps, fungal sinus disease and malignant tumours.

Magnetic resonance imaging (MRI) is sometimes utilised to show the full extent of the inverted papilloma by differentiating it from surrounding inflammatory tissue and mucus. This is particularly useful in less accessible areas such as the frontal sinus. Inverted papillomas are hyperintense to muscle on T1 weighted images and have an intermediate signal intensity on T2 weighted images whereas inflammatory polyps are also hyperintnense on T2 images. MRI cannot differentiate a benign inverted papilloma from a sino-nasal malignancy.

Staging

A number of staging systems have been proposed (Krouse, Han, Kamel, Oikawa, Cannady) but are of limited practical use[12-16].

Management

The management of inverted papillomas is surgical. The diagnosis of an inverted papilloma should be confirmed before attempting complete resection. As much tissue as possible should be sent for histopathological analysis as there may be a focus of malignancy within the tumour or surrounding tissue. The practice of sending all nasal lesions for histological diagnosis should always be encouraged as what may appear to be simple inflammatory
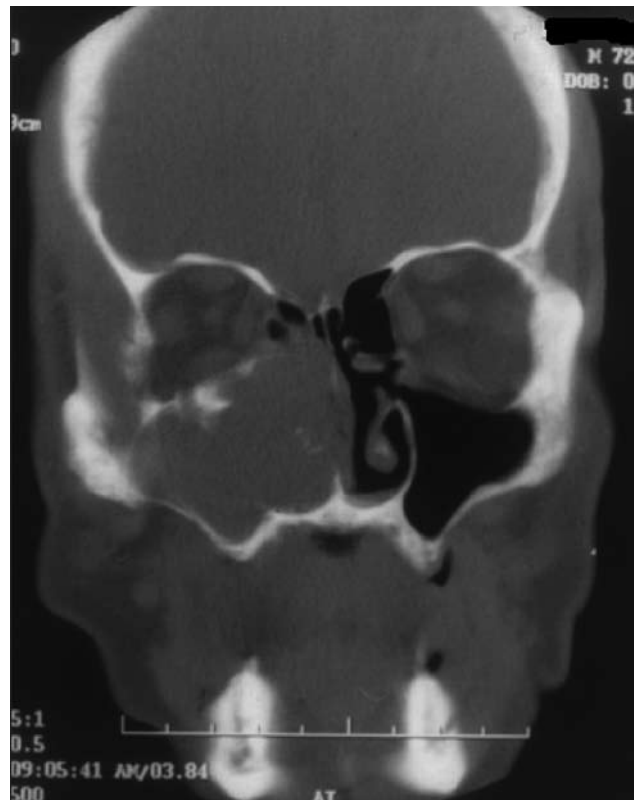

Figure 1: *Endoscopic view of right inverted papilloma showing 'fleshy' colour and papillomatous surface.*

Figure 2: *Coronal reconstruction CT scan of right inverted papilloma showing its unilateral nature, bone erosion and hyperostosis/ sclerosis at the interface (95% positive predictive of inverted papilloma11).*

Table 1: Recurrence rates of inverted papilloma (from European Position Paper on Endoscopic Management of Tumours of the Nose, Paranasal Sinuses and Skull Base[21]).			
Surgical approach	**Recurrence/ case series**	**Percentage**	**Mean Follow up**
Endoscopic resection	173/1190	14.5%	3 yrs 1 month
(documented in 812)	174	2	99
Lateral rhinotomy with medial maxillectomy	207/1239	16.7%	5yrs 2 months
(documented in 899)	29	24	55
Limited resection such as nasal polypectomy	208/606	34.4%	Inadequate data

polyps can have a differing histological diagnosis than what was predicted pre or intra-operatively in approximately 1% of the time[17].

The surgical resection should consist of a clear margin of mucosa around the inverted papilloma as well as the underlying mucoperiosteum. To avoid recurrence any underlying bone which is abnormal should also be drilled/removed[18]. The traditional approach to inverted papillomas had been a relatively aggressive open approach such as a medial maxillectomy via a lateral rhinotomy or midfacial degloving approach or a Caldwell-Luc approach. This strategy has been associated with reported recurrence rates as low as 2% in one series so should always be given consideration[18]. The problem with this approach is the relatively higher morbidity and, in the case of conventional lateral rhinotomy, poorer cosmetic outcome when compared to an endoscopic approach. Endoscopy gives a magnified view to aid the surgeon in discriminating normal from abnormal mucosa; angled scopes allow for visualisation around corners; the avoidance of facial incision confers a shorter in-patient stay, less facial swelling and reduced pain and facial sensory changes. Endoscopic resection of the diseased mucosa and underlying mucoperiosteum is now the treatment of choice for most inverted papillomas[19].

Endoscopic resection is technically more difficult when the tumour is located on the anterior wall and floor of the maxillary sinus. A 450 or 700 endoscope may be of use in these situations. These angled scopes combined with the technique of endoscopic medial maxillectomy have largely superseded combined approaches with a Caldwell-Luc incision to tumours in these locations though an anterior antrostomy can sometimes be useful[20]. The frontal sinus is also a relatively awkward area from which to strip mucosa but it is possible with angled scopes, angled curettes and a median drainage type procedure[20]. Otherwise a combined approach can be utilised.

Recurrence rates from most modern series are at least comparable between open and endoscopic techniques, if not favouring endoscopic resections (see table 1).

Open techniques are now largely reserved for advanced disease with associated malignancy or distorted anatomy from previous surgery[6].

Radiotherapy has no role to play in benign lesions.

Follow up
Long term follow up is required. Although most recurrences occur within 9 months they may be many years later[22]. The 3.6% metachronous primary incidence previously mentioned had a mean lag time of 52 months, emphasising the need to follow up for at least 5 years. Follow up should always include endoscopic examination, with additional imaging and examination under anaesthesia for any suspicious lesions.

Conclusion
Inverted papillomas typically present as a unilateral nasal polyp originating from the lateral nasal wall. They often have features of bony destruction or remodelling, sclerosis and calcification on CT. Excision must be wide and include the underlying mucoperiosteum to avoid leaving any residual tumour behind which would present as a 'recurrence'. This may be done via an endoscopic or open approach. The potential to transform into a carcinoma and association with metachronous carcinomas requires a long and careful follow up.

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expanding possibilities
in ENT surgery

Management of Snoring

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Abstract

Snoring is the cardinal sign of increasing upper airway obstruction ranging from simple snoring to upper airway resistance syndrome to obstructive sleep apnoea. The latter not only carries a psychosocial implication for the patient and their partner but also has been proven to have increased risk to various morbidities e.g. behavioural changes, impaired cognitive function, and increased risk of cardiovascular complications.

Owing to the variability in the pathology and level of obstruction, multiple treatment modalities have been developed with no specific modality being suitable for all patients. Management requires a multidisciplinary approach with an integrated patient care pathway and multi-speciality input.

We explore the tools and modalities available to clinicians to identify the best method of managing their snoring patients taking into account the whole spectrum of sleep disordered breathing.

Keywords

Snoring, snoring management, obstructive sleep apnoea, snoring investigations.

Introduction

Snoring is a very common symptom in the general population with around 35-45% of men and 15-28% of women reporting habitual snoring[1,2] which can a major annoyance to both the patient and their partner.

Snoring is the main symptom to an array of sleep-disordered breathing (SDB) disorders, namely the continuum of upper airway obstruction ranging from simple snoring through Upper Airway Resistance Syndrome (UARS) to different levels of Obstructive Sleep Apnoea (OSA) [fig.1]. Therefore, snoring cannot be considered in isolation but as a symptom of a spectrum of a disease and hence managed in an integrated manner. This will often involve a multidisciplinary approach with a common patient pathway and the expertise of Respiratory physicians, neuropsychologists, ENT surgeons and maxillofacial surgeons.

Sleep-disordered breathing is not only associated with the psychosocial impact affecting both patient and partner but with neuro-cognitive dysfunction and could also be detrimental to the patient's life. In children it has been associated with behavioural problems[3], poor school performance[4], poor quality of life[5], impaired growth[6] and cardiovascular consequences[7]. In adults, UARS and OSA patients other than suffering from daytime sleepiness (40%)[8] and diminished intellectual performance (58%), have been associated with personality changes, impotence in men, nocturnal enuresis[9], type II diabetes[10], carotid atherosclerosis[11], increased sick leaves & work disabilties[12] and significantly increased risk of stroke and death independent from any other risk factor[13].
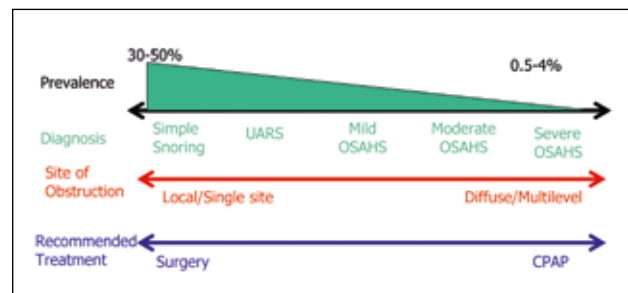

Figure 1: *Sleep related breathing disorders-A spectrum of conditions*

Snoring is caused by vibration of soft tissue in constricted segments in the upper airway, which could prove to be nasal, palatal, tongue base, laryngeal or a combination of more than one level hence the multitude of investigations and treatment options with no single treatment suitable for all snoring patients.

Investigations
Investigations are aimed at:
1. **Identifying associated and predisposing medical conditions.**
2. **Identify the severity of airway obstruction (Sleep studies).**
3. **Localising the obstructive segment/s.**

Certain medical conditions are associated with or cause symptoms (lethargy, lack of energy, daytime somnolence) often associated with sleep disordered breathing. These include anaemia, hypothyroidism, diabetes, acromegaly, motor neuron disease, movement disorders and narcolepsy. These should always be taken in consideration when taking the history and investigated for if suspected. Routinely, all patients should at least have a full blood count and thyroid function test.

The severity of sleep-disordered breathing is a crucial first step in determining the best treatment options. In the authors opinion no treatment options should be considered without first undertaking a sleep study. The gold standard sleep study is overnight polysomnography (PSG) [fig.2]. The classification of levels of sleep study have been defined by the American Academy of Sleep Medicine.

Type 1   In-laboratory Polysomnography
Type 2   Comprehensive portable study
Type 3   Modified portable sleep apnoea testing or cardiorespiratory sleep study
Type 4   Continuous single recording e.g. pulse oximetry

Although type one is the gold standard and recommendation of the American Academy, the practice does vary considerably in Europ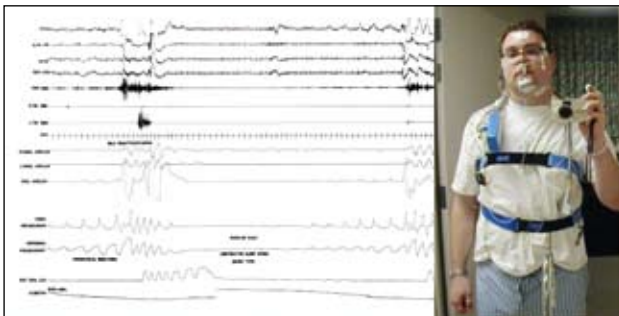e. In UK, ambulatory pulse oximetry is often used as a screening study though it has a notable 20-30% false negative rate and can give false positive in patients with COPD and obesity-related hypoventilation syndrome. Scottish Intercollegiate Guidelines network (SIGN) counsels that provided that concerns related to the limitations are appreciated, then limited type 4 studies maybe useful, cost-effective and convenient for patients and can significantly speed up the investigation pathway[14].

The severity of OSA is determined by the apnoea hypopnoea index (AHI; the number of apnoeas plus hypopnoeas per hour of sleep). An AHI of 5-15 will constitute as mild OSA, 15-30 as moderate OSA and 30 and above as severe OSA.

Pressure measurement using flexible multi-pressure sensors (apnoeagraph®) [fig.3] at pharyngeal and oesophageal levels during sleeping is a method which not only investigates for OSA but also identifies the level of the obstruction to help determine the most effective treatment on an individual basis. Some concerns have been raised as to the invasiveness of the investigation (passing a pressure catheter in the pharynx) and the impact of this instrumentation on the airway during sleep. However, the validity and superiority of measurement of oesophageal pressure notably out ways the criticisms. Topodiagnosis with pressure measurements has been proven very successful[15] and is the only study which assesses the airway throughout a considerable proportion of the natural sleep (6hrs) and through all sleep phases. The author has found this test extremely valuable as it answers both questions (severity and location) simultaneously and that to during natural sleep.

Flexible sedation nasendoscopy of the upper airway is a widely used topodiagnostic test. Although questions have been raised as to the difference between natural and pharmacologically-induced snoring, it has considerable published data supporting its beneficial use in deciding on
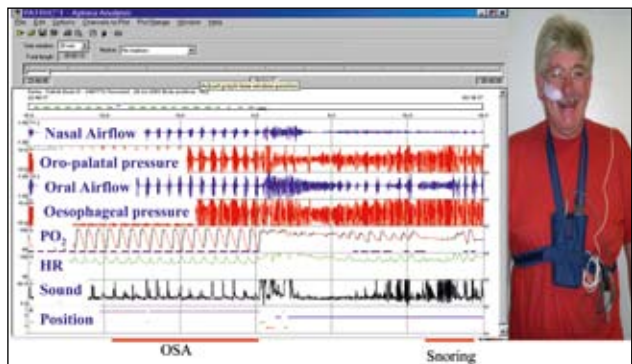

Figure 2: *Polysomnographytrace*

Figure 3: *Pressure Sleep study trace-Apneagraph®*

the level of obstruction and amending the treatment option accordingly[16].

Other investigations to determine the level of obstruction are analysis of recording of the respiratory sounds during sleep e.g. Glan-Clwyd snore box to differentiate between palatal and non-palatal snoring[17], radiocephalometry to determine a retro lingual collapse site, somnoflouroscopy, computer tomography and functional magnetic resonance imaging. Most of these investigations depend on specific instrumentations and have not been used widely hence the scarcity of any evidence to their validity.

Treatment options

1. Non-surgical treatment
Understandably, non-surgical options are attractive options for many patients and worth considering before more interventional treatments are considered.

Weight reduction Obesity constitutes a major risk factor for sleep-disturbed breathing and studies have proven that weight reduction significantly improves OSA. A 10% weight loss has been shown to predict 26% decrease in AHI and a 20% loss to 48% decrease. However, achievement and maintenance of weight loss still remains a challenge. Bariatric surgery is the most effective method of achieving best results.

Over-the-Counter methods Have become more worldwide spread and easily available for trialling whether they are a lubricating spray, nasal strips for nasal airways, pillows to establish head position[18], oil-based sprays[19] or chin lift bands. Unfortunately their trials failed to prove any statistically significant change in snoring.

Pharmaceutical treatment Leukotriene inhibitor and nasal steroids have proven to be useful in reduction of paediatric OSA but not cure[20,21]. In adults there have been trials with different medications including alkaloids, analeptics and methylxanthines with no long term benefit proven[22]. Modafinil is the treatment of choice for Narcolepsy and is also increasingly being used in symptomatic treatment of OSA.

Positive Airway Pressure (PAP) described in 1981[23] as a treatment for sleep-disordered breathing. Applied nasally or orally, it splints the upper airway pneumatically from nares to larynx [fig.4]. In 1999[24] there was a consensus that PAP is the most effective treatment for moderate-severe OSA. It is mainly delivered as a nasal or oral continuous PAP (CPAP) which has a success rate of 50-70%[25]. CPAP has a low individual compliance in long term management. Recent trials of autoadjusting PAP

(APAP) and changing position of sleep[26] or use of expiratory PAP (EPAP)[27] as an alternative have not yet proven more than 40-50% compliance. Although compliance is an issue, CPAP remains the first and main line of treatment for moderate to severe OSA.

Oral appliances Are recommended in the management for mild-moderate OSA and snoring in the form of custom-made mandibular advancement splints to assist with retro-lingual obstructions. There have been recent studies to recommend it for severe OSA with a 75% AHI improvement. Oral appliances also suffer from a low long-term compliance rate, with recent studies to change types[28] or use a tongue retaining device[29] giving 52% compliance in 5 years.

2. Surgical treatment
Different surgical procedures have been used to manage sleep-disordered breathing depending on the level of the obstruction.

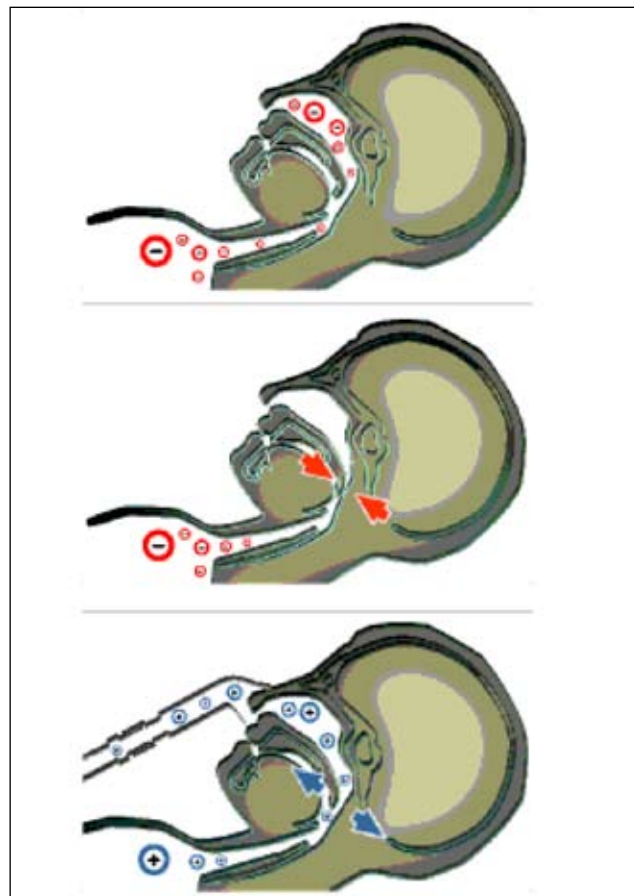Surgery has 40-70% success rate in satisfaction & reduction of snoring with about 40% long-term success rate[34].
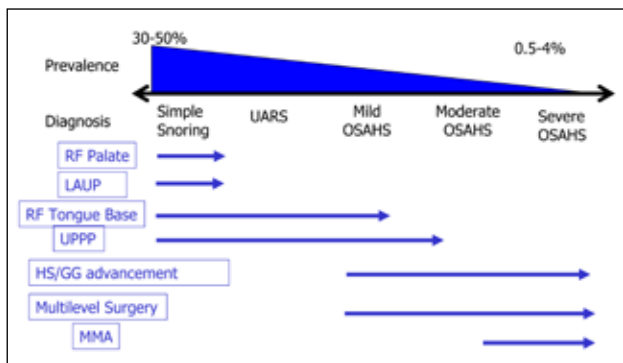

Figure 4: *Continuous positive airway pressure (CPAP)*

Figure 5: *Efficacy of Surgical Treatments in Sleep Disordered Breathing*

Subscript to fig.5
RF-radiofrequency
LAUP-laser assisted uvuloplatoplasty
UPPP-Uvuloplatopharyngoplasty
HS –Hyoid Suspension
GG-Genioglossal
MMA-Mandibuilo-maxillary advancement

Clearly, the efficacy of the surgery is entirely dependent on the thoroughness of the diagnostics and the severity of SDB being treated. Hormann et al recently assessed the evidence related to this, which is summarised in fig.5.

Nasal surgery
Septoplasty and turbinate surgery aiming for achieving a better nasal airway had a few reports including randomised trials[30,31] in comparison to no or sham surgery providing some validity in their ability to reduce snoring and AHI achieving a satisfactory subjective and objective result in SDB patients.

Nasal surgery is effective in some carefully selected patients at reducing their snoring, improving their subjective sleep quality & compliance with first line treatment and possibly their AHI. However, no reliable clinical or investigative indices has been identified that can reliably predict the patients most likely to benefit from Nasal Surgery.

Oropharyngeal surgery
Oropharyngeal Surgery has been performed for years with acceptable results in managing SDB. These procedures widening the oral and retropalatal space by resection, rotation or repositioning of the palate and lateral pharyngeal walls. There has been multiple studies validating and comparing these surgeries in reducing SDB[32-35]. Palatal and oral surgeries are often performed in combination with other surgeries to successfully treat moderate-severe OSA.

Apart from the general post-operative complications, palatal surgeries unfortunately are known for their severe
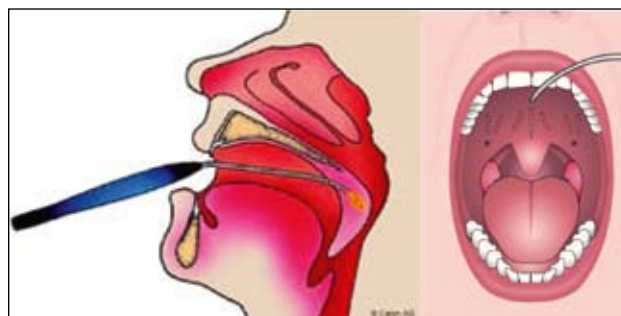

Figure 6: *Radiofrequency Palatal treatment.*

postoperative pain, the incidence of postoperative oedema and respiratory depression, alteration of palatal or tongue sensation and velar insufficiency especially if the musculature of the palatal arch is resected.

Tonsillectomy although first line of treatment and proven beneficial in childhood OSA[36], it has limited value in isolation in adults. In adults, it is usually combined with another palatal or tongue base procedure.

Radiofrequency surgery depends mainly on sub mucosal application of radiofrequency energy (low frequency radio waves) which causes thermal damage leading to fibrosis of the tissue [fig.6].

The original procedure entails using a needle probe and applying radiofrequency at multiple points in the soft palate. The evidence agreed that the greater the number of lesions the higher the effectiveness. The procedure can be performed under local anaesthesia as an office procedure and can be accompanied with similar channelling to large-sized tonsils to reduce size. Most of the studies that were done with radiofrequency achieve about 70-80% satisfaction rate post-operative reduction in snoring 40 but there is little data on long term outcomes.

Palatal implants & Injection snoreplasty Outpatient/ Office procedures involving injecting of sclerosant material e.g. sodium tetradecyl sulphate into the soft palate to lead to fibrosis and palatal stiffness with a claimed 92% success in reduction of snoring and a 75% reduction in 19 months follow up[43]. However, alternative methods are pillar implants[44,45] whereby palatal stiffening is achieved by placing the implants in the palate which induce fibrosis surrounding the implants.

The main benefits of most of these procedure is that they can be performed as an office based procedure under local anaesthesia with less post-operative pain and no bleeding. However, despite their relatively minimally invasive nature complications including palatal fistula in injection palatoplasty[46] and extrusion of palatal implants[47] have been noted.
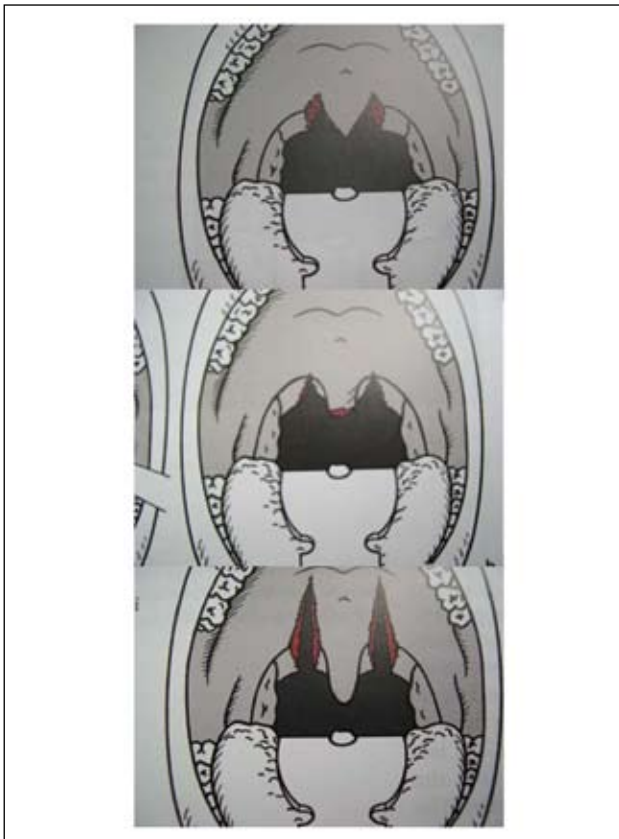
Figure 7: *Laser Assisted Uvulopalatoplasty*

Laser assisted surgery depends on usage of CO2 or KTP laser reduce the mucosal excess in the soft palate and muscular burn to lead to widening and stiffening [fig.7]. It has been studied in a number of publications[41,42] showing a 40-50% success rate in reducing snoring but with minimal long term follow up and sometimes non-significant reduction in AHI.

Uvulopalatopharyngopasty (UPPP) Probably the most widely used procedure, it was first described by Iketmatsu in 1963 and modified by a number of surgeons worldwide including Fujita in 1981[37]. It aims to reduce the excessive tissue components of the soft palate without compromising the muscle [fig.-8]. The surgery entails tonsillectomy accompanied by excision of a semicircular component of the soft palate and tonsillar pillars to create a wide oropharyngeal airway. Due to circumferential nature of the excision and the variable amount of sacrifice of palatal musculature, it has been associated with pharyngeal dryness, swallowing disorders, nasopharyngeal stenosis and velopharyngeal incompetence.

There have been multiple studies[34] proving about 70% improvement in symptoms which decreases to about 50% over the long term[38]. There are also concerns with usability of CPAP subsequent to UPPP.
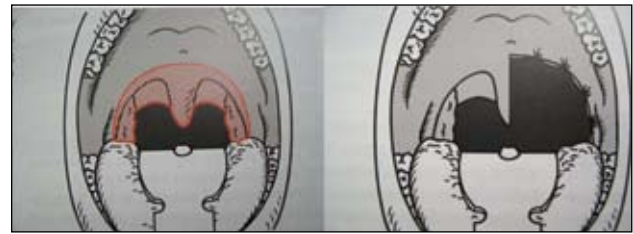
Figure 8: *Traditional UPPP*

Uvulopalatal flap in which a tonsillectomy is performed followed by mucosal resection off the buccal side of the uvula and the midline of the soft palate exposing the musculature, then rotating the uvula upwards on the raw area of the soft palate. There are only a few published studies with a success rate up to 80% post-operatively[39].

Rotational Uvulopharyngopalatoplasty is yet an unpublished technique practised by the senior author. It incorporates the principles of minimally invasive techniques of stiffening the palate with the principles of enlargement of airway integral to the surgical techniques of UPPP and uvulopalatal flap. With the exception of tonsillectomy (if necessary) and partial uvelectomy, there is no resection of pharyngeal or palatal mucosa or muscle. The widening is achieved entirely buy incisions and rotation of pharyngeal mucomuscular flaps [fig.9]. It also overcomes the integral flaw of traditional UPPP of having

Figure 9: *Rotational Uvulopalatoplasty*

a circumferential scar that in-bearably will be prone to cicatrise to the midline. In the author's experience, the technique has stood the test of time with more than 50% reduction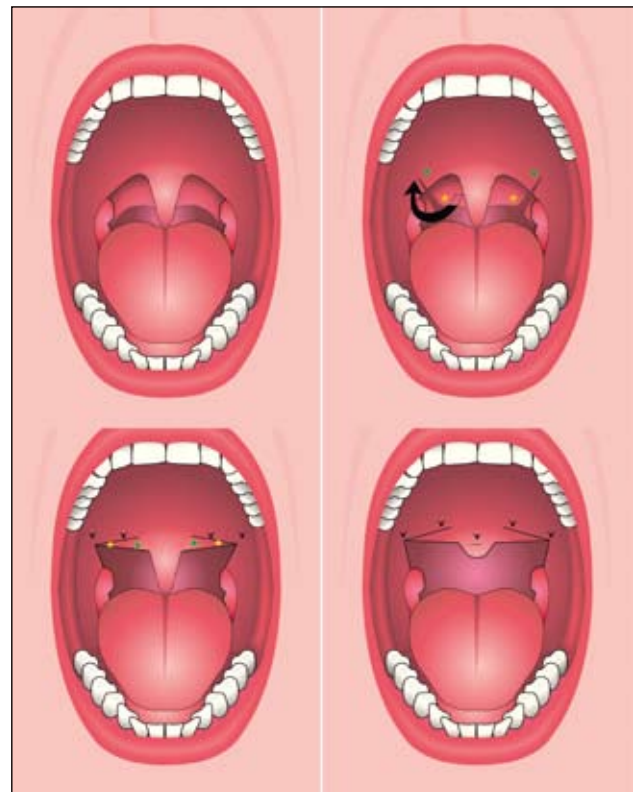 in 80% of patients at two or more years after intervention and a no improvement rate of 6% (unpublished data). Most importantly, there have been no cases of velopharyngeal incompetence or nasopharyngeal stenosis in over hundred cases to date.

Lower pharyngeal/Laryngo-tracheal surgery

In retro lingual and severe OSA patients further surgeries should sometimes be considered to help in achieving a better airway.

Tongue base surgery could involve either reduction of tongue base surgically or using radiofrequency or laser. Unfortunately it carries a higher risk of post-operative functional dysfunction and increased risk of respiratory obstruction. However, in combination with other palatal surgery has proven to achieve better outcomes in severe OSA patients[48].

Maxillofacial surgeries include genioglossus advancement, maxillo-mandibular advancement and distraction osteogenesis operations. The former two are useful in moderate-severe SDB especially in patients with a slight dentofacial deformity with about 90% successful outcomes even on the long term but with increased risks of temporomandibular joint dysfunction[49], hypopharyngeal oedema, hypoesthesia of the lower lip, occlusion disturbances and rarely osteomyelitis & maxillary pseudoarthrosis[50]. The latter surgeries are preserved for severe maxillo mandibular deficiency in syndromic and non-syndromic patients.

Tracheotomy has been the only operative procedure with 100% success rate in reducing the snoring and the AHI[51,52]. Owing to the gravity of this operation and its known post-operative problems especially the social and speech issues, it has never been a surgery of choice in managing snoring or SDB. Meanwhile, it has been used as a temporary measure to prevent or manage immediate post-operative complications for some of the other snoring operations.

Conclusion

Sleep-disordered breathing is affects a substantial proportion of the population and causes both psychosocial, neurocognitive and medical consequences. Owing to the variation in severity, causative reasons and level of obstruction, there are multiple modalities of treatment available, most claiming success rates in the region of 50-80%. The author recommends a multidisciplinary integrated patient pathway, a structured approach to investigation and tailoring of treatments to individual severity of SDB, requirements and anatomical restrictions. To date there is limited data to do with long term follow up in most of these modalities.

The only gold standard and recommended modalities are adeno-tonsillectomy in paediatric patients which should be preceded by a polysomnography. In adult cases, CPAP is recommended in moderate-severe OSA patients but unfortunately the compliance rates can be an issue. Tracheotomy has also a 100% rate but due to its gravity and post-operative lifestyle it has been unfavourable.

In the management of snoring, there is no one investigation or treatment that suits all. However, if the clinician aims to identify the severity of the SDB and localise the level/s of obstruction, the most appropriate modalities of treatment can be identified

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Principles of Augmentation Rhinoplasty

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No competing interests

Introduction

Augmentation of the nasal dorsum is not a new concept and, in fact, there are references to it as far back as the 'Edwin Smith Papyrus in 2500 BC and the teachings of Sushruta, the Father of Indian plastic surgery, in 600 BC[1]. Following these ancient texts, methods and materials were refined by, amongst others, Branca and Tagliacozzi in the 14th and 15th centuries respectively[2] and then later by Carpue in the mid 18th century and Joseph in the early 20th century. Following the later efforts of the American pioneers Foman, Cottle and Goldman, the open approach rhinoplasty was developed and it revolutionized the approach to complex nasal dorsum reconstructions due to the exposure it afforded of the key fixation points[3]. Latterly the emphasis has shifted from the various approaches used to what materials are available to give symmetry and bulk to a defect in the nasal dorsum.

This article will thus address the key questions relating to approach and graft material, emphasizing the pros and cons of each in various clinical situations.

Anatomy

The nasal dorsum can be divided into an upper bony 1/3 with the lower 2/3's comprising the cartilaginous septum interfacing with the upper and lower lateral cartilages. Where the cartilaginous septum joins the bony septum is termed the 'keystone' area and this point, along with the nasal spine, maxillary crest, and upper lateral cartilages, is important in anchoring any potential L-shaped struts in septal / dorsal reconstructions[3]. The principle here is that at least 2 of these points need to be anchored to ensure a stable, long-lasting reconstruction.

The skin / soft tissue envelope is often neglected when nasal dorsal surgery is undertaken but it is crucial to account for the thinner skin of the dorsum when inserting

grafts as it behaves differently to the thicker, more sebaceous tissues of the tip and nasion. It is also helpful to dissect in the avascular, multilayered sliding plane that runs on top of the dorsal perichondrium.

Aesthetics

When assessing the nasal profile, it is helpful to understand the relative ratios of the dorsum to assist in determining what the defect is. These ratios are depicted as follows:

- Length of the dorsum is considered as 1.
- Projection of the nasal tip from alar crease to the tip defining point is 2/3
- Height of the nasal vault from the medial canthus to glabella is 1/3

Line drawing of ratios here

Aetiology of nasal dorsum defects[4,5]

These can be divided into the following areas:

- Congenital or racially related under-projection of the dorsum. Congenital problems are particularly rare but may be related to midfacial deficiency syndromes such as Treacher Collins syndrome.
- Loss of septal support due to over-resection during septoplasty thus compromising the 'keystone' area of the dorsum.
- Trauma to the nose. Blunt trauma to the nose resulting in a septal haematoma may develop into a septal abscess if it is not surgically drained and this, in turn, will necrose the septal cartilage if left unchecked. Nasal bone fracture may result in the development of a platypoid appearance of the upper 1/3.
- Acute or chronic infection of the nasal cavity. Acute septal infections, when they arise, usually follow septal

surgery or trauma whilst chronic infections present as 'granulomatous' conditions e.g. Wegeners, TB, Leprosy and Syphillis. Whatever the infection, it is vital that the infection has been eradicated or rendered quiescent before attempting a reconstruction as any active disease will almost certainly compromise the eventual outcome.

- Partial or total dorsal resection following tumour surgery. Again, complete excision of the primary lesion is vital before undertaking any reconstructive process.

Surgical techniques for Dorsal Augmentation

Approach
As previously mentioned, there are two choices of approach, namely open and closed (endonasal). The choice of approach really boils down to the location of the defect, the amount of undermining needed to place the graft and whether the graft needs to be fixed. To this end, extensive grafting will likely require an open approach whereas the closed approach will suffice for the smaller, more defined defects that require the precise placement of a pocket.

Dissection
In order to facilitate an avascular dissection plane and smooth dorsal profile, dissecting as close to the perichondrium is helpful. This will also enable the precise placement of any potential free grafts needed.

Fixation
This depends on the size and function of the graft. If the graft is non-supportive and/or is required to fill a small pocket, then fixation is usually not required.

However, if the graft is supportive and/or the pocket is extensive then fixation is usually advised. When using a large dorsal graft such as costal or irradiated cartilage, it can be fixed with a screw or miniplate over the nasion. Securing a graft in a wide pocket will require suture fixation or the use of fibrin glue to anchor the graft firmly. An accurate way of suturing the graft is to attach an absorbable PDS suture to the leading edge of the graft. After the graft has been placed, the dorsal skin is punctured with the suture which is then secured with a steristrip or silastic splint.

Regardless of what modality is used, an external (metal / POP) splint will provide extra support and negate any potential dead space that has been created.

Grafting Materials
When considering nasal dorsum grafts, there are various categories of graft to consider:

- Autologous: graft derived from patient e.g. septal / conchal / costal cartilage
- Homologous: graft derived from same species e.g. irradiated costal cartilage
- Xenografts: graft derived from non-human species e.g. irradiated bovine cartilage
- Allografts: synthetic graft e.g. silicone / Goretex® / Medpore®

All of the grafts above have pros and cons but, wherever possible, autologous cartilage should be utilized in order to minimize potential complications and maximize improved outcomes.

Autologous grafts

Septum
Predictably, nasal septal cartilage is the material of choice when reconstructing the nasal dorsum[6]. It is readily available, straight and resilient. To facilitate nasal support, an L-shaped cartilaginous strut of 1cm dorsally and caudally should be left in-situ once the cartilage has been harvested with any "left-over" pieces of cartilage being re-inserted back in between the septal mucosal folds. If the septum is grossly misshapen, either congenitally or through trauma, it can be removed in total, re-shaped and then re-inserted, paying attention to fixing it to at least 2 points as described above. This is called an extracorporeal septoplasty[7,8].

Where a septal cartilage graft is being used as a "filler" graft, light crushing (or dicing)of the graft affords it a degree of malleability without compromising the innate strength of the graft. Smaller grafts can be used alone[9] but bigger ones can be encased in a wrapping of fascia[10] or surgicel[11] for support and camouflage.

Due to their limited size and availability, septal grafts tend to be utilized in partial augmentations but, long term, they tend to maintain their shape and bulk as described by Mao et al[12]. In cases where secondary refinement / filling is needed, any septal segments put back in between the septal folds can be re-harvested or, as in Wong et al[13], previously harvested cartilage can be preserved in isopropyl alcohol and re-inserted as needed!

Pinna
The donor area of the pinna is the conchal bowl. This can include substantial portions of the cymba and cavum concha without compromising the support of the pinna. There are also two options available for harvesting of the graft, namely a lateral approach along the rim of the anti-helical fold which is technically easier but leaves a scar, or from medially, behind the ear, which is a more difficult approach but hides the scar. (Figures 1-7)

Figures 1-7: *showing pre and postoperative pictures using conchal cartilage grafts.*

When augmenting the nasal dorsum, the problems relating to conchal cartilage are obvious: it is curved, thicker and brittle. The curvature can be negated by suturing two curves back-to-back or by scoring the cartilage but these struts are limited in size and thus are used only for smaller, partial dorsal reconstructions[14]. Unfortunately, due to their brittleness, crushing is not usually tolerated and this, along with the curvature, limits their use in filling precise dorsal pockets. If using this graft it is very important to limit any donor site morbidity by filling the potential conchal bowl

"dead space" with a proflavine plug which is then sutured in place for 1 week to prevent haematoma formation[15].

Costal cartilage

There is abundant costal cartilage available for dorsal grafting and it is thus amenable for use in the reconstruction of larger dorsal defects. It is either harvested in the inframammary region from the para-sternal 5th / 6th ribs or from the confluence of the 6th and 10th ribs if a larger or L-shaped graft is needed. The dissection is also in the sub-perichondrial plane, minimising possible damage to the pleura (if damage to the pleura is suspected, submersion of the wound in saline and positive pressure ventilation will demonstrate the site of the leak).

Apart from the relatively small potential for pleural damage and not insignificant pain at the donor site, the major drawback of costal grafts is their potential to warp, particularly in the "under-35" age group. To counter this, paring off of the outer cartilage layers and leaving the graft to settle in saline for at least an hour prior to implantation is sensible and, if warping still occurs, the graft can be split in two and sutured back-to-back. Another risk in the "over-55" age group is calcification of the cartilage but this merely makes carving of the graft slightly more difficult as, later in this text, the use of calvarial bone grafts is described to good effect. In general, the grafts are well tolerated and the aesthetic outcomes are pleasing and long lasting in the majority of patients grafted[16,17]. (Figures 8-13)

Bone

As with many bony implants, the universal problem with them is resorption[18]. Iliac bone grafts are particularly well known for this and have, as a result, been largely abandoned[19]. The principle site of most bone grafts is the parietal calvarium which is both plentiful and strong but they invariably need to be fixed in the region of the glabella with a screw or plating system[19]. Another significant problem with bone grafts is that they are, by their very nature, rigid which induces an unnatural stiffness to the nose. In order to minimize this unwanted side effect, using these grafts in oriental or afro-caribbean patients with comparatively much thicker dorsal skin will help to camouflage and soften the stiff edges of the graft[21].

Other sites utilized for bone graft harvesting include the inferior turbinate bone[22] and the bone within the removed nasal hump[23] and while they have minimal donor site morbidity and add significant support (particularly as a spreader graft in a warped middle 1/3), both studies had a limited follow-up period of under 2 years.

Homologous grafts

Costal cartilage

When there is a significant nasal dorsum defect and, for whatever reason, septal or costal cartilage is not available, then there is a place for irradiated homologous rib cartilage. Kridel et al[24] produced a retrospective paper looking at 357 cases over 24 years, concluding that there was a 1% resorption rate but that, in general, they produced "superb functional, structural and cosmetic results". These were, in the main, supported by other studies[25] although Menger et al[26] showed a partial resorption of 31% but there is still an (unsubstantiated) concern that Jacob-Creutzfeld disease, HIV or Hepatitis could be potentially transferred to the patient when using these grafts.

Soft Tissue

With the increasing use of soft tissue fillers in the face, a vogue has developed for their use in the nasal dorsum. They are minimally invasive, and suit the subgroup of patients that are looking to fill small, subtle dorsal defects without the financial expense, anaesthetic risk or downtime associated with a surgical intervention[27]. A variety of fillers are available, the most commonly used ones being the hyaluronic acid or calcium hydroxyappatite gels. They are safe but only last for 12 to 18 months plus they need to be accurately injected into the sub-dermal layer to avoid nodularity. Other potential but low risks are those of necrosis, infection and thinning of the skin.

Whilst it is effective, silicone injection should be avoided altogether as it is known to cause significant granulomatous reactions.

Alloderm is an acellular dermal implant and Gryskiewicz et al[28] were encouraged by their results in 58 cases but, although it was malleable and gave a soft feel to the nose, it was resorbed in some patients which was not satisfactory.

Xenografts

Use of bovine irradiated cartilage is very limited. Pellegrini et al[29] demonstrated that, in 25 patients over a 15 month period, there was a partial or complete resorption rate of 44% which is clearly unacceptable and underpins why this substance is not widely used!

Allografts

The search for the perfect alloplastic implant material is an ongoing one as it needs to conform to the biological characteristics of autologous grafts which are clearly still the 'gold standard'. They may however be a useful alternative in some patients who are concerned about the potential problems associated with costal or calvarial donor sites or where previous autologous septum has been

Figures 8-13: *showing pre and postoperative pictures using costal cartilage grafts.*

exhausted. Ideally, the incision for the graft placement should be as far away as possible from the recipient site to minimize migration or extrusion of the graft.

Goretex® (expanded polytetrafluoroethylene)

This malleable material, available in blocks or sheets, consists of micropores and this allows for the ingrowth of fibroblasts which enhances the stability of the graft. The biggest problem with these grafts is infection with subsequent extrusion and in Godin et al[30] the extrusion rate was found to 1.2% in primary rhinoplasty and 5.4% in

revision cases over an average of 3 – 4 years. Similar results were found in Jin et al[31] who looked at Goretex® implants in Asian individuals although the grafts produced a softer profile due to the thicker skin covering. To minimize the potential for infection, grafts should be soaked in antibiotic solution prior to implantation and handled with new gloves.

Medpor® (porous polyethylene)

This too is a porous implant that allows for the ingrowth of fibrous tissue and, interestingly, most retrospective analyses

demonstrate very similar tolerances and complication rates[32,33] to Goretex®. Again, virtually all of these papers also conclude that autogenous material is always better if at all possible.

Silicone

Unlike Goretex and Medpor, silicone does not allow for fibroblast ingrowth and it is thus more prone to movement which, in turn, creates potential dead space allowing for infection to develop. On the positive side, however, this does allow for easy removal of this inert graft if necessary. In general, the key to using this implant is appropriate case selection, with the vast majority of patients in the literature being of Asian origin and requiring only mild to moderate adjustments in dorsal height[34]. It is easily shaped and this facilitates formation of L-shaped struts to augment both the dorsum and columella which is particularly useful in the platyrrhine nose.

Clearly extrusion and/or migration is the main concern with all of these grafts. Following removal, if there is gross infection it would be sensible to treat the patient with antibiotics and then to reconstruct once settled although one series of 8 patients were grafted immediately following graft removal, all of which were a success after 3 years[35].

Conclusion

Augmentation of the nasal dorsum can be carried out through either an open or closed rhinoplasty, the open approach lending itself to the insertion of larger grafts which have a supportive function whilst the closed approach is appropriate for insertion of smaller, filler grafts. Grafting material should, if at all possible, be autogenous and, in the author's experience, the use of allografts should only be used in exceptional circumstances when autogenous material is not available.

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Endoscopic Middle Ear Surgery

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Abstract

The use of endoscopy as a diagnostic aid in the middle ear is increasing in popularity due to the improved views of the middle ear cleft, especially the sinus tympani and the facial recess. Endoscopy as a stand alone technique in middle ear surgery is a more recent development that may allow more minimally invasive procedures in certain diseases.

Key Words

Endoscopic, middle ear surgery, otoscopy, cholesteatoma

Introduction

Prior to the advent of endoscopes, the only way to visually evaluate the middle ear cleft was either via surgical entrance, or by the limited view afforded through perforations or with the limited information obtained through the translucent intact tympanic membrane. The advent of otoendoscopy has allowed an improved anatomical knowledge of the previously inaccessible areas of the middle ear cleft, a greater understanding of pathologies affecting the middle ear and, with improvements in both endoscope and image projection, an ability to perform less invasive surgery for certain conditions.

The advantages of using an otoendoscope for the exploration and visualization of the middle ear include the extension of the operative field into the 'hidden' areas of the middle ear (anterior tympanic perforations, posterior retraction pockets, facial recess, sinus tympani and the hypotympanum – Figure 1,2), the ability to look at middle ear structures from numerous angles and the fact that the image is projected onto a screen giving a high definition magnified view. Disadvantages of operating using the endoscope include the need for a one handed technique to operate (the other is holding the endoscope), a 2D image with no depth perception and although the image is magnified, there is little variation in its degree. Aside from this, training is needed if operating using the endoscope[1].

Anatomy

Endoscopy of the ear was described as early as 1967[2] as a method of pre-surgical evaluation of middle ear disease however the advances that were made in the early years were mainly anatomical. The use of endoscopes, especially angulated, gave the operator a greatly enhanced view of the middle ear than was previously available. The surgical anatomy of the posterior tympanum[3] and the sinus

Figure 1 *Retrotympanum*

Figure 2 *Anterior and hypotymapnum*

tympani[4], traditionally the most difficult of the 'hidden spaces' of the middle ear to visualise, were described in the 1960's but even into the new millennium anatomical additions are being made. Endoscopic assessment of the posterior tympanum was revisited as recently as 2008[5] with an the sinus tympani classified into types I to III depending on depth and again in 2009[6] when an alternative classification (Types A to C) was postulated depending on both the depth of the sinus tympani and whether there was posterior extension. As classification systems are concerned with different treatment outcomes and due to the fact that there does not appear to be a differential between different types of sinus tympani and surgical outcome following cholesteatoma surgery, we wonder if this is of use at present but readily concede that any improvement in intra-operative anatomical accuracy can only aid the surgeon.

It is also interesting to ponder that, although middle ear anatomy has been studied for centuries, new variations are still being uncovered. An article published in 2010 noted that 'pneumatization of the sinus tympani and posterior tympanic sinus or both...... may give rise to a recess beneath the pyramidal eminence, which we have called the subpyramidal space[7].' This endoscopic view of the middle ear cleft allows detailed anatomical descriptions of previously elusive areas which will reduce the possibility of residual disease following operation.

Diagnostic

Otoscopes have long been used for diagnostic purposes examining the tympanic membrane. Initially looking with a greater degree of accuracy at the tympanic membrane and perforations with the benefit of magnification, it has been shown that retraction pockets in the pars flaccida can be more accurately delineated with 2/3rds of 27 Grade III and IV retraction pockets examined with an otoscope being deeper than the original estimate made with an otomicroscope[8].
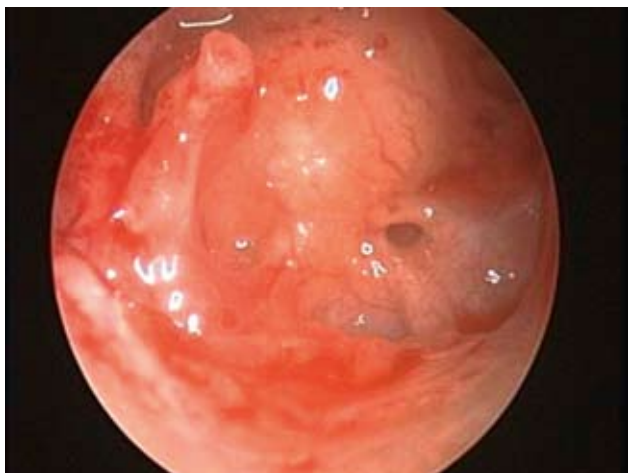
The more recent otoendoscope has helped increase the sensitivity of diagnosis in both conductive hearing losses by directly visualizing the stapes movements[9], for which diagnosis is usually based on clinical and radiological data, and in the examination of peri-lymph fistulae[10,11], the evaluation of which continues to be a topic of debate as there are no objective means to establish a diagnosis[12]. As otoendoscopes have reduced in size without diminishing their image quality, tympanic perforations no longer have to be present to visualize the middle ear. Nomura first described the use of a needle otoscope[13] and a similarly sized fine endoscope has been used to describe the middle ear in patients with otitis media with effusion[14].

Intra-operative Adjunct

Otoendoscopes have been used as an adjunct to standard procedures in both neurotologic and otologic procedures since the early 1990's[15]. The combination of magnification and clear, close-up views give the operator chances to review their progress through the procedure.

During primary mastoid procedures, otoendoscopes can be used alongside traditional 'open' techniques for examination of the retrotympanum to ensure cholesteatoma disease elimination. Studies have shown that this does not remove the need for a second look procedure but does reduce the incidence of residual disease[16]. These studies also confirmed that the majority of residual disease is found in the sinus tympani and that the use of the endoscope also improves the surgeon's confidence level about total removal of disease and has been shown to encourage the surgeon to keep the canal wall intact (Figure 3,4)[17]. Endoscopically assisted procedures have also been described for myringoplasty[18] and via a middle cranial fossa approach for surgical treatment of a petrous cholesteatoma[19].

Figure 3 *View of facial recess, stapes and round window niche.*

Figure 4 *View of anterior recess and Eustachian tube orifice.*

Mainstay of the Surgical Procedure

The logical progression of the above is to forego open technique altogether and operate on the middle ear with the otoendoscope as a fundamental part of the operating armamentarium. No matter how detailed CT scans become, there will always be space that lies between the tomographic slices which is open to software interpretation. It is also impossible to differentiate between recurrence, residual disease, scar tissue or fluid within the middle ear on CT scan so direct visualization is necessary[20]. Therefore after combined approach tympanoplasty (CAT) for cholesteatoma a second look procedure is considered mandatory to exclude the presence of residual disease. Traditionally this has needed to be an open procedure, however a minimally invasive mastoidoscopy as a second procedure using a post auricular stab incision into the mastoid cavity and the passing of an otoendoscope can minimize morbidity due to the reduced operating time and minimal access nature of the surgery[21].

Further to mastoidoscopy, ossicular chain reconstruction may be needed at the 2nd operation. One study published retrospective results on 22 ears that had ossiculoplasty performed endoscopically via a transfacial recess route without lifting a tympanomeatal flap[22]. The main proviso, as opined by the article's author, is that the posterior tympanotomy, and therefore the facial recess, needs to be widely opened at the primary operation and is therefore not appropriate for every ear. Early results are promising and may provide access for prosthesis placement without the need for canal incisions, middle ear packing, and barotrauma and water precautions.

Further to these 'second look' procedures, primary procedures are also performed for attic cholesteatoma. Tarabichi's articles on endoscopic middle ear surgery[1],[23-25], reveal the extent of disease that can currently be operated on endoscopically. 38 middle ear procedures were performed on acquired cholesteatoma by means of transcanal tympanotomy and extended atticotomy[23] with only one converted to open and preliminary follow-up results showing residual disease rates equivalent to open

procedures. Long term follow-up[24] of 69 ears, half of which had cartilage reconstruction and half of which were packed open, showed 3 that were converted to open. Mean follow-up of 41 months showed 6 ears that needed revision surgery. In the latest article, published in 2004, 5 of 73 ears required revision for residual disease and 8 were revised for failed ossicular reconstruction or persistent perforation[25]. With knowledge of the anatomy, its variation and the limitations of the endoscope, it may be that we are near the edge of what is possible to do within the middle ear cleft endoscopically via transcanal, posterior auricular or transfacial recess approaches.

Equipment

To perform middle ear endoscopy for any of these procedures one requires a range of specialist instrumentation. This will vary according to the procedure, however for second look mastoidoscopy the authors use 0o and 30o 10cm or 20cm otoendoscopes (Figure 5, 6) for full visualization of the mastoid cavity and the middle ear cleft via the mastoidoscopy incision, through the previously enlarged mastoid antrum.

Video equipment consists of a high definition monitor and camera and the associated stack system to take both still photos for the operative records and video footage if required (Figure 7).

The Future

Surgical treatment of middle ear disease will remain an area of continuing development as technology progresses. Advances will be made along similar operative lines as are used today; the amount of the middle ear which may be accessed and successfully treated endoscopically will increase, however by its nature and the anatomy involved, this is finite. Accessing the middle ear cleft, as described above, can be done in two ways; via the canal or via a retro-auricular incision. A natural extension of the techniques above is that combination approaches could be employed for well selected patients in which attic disease is passing too far posteriorly to remove totally via the transcanal route. Alternatively, the only natural orifice into

Figure 5 *10cm endoscope range*

Figure 6 *20cm endoscopes*

Figure 7 *Theatre set-up with surgeon, stack system with high definition screen and endoscopes ready.*

the middle ear, the Eustachian tube, can be used to pass tiny endoscopes. This would require ultra-fine endoscopes which need to be flexible enough to negotiate the anatomy, but firm enough to pass through a closed Eustachian tube. Cadaveric studies[26] have hinted at its potential and this may be an area of future research, however as imaging becomes more advanced, middle ear endoscopy as a diagnostic aid may even be discarded altogether - virtual endoscopy using reformats of various imaging modalities has been performed in cadaveric[27] and canine[28] models and in small studies has proved successful.

Conclusion

Since the advent of the endoscope, many surgical techniques using it have been described and are in common usage. However otolaryngology has lagged behind in prospering from this technology as the surgical regions the ENT surgeon explores are small, anatomy is both important and detailed, and only in the last 15 years has the image quality of an endoscope matched that of the operating microscope. With the further introductions of high definition cameras and screens, and endoscopes as small as 1mm in diameter, this barrier is no longer present and more accurate and detailed descriptions of pathology and surgical techniques can be described.

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Update on management of Cholesteatoma

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Introduction

Cholesteatoma is defined as the presence of squamous epithelium within the middle ear cleft. Although Cruveilhier first described the condition in 1829, the anatomist Johannes Müller was the first person to use the name cholesteatoma in 1858 under the mistaken impression that it was a tumour. While cholesteatoma can be managed conservatively in patients with significant co-morbidity the only definitive treatment remains surgery. The first radical mastoidectomy was described by Zaufal in 1890[1]. The biggest development in mastoid surgery in the last century has been the introduction of the operating microscope by Zeiss in 1953. Since the introduction of the microscope surgeons approaches to mastoid surgery can broadly be classified into canal wall up surgery and canal wall down surgery. The debate as to which surgery should be carried out for cholesteatoma treatment has not changed and continues to this day. Developments to the canal wall up and down techniques since the 1950's include mastoid obliteration and canal wall reconstruction. This review focuses on the main two developments over the last 5 – 10 years in mastoid surgery – the use of magnetic resonance imaging and the otoendoscope.

Magnetic Resonance Imaging (MRI)

Computerised tomography is good for showing the bony anatomy of the middle ear and mastoid and the extent of disease but is unable to differentiate mucosal and squamous disease. It can therefore be useful before primary surgery for cholesteatoma although it does not normally influence the need to operate or not. For assessing patients who have had mastoid surgery for recurrent/residual disease it has a high sensitivity but low specificity for detecting cholesteatoma. A number of studies have looked at using MRI imaging to assess patients for recurrent/residual disease. This is particularly important for canal wall up surgery where there is a higher rate of recurrence which

may not be evident on examination in clinic and where patients often undergo second look procedure to check for recurrence. The hope is that MRI imaging may be able to be used to replace this second look procedure.

Due to the large number of variables in carrying out MRI scans it can be difficult to directly compare different protocols but broadly speaking the two main types of imaging that have been used to date are T1 weighted imaging with gadolinium contrast and diffusion weighted imaging.

T1 Weighted imaging with gadolinium contrast

In this type of imaging T1 weighted images are taken approximately 30 - 45 minutes after injection of gadolinium contrast. The principal behind this type of imaging is that cholesteatoma is avascular and therefore does not enhance with contrast as opposed to granulation/inflammatory tissue. This has been shown to be a good technique for evaluating recurrent/residual cholesteatoma with sensitivity, specificity, positive predictive value and negative predictive value of 66-90%, 92-100%, 92-100% and 75-92% respectively[2-5]. The advantages of this technique over diffusion weighted images are that it provides a relatively high spatial resolution allowing better localisation of disease[4]. The disadvantages are that if the timing of the images in relation to the contrast administration is wrong a false negative will be produced, contrast has to be given to the patient, it has a relatively long examination time and the practicality of taking images 30-45 minutes after contrast administration.

Diffusion Weighted MRI Imaging

In diffusion weighted imaging (DWI), each image voxel (three dimensional pixel) has an image intensity that reflects a single best measurement of the rate of water diffusion at that location. It is widely used in imaging the

ischaemic brain. On this type of imaging cholesteatoma shows up as a hyperintense lesion. This has been shown this to be a good technique for evaluating recurrent/residual cholesteatoma with sensitivity, specificity, positive predictive value and negative predictive value of 60-100%, 60-100%, 83-100% and 50-100% respectively[3-4,6-9]. This does not involve contrast administration and is a relatively quick technique compared with T1 weighted imaging with contrast which because of this is more likely to require a general anaesthetic in children.

Both these techniques have their advantages and disadvantages. Both have been shown to have good inter-observer reliability although it appears to be slightly better for the diffusion weighted imaging[3,5,10].

Concerns have been raised about MRI detecting cholesteatoma sac containing no keratin for both diffusion weighted MRI and T1 weighted MRI with gadolinium contrast[7,11]. Another shortfall of MR imaging is its inability to pick up small cholesteatomas. Most authors report a significant improvement in their sensitivity and specificity by excluding cholesteatomas <5mm. They argue that a cholesteatoma of this size would be expected to be of no clinical significance and that by repeating the scan a year or more down the line that they would expect to pick up these cases[2,3,4]. To date no one has published any data looking at this. What is needed is a cohort of patients who have had a mastoid procedure for cholesteatoma who have then had a normal MRI scan and then a repeat scan a year or so later. They would then require either a second look procedure to correlate the findings or a long follow up period of many years to ensure that these patients had no significant active disease. As imaging technology improves the threshold for picking up small cholesteatomas will improve, some centres have already picked up cholesteatomas as small as 2mm.

Problems have been reported with silastic sheeting, which had been placed in the middle ear/mastoid at the primary surgery, being mistaken for cholesteatoma during the interpretation of the imaging[3].

Another advantage of MRI scanning for recurrent disease is the ability to detect herniated brain/dura into the mastoid or middle ear which may not be apparent on CT scanning[12].

With improvement in imaging technology there now appears to be good evidence for the use of MRI scanning – diffusion weighted or T1 weighted with gadolinium contrast to detect residual/recurrent cholesteatomas with the knowledge that small cholesteatomas will be missed and so patients with negative scans will need follow up.

Endoscopy

The introduction of the operating microscope revolutionised cholesteatoma. It provides high magnification with good depth perception and allows the surgeon to operate with both hands. It does however have disadvantages which have led people to using the endoscope to augment or replace the use of the microscope for cholesteatoma surgery. The main disadvantages of the microscope are that you have a narrow field of view which is restricted by the narrowest diameter between the microscope and the object being viewed. This is particularly troublesome with the permeatal approach to cholesteatoma. You are also restricted to a visual field within a direct straight line of the microscope and with higher magnification the brightness of the microscope light appears less to the operating surgeon. Harold Hopkins introduced the first rigid endoscope in the 1960s and Thomasin et al were the first to describe its use for cholesteatoma surgery[13] and since then it has been used by otologists increasingly throughout the world. The otoendoscopes used commonly have either a 2.7mm or 4mm diameter and use 0º, 30º, 45º and 70º viewing angles. There are a number of ways that otoendoscopes have been used to aid surgeons performing cholesteatoma surgery:-

1. In clinic pre and post operatively[14].
2. To supplement the use of the microscope in conventional canal wall down or up surgery to ensure complete removal of cholesteatoma[15-17].
3. To replace the microscope to perform transcanal atticoantrostomy for limited cholesteaoma[18-19].
4. To perform minimal access second look procedures after canal wall up surgery[15].

The two main advantages to using an otoendoscope for cholesteatoma are the wide viewing angle in comparison to microscopes and the ability to see round corners with angled endoscopes which can permit access to areas like the sinus tympani. For limited transcanal cholesteatoma surgery using the otoendoscope only the duration of surgery has been reported to be less compared with a traditional postauricular approach with a microscope[14]. Another benefit of the endoscope over the microscope is there is no problem with the view being obscured by instruments.

There are however a number of problems with using an endoscope for middle ear/mastoid surgery. One hand is required to hold the endoscope leaving only one hand to operate with. This could potentially be a problem when suction is required for a blood filled operating field although the authors carrying out otoendoscope only cholesteatoma surgery have not reported this to be a significant problem[18-19]. There could be potential problems with the heat produced by the endoscope when operating

in a confined space such as the middle ear. Tarabichi reports that this can be avoided by using a regular light source on lower settings which provides more that adequate illumination rather than using a xenon light source. Concerns have been raised about causing trauma to important structures with the endoscope, especially with patient movment[14]. Tarabichi suggests that this risk can be reduced by using a 4mm endoscope which will give a wider field of view and will normally stop the endoscope going beyond the tympanic ring[14].

There is increasing evidence that use of the otoendoscope reduces the risk of recurrent /residual cholesteatoma but does not eliminate it. El-Mesalaty et al operated on 4 groups of patients (n=82) for cholesteatoma – canal wall up with and without use of the endoscope and canal wall down with or without the use of the endoscope. At a mean duration of follow up of 18 months residual/recurrent cholesteatoma was only detected in ears that had been operated on without an endoscope16. In studies where microscopic clearance of cholesteatoma has been achieved with canal wall up and down procedures persistent cholesteatoma has been found in 23 – 76% with the use of an endoscope[20-22]. Despite the clearance of this residual cholesteatoma many authors still report a significant recurrence rate although this is presumably lower that it would have been if the endoscope had not been used to remove residual cholesteatoma. The largest series of patients undergoing otoendoscope only surgery for cholesteatoma limited to the middle ear, attic and antrum shows a recurrence rate of 7% (n=168) with an average follow up of 35 months[23].

Conclusion

The use of MRI and otoendoscopy has been big developments in the field of cholesteatoma surgery and their impact is likely to grow. The use of MRI imaging would appear to promote the use of canal wall up procedures and will hopefully reduce the need for routine second look procedures. More evidence is needed to look at the follow up of patients who have negative scans. As the technology develops it is likely that imaging will be able to pick up smaller and smaller cholesteatomas. Otoendoscopy has the potential to be involved in canal wall up and down procedures as well as limited otoendoscopy only procedures. There have been no reports in the literature of serious adverse events with otoendoscopy and while the level of evidence for its use may not be that high it does not take a randomised control trial to tell you that a better view and removing cholesteatoma that would have been missed with microscope only surgery has to be a good thing.

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ORL Manifestations of Neurofibromatosis: Investigation and Management.

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Abstract

Three major forms of Neurofibromatosis (NF) are recognized as distinct entities on the basis of their genetic origin, pathogenesis and clinical manifestation. These are NF1, NF2 and Schwannomatosis. The cardinal feature of NF2 is the development of bilateral vestibular schwannomas with the consequent risk of significant hearing impairment. The evaluation of patients with NF-2 should include a neurological/ophthalmological examination, pure tone audiometry and cranio-spinal magnetic resonance imaging (MRI) of the entire neural axis with thin cuts through the internal auditory meatus to identify the high incidence of occult tumours. Options for managing the vestibular schwannomas include watchful-waiting with careful surveillance, radiotherapy or surgical excision. Hearing preservation remains a challenge and options for hearing rehabilitation include cochlear implantation or an auditory brainstem implant in selected cases. Bevacizumab, an anti-VEGF monoclonal antibody, may provide tumour stabilization and hearing recovery in a subset of NF2 patients with progressive disease. Neurofibromatosis is an as yet incurable disease with significant morbidity and reduced life expectancy. There are hopes that eventual biologic manipulation of the genetic defect might lead to a cure or at least provide improvements for this devastating condition.

Key words

Neurofibromatosis, Von Recklinghausen Disease, Vestibular Schwannoma, Schwannomatosis

Introduction

Neurofibromatosis (NF) comprises a group of three genetically distinct disorders of the nervous system that are unified by the predisposition to nerve sheath tumours. Such tumours can be divided into 3 subtypes: neurofibromas, schwannomas, and malignant peripheral nerve sheath tumours (MPNSTs). Neurofibromas and MPNSTs are seen in NF1, while schwannomas are characteristic of NF2[1]. There is no gender, race or ethnic bias and the diseases show 100% penetrance but highly variable expression.

Freidrich Von Recklinghausen, a German pathologist, described three cases from the literature and two of his own patients in 1882[2]. The disease that carried his name (also known as peripheral neurofibromatosis) is now classified as NF type 1, an autosomal dominant condition with the genetic defect on chromosome 17q11.2[3]. Neurofibromin, the gene product, is a ubiquitous nervous system protein and is believed to act as a tumour suppressor[4]. The incidence of NF-1 is one in 4000[5] and diagnosis is made in an individual in whom at least two of the following seven features are found[5]:

1) Six of more cafe-au-lait spots larger than five millimetres in children and 15 millimetres in teenagers and adults.
2) Two or more neurofibromas or one plexiform neurofibromas (figure 1)
3) Axillary or groin freckling
4) Optic nerve glioma
5) Two or more iris hamartomas (Lisch nodules)
6) A distinctive bony lesion, such as sphenoid wing dysplasia or thinning of the long bone cortex, with or without pseudoarthrosis
7) A first-degree relative with NF-1 according to the above criteria

Although the first description of Neurofibromatosis type 2 (NF-2) was probably by Wishart in 1822[6], it was not classified as a separate condition until 1987[5] when the genetic abnormality was recognised to be on chromosome 22q12.2, the gene product is Merlin[7], a tumour suppressor. It was previously known as central neurofibromatosis and

Figure 1: *Extensive neurofibromas in NF1*

is now recognised as an autosomal dominant disease with an incidence of one in 60,000 people[8]. A diagnosis of NF-2 is made in an individual that has either[5]:

1) Bilateral vestibular schwannomas (figure 2) or
2) A first degree relative with NF-2 and a unilateral eighth cranial nerve tumour or
3) A first degree relative with NF-2 and two of the following:
   a) dermal or subcutaneous neurofibromas
   b) plexiform neurofibroma
   c) Schwannoma
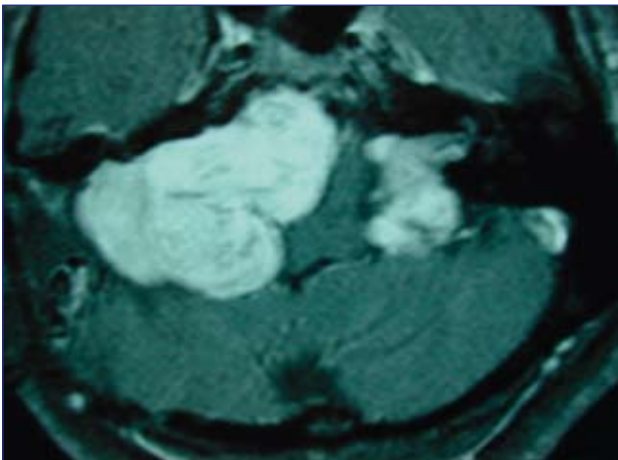   d) glioma
   e) juvenile posterior subcapsular cataract
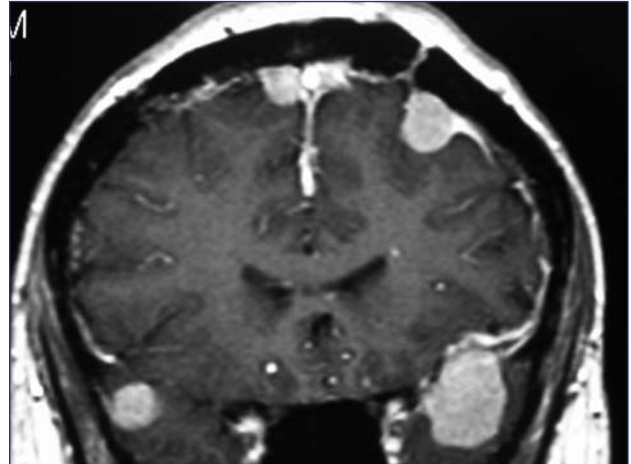

Figure 2: *Bilateral vestibular schwannoma in NF2*

Figure 3: *Multiple meningiomas in NF2*

The diagnostic criteria for NF-2 were expanded by Evans[9] to include patients with no family history who have multiple schwannomas and/or meningiomas, but who have not yet developed bilateral eighth nerve tumours (figure 3). This was to include the 50% of cases with new mutations[7].

There is controversy whether the third variant, schwannomatosis, is a distinct entity from NF-2. Shishiba et al[10] and Purcell and Dixon[11] described cases of multiple schwannomas in the absence of NF-1 and NF-2. It may be that, if followed up for a long time, these patients would have developed VS and would then be classified as NF-2. MacCollin et al[12] argue against this as they followed up eight patients for over 10 years without the development of VS. Furthermore the median age of patients with schwannomatosis in the study by Seppala et al[13] was 43.5 years, whereas NF-2 presents at a younger age. Jacoby et al[14] proposed diagnostic criteria for schwannomatosis which are;

Definite schwannomatosis:
1) Two or more pathologically proven schwannomas and
2) Lack of radiographic evidence of vestibular nerve tumours, at age >18 years

Probable schwannomatosis:
1) Two or more pathologically proven schwannomas, without symptoms of VIII nerve dysfunction, at age >30 years, or
2) Two or more pathologically proven schwannomas in an anatomically limited distribution (single limb or spinal segment) without symptoms of VIII nerve dysfunction at any age.

The clinical features of NF are widespread and include dermal, neurological, ocular, skeletal and cardiovascular

manifestations. This article deals only with the otorhinolaryngological features of NF, principally vestibular schwannoma.

Clinical features

NF1 presents in childhood or adolescence whilst NF2 usually presents in young adults under 40 years of age. Café au lait spots are the usual, early feature of NF1 but there are rarely more than 6 spots in NF2. Posterior subcapsular cataracts would be suggestive of NF2, whereas Lisch nodules would be diagnostic of NF1[8]. Bilateral vestibular schwannoma are essentially universal among patients with NF2 whereas they are found rarely in NF1. NF2 usually presents with auditory symptoms but headaches (intracranial meningiomas), seizures, paraesthesia and paralysis (spinal tumour)[15] may be the presenting feature.

VS most commonly present with auditory symptoms of hearing loss, tinnitus and imbalance. Nausea, vomiting or true vertigo is rarer and brainstem compression and obstructive hydrocephalus can occur in late stage disease. In NF2, auditory symptoms start around age 20 and the average age at diagnosis is 28[15,16], as opposed to the isolated unilateral vestibular schwannomas that present later in life[8]. They are typically slow growing and cause gradual deterioration in hearing.
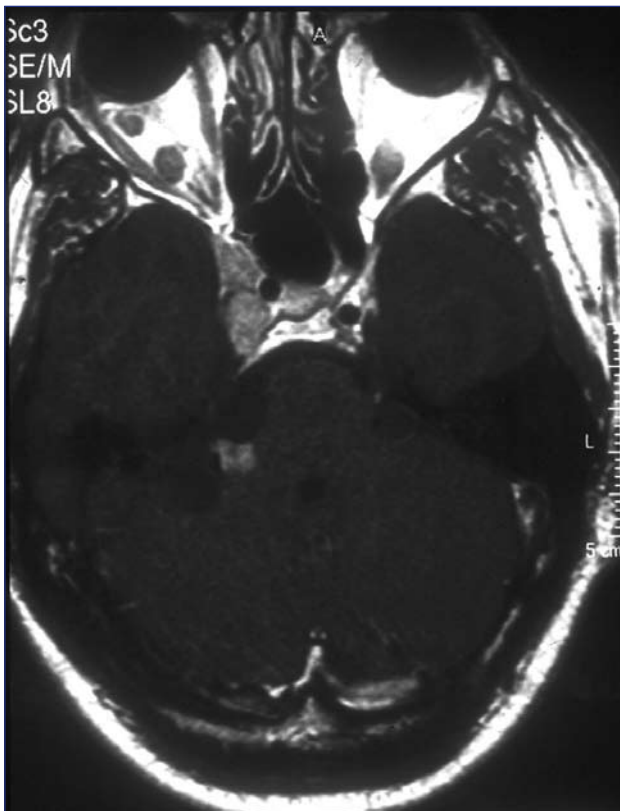

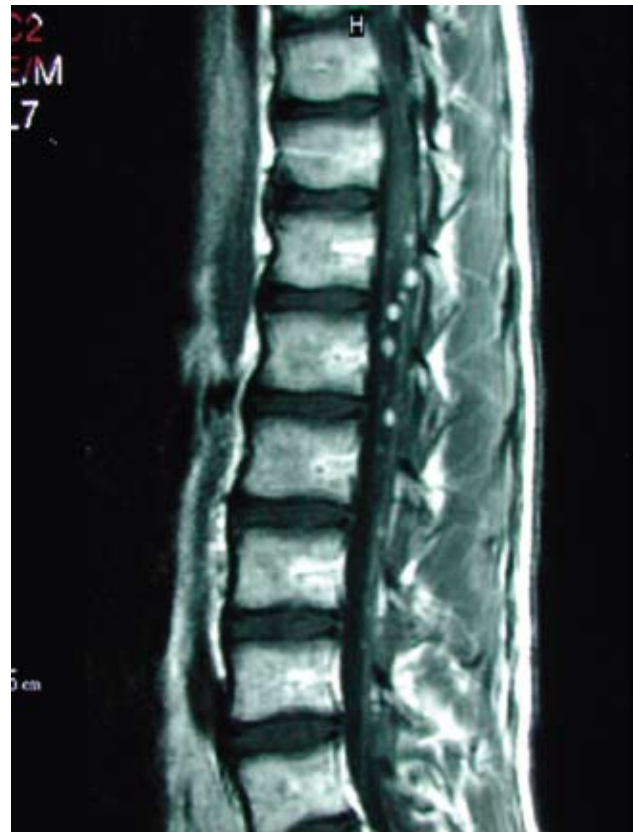**Figure 4:** *Optic meningiomas in NF2*

Figure 5: *Multiple spinal tumours in NF2*

In terms of prognosis, most people with NF1 lead relatively long and healthy lives, but it does reduce life expectancy by around 15 years[17], most commonly due to malignancy. NF2 generally has a worse prognosis with the mean age of death at 36 years in one study[16].

Investigations

The Diagnosis of NF is based on clinical and neuro-imaging studies. A thorough ophthalmologic (slit lamp) and skin examination can be very useful as although there are some similarities between NF-1 and NF-2 (both may have cafe-au-lait spots and neurofibromas), axillary freckling and Lisch nodules are unique to NF-1 while NF-2 patients are prone to posterior subcapsular cataracts.

Evaluation of patients with NF-2 should include an annual neurological/ophthalmological examination, pure tone audiometry and a screening cranio-spinal MRI of the entire neural axis with thin cuts through the internal auditory meatus to identify the high incidence of occult tumours[18]. Gadolinium enhanced, post-contrast T1-weighted sequences in multiple image planes is the most useful sequence although T2-weighted images are performed to help characterise lesions. Schwannomas are usually homogeneous when small but can contain cysts or

areas of necrosis when larger. Vestibular schwannomas typically arise inside the internal auditory meatus and enlarge into the cerebellopontine angle, giving rise to the 'ice cream on a cone' appearance[19].

When following up a patient who has had a translabrynthine removal of a vestibular schwannoma, a pre-contrast T1-weighted scan of the petrous bone is needed because of the high signal from fat used to pack the cavity, making detection of a small enhancing tumour remnants difficult. Patients who have had a cochlear or auditory brainstem implant need to either have the magnet from the receiver-stimulator temporarily removed to allow surveillance MRI scanning undergo high resolution CT scanning.

Genetic counselling is an integral part of the management of NF patients and includes identification of mutations which can then be used to screen family members by linkage analysis[8]. If positive, pre-symptomatic radiologic screening is indicated. Pre-natal diagnosis and pre implantation genetic diagnosis is also possible[20].

Management

Due to the complexities of the manifestations of neurofibromatosis, patients are best served by evaluation and management through a coordinated multidisciplinary team. This should include a geneticist, neurologist, neurosurgeon, neuro-otologist, audiologist, speech therapist, radiologist, ophthalmologist, orthopaedic surgeon, dermatologist, plastic surgeon, neuropsychologist and oncologist.

NF2 represents a challenging management problem with treatment strategy aimed at preserving quality of life and hearing, without increasing the risk of complications to the facial nerve, neurological status or life. Most patients face substantial morbidity and a reduced life expectancy[16]. Options for managing the vestibular schwannomas include watchful waiting with careful surveillance[21], radiotherapy[22] or surgical excision. The factors that need to be considered are the hearing status in each ear, size and rate of tumour growth[21], chances of hearing preservation, signs of dysfunction of other cranial nerves or the brainstem, and most importantly, the opinions and wishes of the patient. Treatment is therefore highly individualised for each patient.

Bilateral hearing loss and total deafness is a real risk in NF2 patients and this provides a challenging dilemma. A watch and rescan approach may be the best choice for patients who have a stable vestibular schwannoma in one ear and no hearing on the other side. These patients require treatment only if the vestibular schwannoma enlarges or if the patient looses their hearing. In cases where there is a large vestibular schwannoma with poor hearing on one side and a small tumour with good hearing on the other, it is straightforward and logical to recommend treatment of the larger tumour with either surgery or radiotherapy. If however, the hearing loss is in the side with the smaller tumour, treating the larger tumour with either surgery or radiosurgery may render the patient totally deaf. Surgical excision with hearing preservation may be attempted but is often difficult as the vestibular schwannoma in NF2 patients have a propensity to invade the cochlear nerve[23]. If hearing is lost bilaterally, cochlear implantation (if the cochlear nerve is spared) is the most effective option[24] and can be inserted simultaneously[25] at the time of translabrynthine vestibular schwannoma removal. Auditory brainstem implant is a valuable tool when the cochlear nerve is sacrificed but the results are limited compared to cochlear implantation[26,27].

Until recently there was no medical treatment available for the treatment of vestibular schwannoma in NF2 patients. Plotkin et al[28] identified that vascular derived endothelial growth factor (VEGF) was expressed in 100% of vestibular schwannomas. Treatment with bevacizumab, an anti-VEGF monoclonal antibody, improved hearing in some, but not all, patients with NF2 and was associated with a reduction in the volume of most growing vestibular schwannomas. This reduction in volume was maintained in 40% of patients during 11 to 16 months of follow-up[28].

Although NF2 is as yet and incurable condition, there are hopes that eventual biologic manipulation of the genetic defect on chromosome 22q12.2 (with replacement of the tumour suppressor product through viral vectors or direct recombination of the NF2 gene) might lead to a cure or at least provide improvements for this devastating condition.

Conclusion

NF1, NF2, and schwannomatosis are inherited cancer syndromes characterised by the development of tumours of the nervous system. NF2 should be suspected in an individual who develops a vestibular schwannoma before the age of 40 years. These patients should undergo a careful dermatological, neurological and ophthalmological examination with appropriate imaging. Management options for the vestibular schwannoma include a watch and rescan approach, radiotherapy and surgery to remove the tumour. Hearing preservation remains a challenge and options for hearing rehabilitation include cochlear implantation if the cochlear nerve is spared and an auditory brainstem implant if the cochlear nerve is sacrificed. Recently it has been shown that bevacizumab, an anti-VEGF monoclonal antibody, provided tumour stabilization and hearing recovery in a subset of NF2 patients with progressive disease.

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The Discharging Ear

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Abstract

The most common causes of ear discharge are inflammatory diseases of the external and middle ear and these include a broad range of pathological conditions. Knowledge of the pathological processes involved in otologic conditions in conjunction with sound history taking and clinical examination are essential to establish a diagnosis. Multi-valent pneumococcal conjugate vaccine has proven efficacy in reducing invasive disease and acute otitis media due to pneumococcus in infants and children. Use of topical Quinolone antibiotics seems to be the safest and most effective means of eradicating ear discharge in COM. Adherence to good surgical technique is a major factor in eradicating post mastoid otorrhoea.

Key Words

Otitis Externa, Otitis Media, Pneumococcal conjugate vaccine, Quinolone antibiotics.

Introduction

Discharging ear is a common presentation to the otolaryngologist; it affects all ages and is more difficult to assess in the pediatric age group where examination under anesthesia may be required to establish the pathogenesis. The most common causes of ear discharge are inflammatory diseases of the external and middle ear and these include a broad range of pathological conditions including acute and chronic otitis externa, acute otitis media (AOM) suppurative or nonsuppurative, granular myringitis, bullous myringitis and chronic suppurative otitis media (CSOM) with or without cholesteatoma. Other causes such as malignant otitis externa and eosinophilic otitis media must also be considered. The wide range and complexity of pathology can pose a challenge to the otolaryngologist. Like any other medical condition, accurate history and a careful clinical examination are mandatory, as the symptoms and signs of ear disease are vital to elucidate the possible differential diagnosis.

History

Symptoms of ear disease include hearing loss, discharge, vertigo, tinnitus, headache and otalgia. Watery odorless discharge and itching ears with or without otalgia points to otitis externa, while cerebrospinal fluid leak presents with a clear fluid discharge and a recent history of head trauma resulting in dural tear. Middle ear cleft discharge is generally foul smelling, long standing and is associated with the presence of mucus either from a tympanic membrane perforation or from an open mastoid cavity. Thick soaked tympanic membrane with multiple perforations should raise the suspicion of tuberculous otitis media[1] or Wegener's granulomatosis. The classical presentation of TB otitis media may have changed due to the common use of ear drops containing Neomycin and Gentamycin as they have a weak anti TB effect[2], however currently it is possible for TB to present in a similar way to that of chronic otitis media. Syphilitic otitis media will show middle ear gummatous formation and osteitis. HIV infection does not affect the ear directly but because of the immunocompromised status it encourages opportunistic organisms causing ear infection and discharge. Diabetic patients with ear discharge pose a challenge and may require hospital admission particularly if malignant otitis externa is suspected. Bleeding from the ear may represent trauma, florid granulation tissue, an ominous sign of malignancy or rare vascular anomalies.

Type of deafness can be determined from the history, for example if the patient complains of inability to hear in the presence of background noise, this generally points towards a sensorineural hearing loss as this is associated with reduced discrimination of speech particularly in background noise. A patient who seems to hear better with background noise suggests a conductive loss, as the speaker tends to raise their voice intensity in the presence of noise. It is equally important to enquire about family history of hearing loss and other systemic diseases such as Diabetes Mellitus. Tinnitus and vertigo are associated with a variety of otologic conditions and their presentation and management are beyond the scope of this paper.

Examination

Ear examination should include inspection for scars, tenderness around the auricle or the tragus, narrowing or congestion of the canal skin, the character of the discharge, the presence of polyps or granulation tissue either in the

floor of the external auditory canal, in the middle ear cleft or in a mastoid cavity. Tympanic membrane perforation if present should be noted for the site, size, edges and structures visible through it. Mastoid cavity should be noted for the adequacy of meatoplasty, middle ear sealing, facial ridge level, residual or recurrent cholesteatoma, adhesions and granulation tissue.

Pathogenesis

Otitis Externa:
Cerumen guards against infection by producing an acidic and lysozyme-rich environment in the ear canal. A break in the normal skin or the cerumen barrier generally in the presence of humidity and elevated temperature can lead to infection. In the United States, acute otitis externa occurs in 4 of every 1000 people annually, while the chronic form affects 3-5% of the population[3]. Although usually referred to as swimmer's ears, it can result from a cycle of itch and scratch causing maceration of the canal skin and infection by fungi or bacteria. Those who do not respond to initial treatment may become chronic, a condition linked to a spectrum of eczema including psoriasis, seborrhoeic and atopic eczema[4]. It has also been suggested that the change of canal skin pH from acidic to alkaline is a local risk factor for the progression into chronic otitis externa[5].

The most common pathogens in acute externa media are pseudomonas, proteus mirabilis, staphylococcus and streptococcus. In a meta-analysis of nineteen randomized controlled trials for the treatment of acute otitis externa Kaushik[6] concluded that topical antimicrobial containing steroids were significantly more effective than placebo, and there was no clinical difference noted in the cure rate between the various topical drops used. The authors also conclude that acetic acid is less effective compared to antibiotic/steroid drops, and that no trial to date evaluated the effectiveness of ear cleaning.

Chronic otitis externa and its recurrent exacerbation represents a challenge for the otolaryngologist and the introduction of the novel topical immune modulator tacrolimus is considered a milestone in the treatment of noninfectious chronic otitis externa[7]. Topical application of 0.1% tacrolimus ointment in the external ear canal appears to be an effective and well-tolerated new option in the treatment of chronic therapy-resistant otitis externa. Tacrolimus (protopic) attenuates the relapsing course of the disease and reduce the number of exacerbations[8].

Otitis Media
Otitis media (OM) continues to be one of the most common childhood infections and is a major cause of morbidity in children. The pathogenesis of OM is multifactorial, including adaptive and native immune system, Eustachian-tube dysfunction, viral and bacterial pathogens, genetic and environmental factors[9].

Acute Otitis Media:
Acute otitis media (AOM) is most prevalent in children younger than 2 years[10]. The two main bacterial pathogens that cause the infection are Streptococcus pneumoniae and non-typable Haemophilus influenzae. Prevention of otitis media would be of great advantage in reducing morbidity, antibiotic consumption and cost of treatment. The advent of pneumococcal conjugate vaccines has shown promise in these regards. They have proven efficacious against invasive disease and pneumonia caused by pneumococcal serotypes covered by the vaccine[11]. The licensed 7-valent pneumococcal conjugate vaccine (7vCRM, Prevenar/ Prevnar) has successfully reduced invasive disease in the USA, but serotype coverage is incomplete and there is evidence to suggest that serotype replacement has occurred. Recently, a new 10-valent pneumococcal nontypeable Haemophilus influenzae (NTHi) protein D (PD) conjugate vaccine (PHiD-CV, Synflorix) has been licensed in more than 40 countries, including Europe, for the prevention of invasive disease and acute otitis media due to pneumococcus in infants and children. The vaccine is administered as a three-dose primary vaccination and has a safety profile comparable to that of 7vCRM[12]. A panel of researchers have described declining rates of diagnosis, antibiotic prescription, office visits for OM and middle ear surgery since the licensure and routine use of pneumococcal conjugate vaccine in infants[13].

Otitis Media with Effusion:
Otitis media with effusion is at the opposite end of the scale to acute otitis media in the spectrum of pathology that affects the middle ear cleft in infants and children[14]. It is characterized by the accumulation of non-purulent fluid within the middle ear cleft with an intact tympanic membrane. Most frequently, the fluid is mucus and thick, but sometimes it is serous and thin in consistency, it is also referred to as secretory otitis media[15]. The insertion of ventilation tubes (grommets) is one of the most common surgical procedures performed on children. Postoperative otorrhoea is the most common complication with a reported incidence ranging from 10% to 50%. In the UK, many ENT surgeons treat post grommet insertion otorrhoea with topical antibiotics/steroid combinations, but general practitioners are unlikely to prescribe these and choose systemic broad-spectrum antibiotics mainly through fear of ototoxicity[16]. In a recent meta-analysis of the few good quality randomized clinical trials available, the authors were unable to identify the most effective intervention and recommended that urgent research is needed into the effectiveness of oral versus topical antibiotics in this group of patients.

Chronic Otitis Media (COM):

The current classification of chronic otitis media is that by Browning et al[17] which omits the words "suppurative" and "non-suppurative", since it is a progression of the same pathologic process. Furthermore, one could lead to the other depending on the prevailing factors. Thus, chronic otitis media could be further described as "active", "inactive" and "healed" (Table 1).

COM is more common in the developing countries, with a prevalence range as high as 6-11.1% across the different age groups[18,19]. The bacteriological agents most commonly associated with COM include Pseudomonas aeruginosa, Staphylococcus aureus, followed by the gram-negative organisms, Klebsiella and Proteus. The anaerobes (Bacteroides, Peptostreptococcus, Peptococcus) and fungi (Aspergillus, Candida) complete the spectrum of organisms in COM.

Active mucosal COM can be managed via aural toilet and appropriate topical and systemic antibiotics. Assessment of the ear from a hearing loss point of view, the expected improvement in same with successful surgery, the desire to swim/have a trouble-free ear, the age of the patient (child), and the recurrence rate of the ear infections are all factors in deciding whether or not to proceed to surgical intervention in the form of myringoplasty or tympanoplasty. The old argument among otologists as to whether or not total dryness should be achieved before reconstructive surgery[20], still to some degree exists in the developing countries, as in their experience a dry ear prior to reconstruction is favoured, considering the limited resources and the cost of failure in such reconstruction.

Active squamous COM does not respond effectively to medical treatment, and surgery which is tailored to the extent of the disease in the form of canal wall up or canal wall down, is regarded as the treatment of choice. However some ears, particularly those with a canal wall down cavity continue to discharge long after surgery and common causes for this problem include high facial ridge, an open middle ear segment, an inadequate meatoplasty and recurrent cholesteatoma. Poor performance of the open technique is the most important factor in failure[21].

The majority of otolaryngologists treat discharging ears with topical antibiotics and many do not routinely send microbiology specimens unless the discharge is refractory to treatment. ENT-UK recommends that when treating a discharging ear with a perforation or patent grommet, that a topical aminoglycoside should only be used in the presence of obvious infection. Topical aminoglycosides should be used for no longer than two weeks. The justification for using topical aminoglycosides should be explained to the patient. Baseline audiometry should be performed, if possible or practical, before treatment with topical aminoglycosides[22].

With the popular use of ear drops, it is important to look at their safety profile and their limitations. In the English literature, there are a number of papers reporting more than 165 documented patients who developed sensorineural hearing loss from the use of otic drops in otitis media[23]. A survey of a large cohort of otolaryngologists showed that 3.4% reported irreversible cochlear damage attributable to otic drops[24]. Ototoxicity from Gentamycin is well documented, however given the popularity of its use all over the world this complication seems rare. In normal ears, Dexamethasone, Hydrocortisone and Methylprednisolone have been documented as capable of traversing the round window membrane but appear to be safe[25].

Topical Quinolone antibiotics (Ciprofloxacin and Ofloxacin) have great activity against pseudomonas, and Ciprofloxacin is also effective against Staphylococcus

Table 1: Summary of the current clinical and histological classifications of COM according to Browning.		
COM Classification	**Synonyms**	**Otoscopic findings**
Active (squamous)	Cholesteatoma	Retraction of pars tensa/flaccid, retained squamous epithelium, debris and pus
Active (mucosal)	-----	Permanent defect of TM on pars tensa, inflamed middle ear mucosa, mucous discharge
Inactive (squamous)	Retraction	Retracted pars tensa/flaccid usually at postero-superior segment, with potentials of becoming active with retained debris
Inactive (mucosal)	Perforation	Permanent perforation on pars tensa, inactive middle ear mucosa
Healed	Healed perforation, tympanosclerosis	Thinning and/or local or generalized opacification of the pars tensa without perforation or retraction

aureus, the other major pathogen in chronic otitis media. Topical Quinolone antibiotics can clear aural discharge better than no drug treatment or topical antiseptics; non-Quinolone antibiotic effects (without steroids) versus no drug or antiseptics are less clear[26]. Quinolone concentrations achieved through topical use are substantially higher than those achieved by other forms of administration, and thus there is a better chance of eradicating the infection[27]. Quinolones are superior to the aminoglycosides in terms of safety, bacterial eradication and clinical cure, and seem therefore to be the drops of choice for treating otorrhoea[28]. Recently, the use of bacteriophage preparation (Biophage-PA) in chronic otitis caused by resistant pseudomonas organism shows a promising new frontier in the management of discharging ear[29].

Role of Imaging
Imaging in external ear pathology is generally not required if the cause of ear discharge is obvious, but if warranted a high resolution CT of the temporal bone is the most appropriate modality and is absolutely warranted in cases of suspected malignant otitis externa. Otitis externa appears as thickening of the soft tissue of the external canal, while canal cholesteatoma will appear as a soft tissue mass filling part of the canal. Squamous cell carcinoma or basal cell carcinoma shows bone erosion that appears irregular or lytic in nature[30].

As with the external ear, high resolution CT is the preferred modality for assessing the middle ear. Acute otitis media appears as opacification of the middle ear and mastoid air cells. In the setting of active squamous COM (cholesteatoma), particular attention should be paid to the scutum area for bony erosion and also for the presence of soft tissue mass in Prussak space. It is difficult to differentiate between fluid and cholesteatoma on CT scan. On MRI, both fluid and cholesteatoma appear bright on T2 images, however both primary and recurrent cholesteatoma have been found to show increased signal on diffusion weighted imaging, which can distinguish them from fluid[31,32].

Conclusion
Ear discharge is a common presentation to the otolaryngologist. Ample knowledge of the pathological processes involved in otologic conditions is essential to establish a diagnosis. Multi-valent pneumococcal conjugate vaccine has proven efficacy in reducing the number and severity of pneumococcal otitis media infections. Use of topical Quinolone antibiotics seems to be the safest and most effective means of eradicating ear discharge in COM. Adherence to good surgical techniques is a major factor in eradicating post mastoid otorrhoea.

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A review of Tinnitus Treatments Part 1

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Abstract

This paper reviews the various treatments for tinnitus including; tinnitus retraining therapy, cognitive behavioural therapy, sound therapies, such as masking devices, neuromonics, hearing aids, tinnitus phase-out treatments, alternative treatments such as ginkgo biloba, hypnosis, electromagnetic stimulation, ear canal magnets, low-power laser, acupuncture, homeopathy, ultrasound and surgical treatments. The efficacy of the various treatments are examined with particular emphasis on double-blind placebo controlled trials.

Key Words

Tinnitus, treatments, review.

Introduction

Tinnitus is the perception of sound in the absence of external acoustic stimulation. 10 to 15 % of the population are affected with a greater prevalence in the elderly[1]. Tinnitus is classed as being subjective i.e. can only be heard by the patient or objective in which case the tinnitus can be heard by the clinician, which accounts for only 1% of tinnitus presentations[2].

Severe and persistent tinnitus can interfere with concentration and sleep and in some individuals can cause severe psychological distress, and in a small minority of cases can even lead to suicide. Whereas the majority of individuals cope with tinnitus, in a small minority, 1%, the tinnitus becomes a significant and serious problem [3].. In the current paper the various treatments for subjective tinnitus are discussed.

Treatments such as yoga, aromatherapy and t'ai chai are omitted from this article because of the difficulties in carrying out placebo-controlled trials on these treatments, although the authors accept that these treatments may confer significant benefits to patients with tinnitus.

Tinnitus Retraining Therapy [TRT]

Tinnitus retraining therapy is designed to help a person retrain the brain to avoid thinking about tinnitus. It employs a combination of counselling and a non-masking white noise which decreases the contrast between the sound of the tinnitus and the surrounding environment[4]. Both the neurophysiological model and the psychological model propose habituation as the key mechanism in the alleviation of tinnitus distress.

Tinnitus retraining therapy is based on a neurophysiological model which suggests that tinnitus distress can be explained by a classical conditioning paradigm. This model suggests that, brain processes and the autonomic nervous system play a significant role in the perception of tinnitus. It suggests that tinnitus becomes problematic because of it's association with a negative entity. Once it becomes associated with a negative emotional state, continuous tinnitus causes prolonged activation of the autonomic nervous system, which prepares the body for "fight or flight" and there is also activation of the brain's limbic system which is responsible for emotion, memory and learning.

The neurophysiological model stresses the importance of unconscious conditioning unlike the cognitive behavioural model which stresses conscious cognitive processes[5]. The emphasis in the neurophysiological model is on mechanistic learning rather than conscious cognition.

Jastreboff[6] proposed that the key element in TRT is the process of passive extinction. Extinction occurs when the neutral stimulus is presented without the provocative stimulus which breaks the association between the two. He also suggests that the provocative stimulus is removed by counselling the patient about the benign nature of their tinnitus, thus lowering the activation of the autonomic nervous system and decreasing the negative reinforcement of the stimulus and so reducing the strength of the conditioned reflex. Sound therapy with a white noise generator, the second component of the treatment, then reduces the signal to noise ratio, which reduces the perceived intensity of the tinnitus which leads to further reduction in the activation of the autonomic nervous system (ANS).

In a comparison of tinnitus retraining therapy and tinnitus masking[7], TRT with continued use over time (12-18

months), provided the greater long term improvement, while tinnitus masking provided the greater short term improvement (3 to 6 months).

A review of the evidence for tinnitus treatments[8] concluded that due to the low methodological qualities of the studies available on TRT, it is difficult to draw any firm conclusions about its effectiveness in the management of tinnitus. A further review[9] also concluded that as there has been no published study using a randomised group design, the effectiveness of TRT for the management of tinnitus awaits scientific corroboration.

Cognitive Behavioural Therapy [CBT]
Cognitive behavioural therapy is used to identify and alter negative behaviour and thought patterns. The focus of cognitive therapy is on the interpretation that people place upon events rather than the events themselves. If tinnitus per se caused psychological distress, then everyone experiencing tinnitus would experience similar psychological distress which is clearly untrue. Whereas some patients with tinnitus feel that it indicates the presence of a catastrophic illness, others interpret it as a feature of aging and some patients see their tinnitus in a more positive light. A study carried out in the Welsh Hearing Institute 10 on 121 patients with tinnitus and balance problems asked patients to list any positive experiences as a result of tinnitus, 41.3% of patients gave 98 positive responses, 37 gave no response and 34 listed only negative effects of tinnitus. Cognitive therapy seeks to address and change the negative distorted beliefs which surround tinnitus.

A study by Andersson[11] et al, conducted a randomised controlled trial of internet-based CBT on individuals with tinnitus for more than 6 months duration. Immediately following the randomised controlled phase, significantly more patients in the treatment group showed an improvement of at least 50% in the Tinnitus Reaction Questionnaire. At the uncontrolled follow-up, 27(31%) of all participants had achieved a clinically significant improvement.

Sound therapy

Masking devices
Masking devices were introduced because of the observation by patients that their tinnitus is more pronounced in quiet surroundings[12]. The volume on the initial masking devices were increased to the point where tinnitus was no longer audible. The results of outcome studies cast doubt on the benefits of asking[13]. Another study showed that masking in conjunction with psychological therapy resulted in greater benefit than psychological therapy alone[14]. Current masking devices are used to obscure rather than obliterate tinnitus. The obliteration of tinnitus is seen as being counterproductive in terms of the habituation process, as one cannot habituate to tinnitus which is not audible due to masking.

A systematic review of the evidence for tinnitus treatments by BMJ Clinical Evidence[8] concluded that tinnitus masking devices are of unknown effectiveness because of the very low-quality evidence.

Neuromonics
In neuromonics the patients works with an audiologist who matches the frequency spectrum of the tinnitus to music, which overlaps this sound spectrum. The music is designed to stimulate the auditory pathways deprived by hearing loss, the limbic system and the autonomic nervous system, thereby facilitating the desensitisation to tinnitus. A study[15] on 35 subjects with moderate to severe tinnitus showed that neuromonics tinnitus treatment provides rapid and profound improvements in the severity of tinnitus symptoms, with consequent improved quality of life.

Hearing Aids
Hearing aids are being increasingly used to treat tinnitus. Digital hearing aids appear to alleviate tinnitus more effectively than analogue aids as they can selectively amplify the high frequencies at which tinnitus usually occurs. Kochkin & Tyler[16], 2008 carried out a survey on 230 hearing care professionals in the America and found that 88% of the hearing care professionals used hearing aids to treat their patients' tinnitus They found that 60% of patients report some relief from their tinnitus when wearing hearing aids and 22% report major relief. Most people with tinnitus also have hearing loss. They concluded that hearing aids improve communication in addition to helping tinnitus.

Tinnitus Phase-out treatment
Tinnitus phase-out utilises the same concept as noise-cancelling headphones. This concept holds that every sound has an apposing sound which can completely neutralise it, this is known as phasing. Tinnitus phase-out treatments customises a treatment sound pattern to match the specific frequency and volume of a patient's tinnitus. The treatment is suitable for tonal tinnitus only.

A study of 35 patients with pure tone tinnitus, resistant to all previous treatments was carried out in Belgium[17]. They reported a significant tinnitus reduction was obtained in 60% of the patients after three in-office Tinnitus Phase-Out System therapy sessions. A study carried out in London[18] also reported a high success in that of 81 subjects with tinnitus, 70% of patients benefited from phase-out treatment.

Table 1: Hypnotherapy in the treatment of tinnitus				
Reference and location:	Number of subjects and type of intervention	Type of study	Outcome	Comments/Study weaknesses
Marks[21] 1985 UK	N =14 Active treatment: trance and use of imagery, Imagery related to the subjective nature of the subjects' tinnitus to cause the subjective appreciation of the volume of sound to diminish or (second active group) imagery using switches / switchboard sockets and subject operating switches/plugs until tinnitus noise altered Placebo: induction of hypnosis followed by ego strengthening	Randomised controlled, cross-over trial	5 of the 14 patients found the treatment beneficial in that they achieved a degree of relaxation although this did not alter the tinnitus, they found it made the noise more bearable. No improvement in tinnitus matching test or visual analogue scales apart from one patient.	No power calculation despite small number of patients. Heterogenous imagery with limited standardisation
Mason[22] 1994 UK	N = 86. 44 patients underwent hypnosis and 42 underwent counselling Given 3 sessions of client centred hypnosis or 1 counselling session. Assessed 1 week and 3 months after therapy	Randomised controlled trial	No difference between the 2 groups when matched for tinnitus loudness, tinnitus severity, linear analogue scales and need for further treatment. 20 of the 44 subjects reported a general sense of well being versus 6 in the counselling group	The quantity of counselling (one session) and hypnosis (3 sessions) input were different which may explain the difference in sense of well-being between cases and controls.

Alternative Treatments

Ginkgo biloba
Ginkgo refers to a tree originally found in China. High quality extracts from the leaves of the tree are used to make Ginkgo biloba which is used for the treatment of cerebral insufficiency, memory disturbance and tinnitus. A review of studies[19,20] on Ginkgo biloba for the treatment of tinnitus showed that, three studies showed no significant difference in outcome measures between the treated and placebo group. Three further studies showed a significant reduction in tinnitus intensity in the group treated with Ginkgo biloba.

Hypnosis
The goal of hypnotherapy is to gain self-control over behaviour, emotions or physiological processes. The conscious mind is subdued, allowing easier access to the subconscious mind which is more responsive to suggestion. In a study by Marks et al, 1985, 5 of the 14 patients found hypnotherapy beneficial in that they achieved relaxation which made the tinnitus more bearable, although there

was no alteration in the tinnitus[21]. A further study, by Mason and Rogerson[22], in 1994 showed that although there was little improvement in the symptom of tinnitus, 20 of the 44 subjects given hypnotherapy reported a general sense of well-being compared with 6 in the counselling group. The main benefit of hypnotherapy appears to be that it confers a sense of well-being and relaxation which makes the tinnitus more manageable. The results are summarised in Table 1.

Electromagnetic stimulation
A suppressive effect of electrical stimulation on tinnitus has been observed in patients with cochlear implants. Various studies[23,24] have found a suppressive effect on tinnitus using direct current stimulation of the cochlea. Stimulation of the round window membrane is the most effective, but suppression only lasts during current flow with only anodal stimulation being effective.

Other studies[25,26] showed no significant benefit from electromagnetic stimulation yet another study from Liverpool[27] showed a significant benefit from

Table 2: Electromagnetic stimulation in the treatment of tinnitus				
Reference and location:	Number of subjects and type of intervention	Type of study	Outcome	Comments/Study weaknesses
Roland[27] et al, 1993	N = 58 Electromagnetic monophasic pulses of a complex waveform, frequency 0.5 to 17 Hz, components and harmonics ranging up to 2.5 MHz, 15 minute daily sessions for one week	Double blind placebo controlled trial.	Active device produced significant improvement in symptom score and tinnitus matching 45% of patients versus 9% in the placebo group	Age range = 36 – 82 years No power calculation
Thedinger[25] et al, 1987 US	N = 30 16 Hz carrier tone, modulated by sweeping audio frequency signal (200 Hz to 20kHz) in 4 minute periods with an output of 1.77 volts rms and a current of 3 mA rms. Schedual: one hour the first day etc, up to 5 hours the fifth day. Treatment sequences separated by 2 days rest before cross-over, placebo: identical design, no emission of stimulus,	Single blind, randomised cross over trial	No significant reduction in subjective tinnitus severity	No documented statistical analysis Validation of symptom score used unclear
Fiedler[26] et al 1998 UK	N = 48 Electromagnetic monophasic pulses of a complex waveform, frequency 0.5 to 17 Hz, components and harmonics ranging up to 2.5 MHz, 15 minute daily session over one week	Double blind, randomised trial.	No significant difference in improvement of tinnitus or tinnitus sensation	Methodology incompletely described

electromagnetic stimulation with improvement in 45% of individuals treated with the active device compared with improvement in 9% of those treated with the inactive device (Table 2).

Transcranial Magnetic Stimulation [TMS]
Neurophysiological and neuroimaging data suggests that chronic tinnitus resembles neuropsychiatric syndromes characterised by focal brain activation. It has been speculated that tinnitus is an auditory phantom perception 28,and therefore resembles phantom limb pain with maladaptive cortical reorganisation occurring in response to a peripheral injury.

In a review on transcranial magnetic stimulation for the treatment of tinnitus 29 the authors concluded that the results of the various studies are highly encouraging,

stating that as low-frequency TMS has been effective in reducing cortical activity in other pathological conditions, a beneficial effect in tinnitus would be consistent with current medical knowledge. However, they concluded that further larger studies are required before conclusions can be drawn as to its benefits.

Ear-canal Magnets
These studies involved sandwiching a circular 1800 G samarium-cobalt magnet between two thin pieces of cotton and placement against the tympanic membrane. The initial study by Takeda 30 reported an improvement in 66% of ears with tinnitus in an uncontrolled prospective observational study on 50 patients. The only randomised controlled study in this area by Coles et al 31, failed to show any beneficial effects from ear-canal magnets (Table 3).

Table 3: Ear canal magnets in the treatment of tinnitus				
Reference and location:	**Number of subjects and type of intervention**	**Type of study**	**Outcome**	**Comments/Study weaknesses**
Coles[31] et al, 1991 UK	N = 50 2550 G neodymium-iron-boron magnets as the active magnets with the same material unmagnetised used as placebos for 4 weeks. These were inserted in the ear placed against the tympanic membrane	Double blind, placebo controlled crossover trial	No improvement in minimal loudness match and minimal masking level changes and subjective tinnitus severity assessments	No statistical analysis reported

Low-power laser

A low-power laser which has about one hundredth of the power of a surgical laser, has been reported to accelerate the healing of injured peripheral nerves and soft tissues and to reduce inflammation and pain[32]. The results of randomised, placebo controlled trials of low-power laser in the treatment of tinnitus failed to show any significant response in several separate studies[33,34]. A prospective randomised double-blind study by Gungor et al[36], 2008 showed that the loudness. duration and degree of annoyance of tinnitus was reduced in up to 48.8, 57.7 and 55.5% of patients in the active laser group (Table 4). Meanwhile, no significant difference was observed in the placebo laser group.

Acupuncture

Acupuncture is defined as the insertion of needles into the skin and underlying tissues in special sites, known as points, for therapeutic or preventive purposes. A study by Marks[36] et al.in 1984 showed no significant difference using objective tinnitus matching and visual analogue scales. However 5 out of 14 patients on active treatment showed subjective improvement as apposed to none out of 14 in the placebo group. Three further studies[37-39] showed no significant difference between the acupuncture and the placebo groups. Results of randomised placebo-controlled trials are summarised in Table 5.

Homeopathy

Homeopathic principles advocate the use of 'likes' to treat 'likes' on the basis that a substance that in large doses can provoke a symptom may be used in 'homeopathic' dose to stimulate a physiological reaction against the symptom, thereby relieving the condition. A study by Simpson[40], in 1998 on tinnitus loudness, awareness, annoyance and

Table 4: Low-power laser therapy in the treatment of tinnitus				
Reference and location:	**Number of subjects and type of intervention**	**Type of study**	**Outcome**	**Comments/Study weaknesses**
Gungor[35] et al, 2008	N=45 650 nm 5 mW laser, or placebo laser transmeatally for 15 minutes once daily for 1 week	prospective double blind randomised placebo controlled	Loudness, duration and degree of annoyance of tinnitus were improved in up to 48.8, 57.7 and 55.5 % of patients in the active laser group and no significant improvement in placebo group	
Teggi[34] et al, 2009	N=60 650-nm, 5-mW soft laser 20 minutes/day for 3 months Placebo subjects received a dummy device	Prospective double-blind randomised controlled	No significant difference between the 2 groups in the Tinnitus Handicap Inventory total score and visual analogue scale for self perceived loudness of tinnitus.	

Table 5: Acupuncture in the treatment of tinnitus				
Reference and location:	Number of subjects and type of intervention	Type of study	Outcome	Comments/Study weaknesses
Vilholm[39] et al, 1998. Denmark	N = 54 Acupuncture points selected SI19, G2, SJ17, SJ19, Du20, non specified variable distal points and methods of manipulation. 25 treatment sessions for 2 months distributed over 3 treatment periods of 10, 5 and 10 treatments separated by a pause of 1 and then 2 weeks, daily treatment duration 30 minutes, bilateral treatments given irrespective of whether unilateral or bilateral tinnitus placebo group; acupuncture by Japanese acupuncture needles at random non acupuncture sites	Double blind randomised placebo controlled	No statistically significant difference in the annoyance, loudness and awareness of the tinnitus between the groups	No documentation of distal points and methods of manipulation used Previous unsuccessful tinnitus treatments not documented
Hansen[37] et al., 1982. Denmark	N = 17 Acupuncture points used L2, K3, SJ17, SJ21, Gb2, SJ3. Unilateral, placebo acupuncture inserted in non-acupuncture points. 15 minute treatments over 15 weeks, twice weekly. 3 weeks of Chinese or placebo acupuncture followed by an interval of 3 weeks followed by crossover	Double blind randomised crossover placebo controlled	Period index calculated from days with less severe tinnitus, number of days with unchanged tinnitus and number of days with more severe tinnitus. No significant difference between acupuncture and placebo	Number of patients not based on sample size calculation Sensation of needles different in placebo group
Marks[36] et al., 1984.	n = 14 2 weeks of placebo or true acupuncture followed by 3 weeks of no treatment followed by 2 weeks of cross-over, Active acupuncture: electro-acupuncture with alternating low (6-10 Hz) and high (100 Hz) frequencies for 20 minutes. Placebo: non-penetrating acupuncture. Acupuncture points: Colon 4, 5, small intestine 4, 5, 19, kidney 6, pericardium 9, gallbladder11, 12, triple heater 17 and an auricular point for vertigo	Double blind randomised cross-over placebo controlled	Subjective improvement in 5 out of 14 patients on active treatment as opposed to none out of 14 in the placebo group. No significant difference using objective tinnitus matching tests and visual analogue scales. Authors conclude that a minor improvement may have occurred	Patients between 25 and 70 years of age. No power calculation despite small number of patients included in the trial.
Axelsson[38] et al., 1994. Sweden	N = 20 Acupuncture sites: Si17,Gb20, Sj19, Li4, Li2, K3, Sj3, for 30 minutes, Placebo: surface electrodes placed on the same regions as acupuncture needles and connected to a Chinese acupuncture electro stimulator. Treatment for 5 weeks, 3 times a week followed by a gap of 2 weeks followed by crossover for 5 weeks	Single blind randomised placebo controlled crossover trial	No significant difference was found in annoyance, awareness or loudness of the tinnitus	Placebo treatment not resembling acupuncture Number of subjects not justified by sample size calculation

Table 6: Homeopathy in the treatment of tinnituss				
Reference and location:	**Number of subjects and type of intervention**	**Type of study**	**Outcome**	**Comments/Study weaknesses**
Simpson[40] 1998 UK	N = 28 2 tinnitus tablets (sodium salicylate, ascaridole, conine, quinine at D60 homeopathic dilution once daily for 12 weeks, washout of 1 to 2 weeks and crossover	Double blind placebo controlled crossover trial	Annoyance, awareness, loudness and audiological measures (narrow band masking) did not show any differences between the groups	Exclusion of subjects below 15 and above 75 years of age Number of subjects not justified by sample size calculation

audiological measures (narrow band masking) showed no difference between the placebo group and those receiving the homeopathic preparation containing quinine, conine, sodium salicylate and ascaridole (Table 6).

Ultrasound

The concept of ultrasound as a treatment for tinnitus was discovered accidently in a patient who had ultrasonic investigation of his maxillary antrum. He claimed relief from his tinnitus during the procedure. Although the improvement was short-lived, it was repeatable[41]. A

further study by Rendell[42] et al, on 40 patients with tinnitus showed no significant difference in tinnitus loudness matching, rating scales analysis and verbal reports between the placebo group and the ultrasound treated group (Table 7).

Surgical Treatment of Tinnitus

Microvascular decompression

Microvascular decompression has been used in the treatment of trigeminal neuralgia with favourable clinical

Table 7: Ultrasound in the treatment of tinnitus				
Reference and location:	**Number of subjects and type of intervention**	**Type of study**	**Outcome**	**Comments/Study weaknesses**
Rendell[42] et al, 1987 Wales	N = 40 100 microsecond pulse of 500 kHz at a repetition rate of 355 Hz and a peak pressure of 57 kPa at one cm in water with a spatial peak temporal average of approx. 4 mWcm-2 Placebo: identical looking device without ultrasound emission.	Double blind randomised controlled trial	No significant difference in tinnitus loudness matching, rating scales analysis and verbal reports	Subjects with incomplete data collection were included in the study (rating scale analysis and verbal reports)
Carrick[41] et al, 1986 Wales	N = 40 Intervention: 100 microsecond wide signal at a Pulse repetition Frequency of 350 Hz for 10 minutes. This stimulates a piezo-electric crystal which emits a 100 microsecond pulse of 500 KHz ultrasound with a power output of 4 mW/cm2 (SPTA) at one cm in water Placebo: identical looking device without ultrasound emission.	Double blind, randomised controlled	Subjective feeling of improvement significantly more frequent in patients using the active device	Benefit only while wearing the device. No objective estimate of tinnitus severity obtained.

outcomes[43], although the value of this surgery has been debated. Similar techniques have been used in patients shown to have vascular compression of the eighth cranial nerve, who suffer unilateral tinnitus. Such studies have shown promising clinical outcomes[44] but remain controversial as the presence of a vascular loop in contact with the 8th nerve in cases of unilateral tinnitus is a common finding radiologically and can be as common in the asymptomatic side as the symptomatic[45,46]. The presence therefore of a vascular loop in unilateral tinnitus is in itself not indicative of causation. The challenge therefore remains to identify patients, if any, who may benefit from this invasive intracranial surgery, any effects of which may solely be related to the placebo effects of surgery and cognitive dissonance.

Stapes surgery
Tinnitus is a common symptom in patients with otosclerosis with the majority of patients complaining of some degree of tinnitus. Prevalence figures vary from reports with three large series indicating a prevalence of 65% - 85% in over 4000 cases[47,48], which appears consistent with other smaller series.

In the majority of cases surgery gives favourable results in those with tinnitus with improvement or abolition of tinnitus seen in 68-91%[49–51]. Worsening of tinnitus is reported in around 1-6% of cases with one study of principally larger fenestra technique indicating 11% of patients were worse[52]. In a number of studies no patient developed tinnitus as a result of surgery although this has been documented and is clearly a risk[53]. Although the risk of tinnitus developing or worsening as a result of surgery is small, the patient must be carefully counselled with respect to this as development of post-operative tinnitus or worsening of pre-existing tinnitus may be intractable and distressing.

Where surgery is successful in improving overall hearing, symptoms of tinnitus might reasonably be expected to improve, and has been confirmed[54]. However other reports have indicated that the success of surgery or otherwise is not a predictor of tinnitus symptoms, with some cases of poor audiometric outcome gaining benefit[55,56].

Other factors have been implicated in the successful amelioration of tinnitus symptoms but the findings of studies have not been consistent. Some studies have indicated that the outcome with small fenestra techniques is more favourable[49,56] while others have shown no consistent difference[51]. Pitch of tinnitus has been considered an important factor with low-pitched carrying good prognosis[57] but this has not been corroborated by other studies[56].

Cochlear Implantation
While variable outcomes with regards to tinnitus have been reported in patients undergoing cochlear implantation for severe-profound bilateral hearing loss, when cochlear implantation is performed for unilateral tinnitus associated with hearing loss, a substantial and sustained improvement in tinnitus is observed in the vast majority of cases[58]. Of 21 patients treated for severe intractable tinnitus, resistant to other forms of treatment undergoing cochlear implantation, 20 patients received substantial improvement in their symptoms with activation of the device. Cochlear implants have been shown to suppress tinnitus in up to 92% of patients[59,60]. This could be due to electrical stimulation of the auditory nerve or masking due to ambient sound.

Direct Brain Stimulation
In a group of seven patients implanted with thalamic deep brain stimulation systems for movement disorders who also suffered from tinnitus, three of this group reported reduction in the severity of the tinnitus with the device switched on and with some residual inhibition after the device was switched off[61].

In a further study of two patients suffering intractable tinnitus, an electrode was implanted intracerebrally. The procedure was different on the two patients, one of which was successful in producing sustained reduction of tinnitus to near elimination bilaterally. In this case the quadripolar electrode was advanced into the brain tissue in Heschl's gyrus for a distance of 3.2 cm, placed after mapping with functional magnetic resonance imaging (fMRI) and magnetoencephalography(MEG) using neuro-navigation. In the second patient only the fMRI tonotopic map was performed prior to inserting a bipolar electrode and in this patient a temporary reduction in tinnitus was achieved[62].

Conclusions
Although, a significant breakthrough in tinnitus treatment has not materialised as yet, significant progress has been made in recent years with ever more novel treatments being explored. Treatments which look promising include neuromonics which originated in Australia, repetitive transcranial magnetic stimulation (rTMS) and phase-shift treatment. Hearing aids are being increasingly used to treat tinnitus, with digital as apposed to analogue hearing aids being particularly useful in this regard, as they can selectively amplify the higher frequencies at which tinnitus usually occurs.

The oldest and most important treatment for tinnitus is the reassurance and support of an understanding clinician who is prepared to exclude any underlying serious pathology.

Drug treatments for tinnitus will be discussed in Part II of this article.

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Why do we follow up head and neck cancer patients?

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Abstract

Head and neck cancer following treatment commences at the time of discharge from hospital. The purpose of such follow-up has many aims, not only at the early detection of recurrent disease but the long term detection of a second primary cancer. In order to achieve these goals patients need to cooperate with members of the MDT, become educated in the symptoms and signs of likely recurrences and other cancers and get involved in cessation of smoking and alcohol abuse.

Much of the follow up currently is not necessarily for the detection and management of the tumour, but the assessment of functional, social and psychological effects on patients and their carers / families. Should this work remain the preserve of the clinical specialists or should other specialist members of the head and neck team become more involved in patient follow-up! Newer techniques at earlier diagnosis should be used to detect early cancer, before onset of symptoms, and should be used only on selected patients in whom curative treatment strategies can still be available.

Key Words

Head and neck cancer, follow-up patterns, recurrence, second primary cancers, QoL, co- morbidity, cessation of smoking and alcohol abuse.

Introduction

The term "head and neck cancer" usually refers to squamous cell carcinomas arising from the mucosal surface of the upper aerodigestive tract. These tumours make up greater than 95% of the cases of head and neck cancer. Within this article "head and neck cancer" refers to these cases unless otherwise stated. There are two options for treatment surgery or radiotherapy either alone or in combination with the addition of chemotherapy or a novel therapy when indicated. To the individual patient however the impact of this disease is enormous. Radical surgery and irradiation can leave the patient with permanent cosmetic deformities and functional deficits. This may result in social isolation and psychiatric illness. A previously employed person, as a consequence of the sequelae of treatment may never return to work[1].

Head and neck cancer is the sixth most common human malignancy. The geographical distribution of these cases is non-uniform, with areas of high incidence in China, the Indian subcontinent, and parts of Europe. The aetiology of head and neck cancer is strongly correlated with the intensity and duration of use tobacco and alcohol abuse. More recently younger patients who have never smoked nor indulged in alcohol abuse are presenting, and head and neck cancer is associated with the presence of the HPV 16 virus. Other causes in fewer cases are associated with exposure to environmental and therapeutic irradiation and others to exposure to industrial metals and chemical.

The prognosis of patients with head and neck cancer is intimately related to the stage of disease and its location. In general patients who present with stage I or II have a 60 – 95% survival rate. Advanced –stage lesions, stage III or IV have a much lower cure rates, approximately 10 – 50%. The presence of a metastatic cervical lymph node is said to decrease the cure rate by 50%, and the presence of more than one nodal group further decreases survival by another 50%. Recently use of concurrent chemotherapy has shown a survival advantage of more than 8% in 5 year survival than if irradiation is use alone[2]. Because of its aetiology there remains a risk of developing a second primary carcinoma in previously treated patients. The term "field cancerization" was proposed by Slaughter et al[3] because of the chronic exposure to environmental carcinogens in these patients, and as such, have an increased risk of developing another distinct squamous cell carcinoma for the remainder of their lives. The lifetime risk of developing a second primary is approximately 8% per year of survival, and with a higher risk seen in patients who continue to abuse alcohol and smoke cigarettes [4].

Dilemma after treating patients with a head and neck cancer is whether the resources of time, personnel and equipment put into follow-up clinics are best used for patients outcome, as there is little evidence that follow-up are effective on improving survival and there are financial implications of these long running weekly clinics[5]. Equally important is the care owed to patients who have often

significant therapeutic interventions, the ongoing responsibility to their physical and mental wellbeing and to support patients and their families.

Objective of Follow-up care:

The potential and theoretical goals for follow up care of head and neck cancer patients are several;

1. The early detection and treatment of the index tumour be it local regional or distant

2. The early detection of a second or metachronous primary cancer

3. The detection and treatment of functional disabilities relating to the primary treatment

4. Psychological and emotional support for patient and their carers

5. Aggressive counselling and treatment regarding the cessation of alcohol and tobacco use.

6. Evaluation of treatment results and endpoint reporting

7. Evaluation of patients satisfaction and treatment comparison by use of QoL data, ACE-21

8. Research – Tumour markers, genetic analysis, chemoprevention etc

9. Curiosity and availability for teaching purposes.

The process of "follow-up" commences at the time of discharge from hospital once treatment has been completed. The almost universal schedule[6] for follow-up is shown and generally is followed by clinicians for a period of up to 5 years[7-10] others recommend live-time "follow-up" for selected patients – salivary gland tumours etc [Table I]. Selected topics will be discussed further in this review article.

The early detection and treatment of the index tumour:

This schedule arose from the empirical observation that most tumour recurrences (80%) occurred in the first 3 years following completion of treatment. The search for recurrences of cancer at routine follow-up pre-supposes that new manifestations of the disease are more likely to be cured if detected at the earliest possible moment. This hypothesis has been investigated for cancer of the breast, colon, chest etc. But so far all of these studies have shown that regular follow up is of limited benefit in terms of increased survival.

Successful treatment of recurrences was almost only possible when detected locally only and more so for laryngeal cancer and some oral cavity cancers, initially

Table 1: Follow-up of patients with head and neck cancer following completion of treatment as practised in the U.K.					
	Year				
Office Visit	1	2	3	4	5
Clinical Examination / Nasendoscopy	12	6	4	2	1 -2
Radiological Imaging (CT, MRI, PET-CT)	1 – 2	1 – 2	1 – 2	1 – 2	1 – 2
Thyroid Function Tests	1 – 2	1	1	1	1
Other tests as indicated					

treated by radiotherapy or local excision (Excision using laser or partial laryngeal surgery), it has been estimated that up to 40% of primary tumour sites can be salvaged[11,12]. The results of secondary treatment of patients with local recurrences previously treated with radiotherapy and extensive surgery, as well as for regional and distant disease, is generally disappointing[13]. It has been suggested that follow-up of patients treated with combined surgery and radiotherapy should mainly be for care taking and support giving on an individual basis rather than within a strict regular follow-up scheme[14]. Reports suggest that currently most clinicians will follow-up all patients treated with a head and neck cancer irrespective of TNM stage[15,16].

Follow-up with the intention of detecting curable recurrences is thus only meaningful in patients for whom there remains curative treatment options remain. Some of the unsuccessfully treated recurrences may have gained some palliation, but to what extent this has increased the likely time of survival is usually unknown.

Methods of screening for recurrent disease has changed greatly over the past 20 years, from clinical examination, with an annual or biannual chest radiograph and thyroid function studies[17], to a recent survey suggests that the role of imaging has expanded to include computer tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET)[10].

There is debated the real need for clinical examination follow-up as a routine (physician based) as against patients symptom (patient based) precipitated clinical needs? Physician based or led clinical follow up has many attractions for patients treated; the significant reassurance and relief psychological distress when informed that they

are clinically disease-free and thus appropriately require and seek regular interaction with their physician[18]. These attendances at clinics are associated with significant direct and indirect cost both to the patient and to society. The treatment of head and neck cancers are becoming more concentrated in tertiary centres, many patients find themselves having to take time and make significant effort to travel distances resulting in disruption to themselves, family, friends and their employer.

A recent study suggests that head and neck patients reporting new symptoms or findings, almost 40% of these patients were diagnosed with recurrent cancer, as distinct to the findings of recurrent cancer in only 1.2% of those patients who reported no change or new symptoms. These findings suggest that in head and neck cancer patient when educated about significant development of new symptoms and possible signs may be a more useful component on early detection of recurrence or even new cancers as a component of all routine surveillance regimens[19]. In a study of laryngeal cancer treated curatively it has been recorded that to detect more recurrences at an asymptomatic stage, would require and enormous number of prescheduled visits would need to be added to the follow-up programme, due to the (estimated) short lead time[20]. It has been well documented that the persistence or recurrence of pain after treatment of a head and neck cancer can be an ominous symptom and must be addressed, investigated and appropriately treated[21,22].

Boysen[13] et al have calculated that the "recurrence pick-up rate" for a group of patients initially treated with combined irradiation and major surgery is in the order of 1: 250 consultations.

Therefore who should follow-up the treated head and neck patients? If a consultations are necessary for identification of index tumour recurrence, and the period of high risk is within 3 years, then the "other consultations" indicated for functional, social and psychological adjustments then the involvement of the "surgical and oncology teams" could be reduced, or substituted by alternative specialists. Such a formula could be the use of clinical nurse specialist (CNS) or even dietetics, speech and language therapists as well as psychologist! The prime use of such specialist persons, is to maintain open the lines of communication between the patient and the clinical team, should problems be identified or considered by the patient. This may avoid the patients waiting for their planned appointment, who in fact have symptoms and potentially may have a change in their disease status, and who's appointment can be expedited!

Early detection of metachronous or second primary cancer

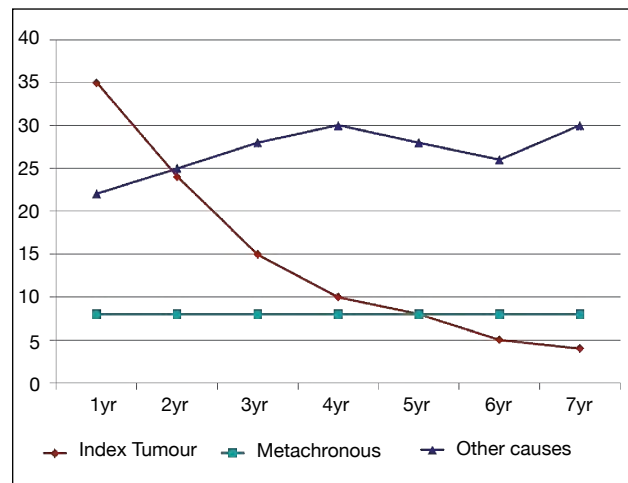Sadly while there have been improvements in locoregional

Figure 1: *Graph showing relative risk of death from index tumour, metachronous or second primary tumoue or other causes as a function of survival time following index tumour diagnosis.*

control of head and neck cancer over the past decades there does not appear to be any improvement in the final survival of these patients mainly due to the appearance [Figure 1] of disease progression, treatment sequelae, co-moridities, distant metastases, second primary cancer[23,24]. It has been recorded, in a multicentric study, that the prevalence of synchronous second neoplasm in patients with a head and neck index cancer is 6% [25]. The risk of a metachronous second primary cancer remains constant at an annual rate of approximately 6 – 9%[26]. Recent reports have confirmed that the risk of developing a second primary tumour is clearly correlated with tobacco and alcohol abuse, and is estimated to be double that as non-smokers[27]. In a case-control study it was identified that the odds ratio of a second primary cancer for patients who continued to smoke was 2.9 (95% confidence interval (CI): odds ratio (OR) 1.8 – 4.1) and for patients who continued to use alcohol was 5.2 (95% CI: OR 3.3 – 7.9). They concluded that persistent tobacco and alcohol could be responsible for one-third of second primaries[28].

Analysis of cancer-specific survival demonstrated that the majority of head and neck squamous cell carcinomas recurred within first 3 years after treatment of the index tumour, whereas the interval between the index tumour and the development of the second primary tumour was more than 4 years[26]. Patients who's index tumour relates to tobacco and alcohol use (oral cavity, oropharynx and larynx), 80% of the second primary was again found in the oral cavity, oropharynx and larynx. Second primary tumours have a tendency to follow either the respiratory axis (larynx – lung) or a digestive axis (pharynx – oesophagus)[23].

Therefore there is a rationale for screening for second

primary head and neck cancer patients. But currently patients with very advanced disease are currently treated by a combined chemoradiotherapy protocol who would otherwise have been deemed inoperable surgically as designated by their tumour stage, Stage IIIc disease, and some of these patients are cured by such treatments, thus making selection of any form of future cancer screening programme expensive and the likely possibility of subsequent curative treatment including surgery most unlikely.

Newer techniques have become available for the early detection of dysplasia and cancer of the head and neck, including the oesophagus, trachea and lungs. The use of fluorescence spectroscopy aims at high-lighting malignant tissue, especially when there is no evidence of any abnormality when viewed under white light and presents an objective picture which is reproducible and suitable for elective analysis. Two recent studies, larynx and oral cavity, using high-definition television and narrow band imaging, have demonstrated that this technology is significantly accurate in recognising true positives and distinguishing at the same time, the true negatives[29,30]. A suggested "ideal surveillance protocol" has been proposed[31].

Cessation of alcohol and smoking abuse
As described above the association of smoking and alcohol abuse is uncontroversial with the aetiology in head and neck squamous cell carcinoma, and cessation of these habits protect against the development and can even reverse further risk of developing further cancers[32]. There is evidence that cessation of smoking may be improved by clinic-based, nurse administered interventions. Moreover by treating comorbid depression and alcohol, both known to exacerbate smoking, may improve cessation rates[33]. There is an strong interrelationship between smoking, alcohol use and depression and frequently encountered in patients with head and neck cancers, and strategies at treatment of these disorders should encompassed targeted therapy combined rather than individually as failure at achieving satisfactory outcomes will be more likely.

Psychological support for patients and careers
Patients report that their priorities of their desired treatment of a head and neck cancer, their three most frequently ranked items were "being cured of cancer", living as long as possible" and "having no pain"[34]. This "fear of recurrence" which has been ignored is currently being researched[35,36]. The ability to involve patients in their own care has been advanced by the development and piloting of a "Patient Concerns Inventory" (PCI) which helps to reveal patients concerns in advance of their consultation at a follow-up head and neck clinic[37]. A review of the psychological needs of the not only the patients, but their careers as well as the clinical staff, highlights the need for a professional psychologist to be a core member of head and neck cancer MDT[38].

Patient's evaluation of treatment – QoL and ACE 21
Routine use of QoL measures in the clinical setting continues to be questioned, presumably because functional outcome and symptom scores do not correlate with QoL[39]. However, patient surveys suggest that at least patients find it useful as an aide-memoire prior to their consultation[40]. Even so, most research funding bodies require – and professional bodies such as the British Association of Head & Neck Oncologists (BAHNO) recommend – that a quality of life component be included in the dataset for head and neck cancer.

The term comorbidity refers to disease processes that coexist and are not related to the index disease being studied. Patients with head and neck cancer (HNC) often have a history of tobacco and alcohol abuse, which increases the incidence of comorbid ailments. Several instruments have been used to assess, quantify and grade the degree of comorbid burden using ordinal scales. Most indices have been exclusively developed for the purpose of grading the comorbid burden, such as the Adult Comorbidity Evaluation 27 (ACE 27), Charlson Index (CI), and Cumulative Illness Rating Scale. The ACE 27, as its name suggests, has 27 different elements that need to be assessed to grade comorbidity. This index, derived from the original Kaplan-Feinstein index (KFI) which was developed for assessing comorbidity in diabetes mellitus, has subsequently been modified and validated to include items relevant to cancer. There has been considerable world-wide experience with this index, and it has been extensively validated in head and neck cancer for the purpose of predicting survival, complications, functional outcome and quality of life[41 - 43]. ACE 27 has been shown to be especially predictive of survival in the elderly. Drawbacks include difficulty in grading some items, especially those that need a laboratory or invasive confirmation (e.g, evaluation of the respiratory system includes pulmonary function testing and blood gases) or those that require a specialist evaluation (e.g., neurology consult if dementia is suspected). Comparing treatment results between centers and population based epidemiological studies will need to take comorbidity into consideration. Most clinicians would recognize that comorbidity plays a subtle yet important role in treatment selection, but this has been difficult to categorize. Unless rigorous prospective data collection is performed, augmented by robust analysis, it will be difficult to generate conclusions that can be widely accepted. Apparent improvements in treatment outcome following newer

therapeutic modalities will have to take into account any changes in the comorbidity type and burden over time. The presence of accurate comorbid information will also improve the conduct of and generalization of results from clinical trials [44].

Summary:

Head and neck cancer patients necessitate follow-up for many reasons, not only to evaluate treatment given, function, mental health, and evidence of cure, but also to detect early recurrence cancer (80% within 3 years) but to also to detect early second primary cancer (risk 6 – 9% per year of survival). Other reasons include rehabilitation of physical and psychological life, as well as making efforts to modify their life-style by embarking on a cessation programme of smoking and alcohol abuse. Newer method for patient evaluation, have been developed, including radiological imaging and narrow band imaging using fluorescence spectrometry to detect early pre-malignant mucosal disease before symptoms have developed. Is it possible to separate patients who are more likely "cured" than those who "are likely to die of their disease" as the work load increases exponentially on an annual basis? However, it is important that the correct patients are appropriately selected for further investigation and screening of a second primary cancer, those who have a curative treatments available and are likely willing to be further treated should their second cancer be treatable.

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The Effects of Stored blood transfusion components in Head & Neck Squamous Cell Cancer

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Background

The recognition that blood transfusion carried the risk of infection forced a re-evaluation of the indications for transfusion. A link between perioperative blood transfusion and worsened cancer prognosis was first proposed by Francis, since then it has been established in colorectal, cervical, breast and prostatic carcinoma. This effect has now been purported to occur in head & neck squamous cell carcinoma following blood transfusion.

Discussion

The data presented in this article appears to show a direct effect on tumour growth by exposure to extracellular accumulated bioactive substances leached from blood products. In addition more mediators are released as blood products age. Also, there appears to be an optimal total blood product transfusion (less than 3 units) before the adverse sequelae of the accumulated leached growth factors become clinically evident. Simple washing of transfusion products would significantly reduce this accumulation, as would the use of blood stored for shorter time lengths (2 weeks old).

Key words

Blood transfusion, Head & Neck Cancer, Prognosis, Vascular Endothelial Growth Factor, Vascular Mimicry.

Introduction

The perception of blood transfusion in the perioperative setting has changed from a benign intervention, occasionally life saving, to an outcome to be avoided 1. The recognition in the mid 1980's that blood transfusion carried the risk of infection forced a re-evaluation of the indications for transfusion[2] [Table 1]. In the area of England & North Wales covered by the National Blood Service (NBS) during 1996/97, approximately 1,907,000 donors donated 2,215,000 units of usable blood [Table 2][3-5]

The present day rationale for blood transfusion is rooted in the physiology of oxygen delivery. Since the oxygen requirements of tissues is increased during acute stress, it is tenable that maintaining adequate oxygen delivery will result in improved clinical outcomes[6] . Oxygen is also fundamental to the efficacy of radiotherapy. Due consideration must also be given to the cellular microenvironment and the cell's response to hypoxia and altered resistance to chemotherapeutic insult[7].

Current indications for blood transfusions (transfusion triggers)

The decision to transfuse must balance the known risks of transfusion with the need to provide adequate tissue oxygenation [Table 2]. The trigger for this decision is not defined.

Numerical triggers

The basis of the '10/30' rule of when to transfuse represents the popular notion that patients were considered optimally treated, if their haemoglobin level and haematocrit remained above 10g/dL and 30%, respectively.

Table 1: Showing the Indications for red cell transfusion in the UK		
	No (% of all transfused) of units (n=9774)	Mean (SD) age (years) of recipients*
Medicine:		
All uses	5047 (51.6)	64.6 (19.7)
Anaemia	2269 (23.2)	67.1 (17.1)
Haematology	1514 (15.5)	61.2 (20.5)
Gastrointestinal bleed	1054 (10.8)	69.2 (15.5)
Other	148 (1.5)	55.5 (23.0)
Neonatal top up/ exchange transfusion	62 (0.6)	0
Surgery	3982 (40.7)	64.1 (18.2)
Obstetrics and gynaecology:		
All uses	612 (6.3)	38.7 (18.0)
Gynaecology	307 (3.1)	47.7 (19.5)
Obstetrics	305 (3.1)	29.7 (10.5)
No clinical details	133 (1.4, 1.1 to 1.6)	60.5 (20.14)
*Modified from Wells et al (2002)		67.2 (20.1) all transfusions

The first published reference to the "10/30" rule was by Adams and Lundy (Mayo clinic) based on clinical 8 and animal experimental evidence[9-12]. This was supported by the WHO criteria of anaemia [Table 3].

As the oxygen requirements by tissues increase during acute stress, it seems reasonable that maintaining adequate oxygen delivery may result in improved clinical outcome.

Table 2: Showing a pie chart of blood usage in the UK[4]	
General Surgery	22%
General Medical	15%
Cardiothoracic	13%
Orthopaedics	11%
Haematology	9%
A&E	8%
Renal	6%
Paediatrics	6%
ITU	4%
O&G	4%
Other	2%

Table 3: WHO Grading systems for anaemia[75]	
Severity	World Health Organisation
Grade 0 (WNL)	11.0 g/dL
Grade 1 (mild)	9.5 to 10.9 g/dL
Grade 2 (moderate)	8.0 to 9.4 g/dL
Grade 3 (serious/severe)	6.5 to 7.9 g/dL
Grade 4 (life-threatening)≥	< 6.5 g/dL

Unfortunately, the benefits of supra-normal oxygenation are not borne out by randomised controlled trials of isovolemic haemodilution to a haemoglobin of 5g/dL or less does not result in biochemical evidence of anaerobic metabolism[13]. Jehovah's Witnesses who have experienced major bleeding confirm the ability to tolerate haemoglobin levels well below those conventionally accepted by physicians[14,15] if their intravascular volume were kept normal 16. Despite these observations, the '10/30' rule is still considered the standard of care.

The growing concern over 'blood borne' viral and prion transmission has led to a reconsideration of the indications for transfusions with an ultimate conclusion that an absolute number (either haematocrit or haemoglobin level) is insufficient for the purpose of justifying blood transfusions in all patients. Hence other triggers to the decision to transfuse were explored.

Symptom triggers
Relying on just signs or symptoms alone to guide transfusion may result in under-transfusion in some cases. Studies have shown that exertional dyspnoea does not occur until haemoglobin concentration falls below <7g/dL [17], whilst it was also found that at levels of <6g/dL only 54% of patients experienced tachycardia, 32% hypotension, 35% impaired consciousness and only 27% had dyspnoea[18]. The levels of anaemia have to be even more severe to produce symptoms in children because of their compensatory mechanisms.

Physiological triggers
In-vitro normovolaemic animal studies suggested a minimal haemoglobin level is about 3-5g/dL 19,20. However cardio-respiratory disease prevents compensation to severe anaemia, suggesting that the impact of a given degree of anaemia is unique to each patient. Use is commended of the revised triggers of 5-6g/dL for well compensated patients without heart disease; 8g/dL for patients with stable coronary artery disease with less than 300mL blood loss anticipated and 10g/dL for older patients and those with postoperative complications who cannot increase cardiac output.

Restrictive transfusion policies

The risk: benefit calculation is fundamental to the recent shift in thinking from the static numerical triggers to transfusion; to now regarding the transfusion trigger as dynamic and physiologically patient dependent.

A multicenter randomized controlled clinical trial in Canada demonstrated a successful restrictive strategy of blood transfusion in which patients were transfused only for a haemoglobin level of less than 7g/dL. This was found to be as effective as and possibly even superior to a liberal transfusion strategy in critically ill patients[21]. If these data are examined in the context that a threshold amount of blood needs to be transfused to impact outcomes, it becomes even more important to limit transfusion to only the amount that is essential[22].

Restrictive transfusion policies have also been successfully applied to head & neck cancer patients. In a retrospective study of 124 patients (age 48±18 years, ASA classes I-III) underwent major maxillofacial surgery in a university hospital (68% tumour surgery). Acute normovolemic hemodilution was suggested to be a practical, safe and economic blood conservation technique that allowed for the complete avoidance of allogeneic RBC transfusion in 89% of the patients undergoing surgery[23].

Known complications of blood product transfusion [Table 4].

Transfusion is in essence a transplant of allogenic cells and its risks are not negligible. Allogeneic blood transfusion is the most frequent allo-transplantation procedure performed on a routine basis with no prior HLA-typing[24]. The potential for transmission of unidentified infections is unknown. Transfusion is also known to be immunosuppressive, and is an independent risk factor for nosocomial infection and the recurrence of malignancy[25].

The blood transfusion in cancer patients [Table 5]

The factors that worsen cancer prognosis are tumour growth and spread. If these are facilitated in some way by transfusion, the overall prognosis would decline. Recent experimental observations tend to support this effect (Fig 1). Such facilitation may be active (i.e. a direct effect) or passive (i.e. an indirect immuno-depressive effect). Literature and previous research has traditionally focussed upon the latter passive effect, regarding a blood transfusion as simply a means of delivering oxygen carrying capacity and volume expansion with little regard either to the other cells and components also transfused within the red blood cells or even the non-haemoglobin contents of the red cells themselves.

Table 4: Some of the risks of transfusion[43]
Febrile non-haemolytic
Acute transfusion reaction from mismatch
Acute haemolytic
Delayed haemolytic
Allergic
– Anaphylactic
– Human leukocyte antigen sensitization
– Red blood cell allo-sensitization
– Graft-versus-host-disease
Clotting disturbances
Electrolyte disturbances
Volume overload in the young and elderly
Transfusion-related acute lung injury
Peri-operative infection susceptibility
Blood borne infections-viral (HIV, Hepatitis B & C, HTLV-1 and 2, West Nile Virus, CMV), bacterial prions (variant Creutzfeldt-Jakob Disease), parasites (malaria, Chagas Disease)
Increased tumour recurrence from perioperative transfusion
Worsened cancer prognosis from perioperative transfusion

A link between perioperative blood transfusion and worsened cancer prognosis was first proposed by Francis in the Lancet[26] based on animal studies. Since then it has been established in colorectal, cervical, breast and prostate cancer[27].

| Table 5: showing why the Cancer Patient May Need a Blood Transfusion[43] |
| --- |
| Bone marrow replacement by primary tumour (i.e. leukaemia) |
| Bone marrow involvement by metastatic tumour (i.e. breast, prostate) |
| Bone marrow reaction (i.e. fibrosis) |
| Myelosuppression by chemotherapy or radiotherapy |
| Peripheral destruction (i.e. immune haemolysis, disseminated intravascular coagulation, splenomegaly) |
| Derangement of normal physiology |
| Nutritional deficiency (i.e. folate, Fe2+, negative N2 balance) |
| Abnormal feedback (i.e. stimulation/inhibition of haematopoiesis) |
| Blood loss—surgery/erosion of great vessel by disease or its treatment |
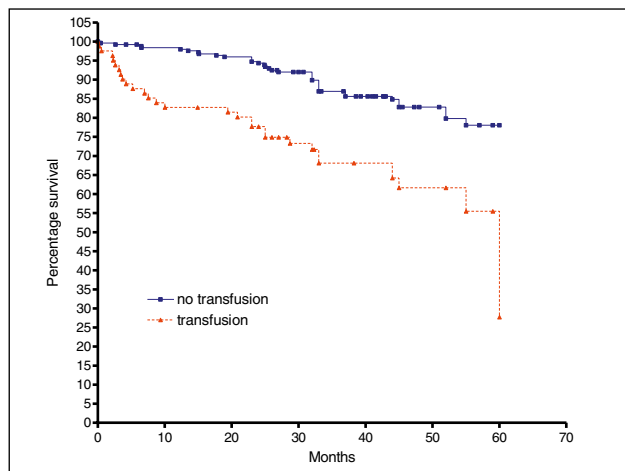
Figure 1: *A 10 year retrospective review of notes was undertaken at the University College Hospital Head & Neck Unit showing a deleterious effect of perioperative transfusion of leukocyte depleted packed cells on survival in a cohort of 334 patients with squamous cell carcinoma of the head and neck requiring ablative resection when followed up for 5 years (p<0.001). A common criticism of previous studies is their inadequate controls for confounding factors such as the (pre-morbid) medical state of the patient.The preoperative co-morbidity index (Charlson score) was not associated with the need for transfusion (p>0.05).*

The adverse oncological effects of transfusion in head and neck cancer

The contrasting conclusions drawn from a number of retrospective analyses with different methodologies

Table 6: Showing the weaknesses of previous studies[43]
Many studies did not document the amount of transfusion
Many studies did not reveal the timing of the perioperative transfusion
Many studies did not indicate the nature of the transfusion product
Investigators used differing leuco-depletion protocols whilst some used whole blood
Researchers followed up patients for differing lengths
Experimenters used heterogeneous tumour groups
Studies had a poorly matched control group
Studies were retrospective
The patient numbers were small
They had the erroneous conclusion that if the effect was not found in one tumour that this conclusion was valid for other tumour groups
Detailed scrutiny of both supportive and negative studies suggests several underling weaknesses including the lack of prospective data and the absence of hypothesis driven data analysis.

created a landscape that is difficult to interpret. Some preliminary studies have occurred in head and neck but the results from these were conflicting due mainly to the lack of consideration to confounding factors [Table 6]. Due to the scope of head and neck cancer resection, the need for blood transfusion cannot be eliminated.

There is growing evidence of the deleterious effects of perioperative transfusion in head & neck cancer patients (p<0.001)[28,29,30]. The studies which show a deleterious effect of blood product transfusion tend to be disease specific and centred upon squamous cell carcinoma and later stage disease[31,32,33,34]. It may be that their poor selections of controls did not account for confounding factors that would otherwise not allow a significance to become apparent.

Possible mechanisms of worsened prognosis of perioperative blood transfusions

The adverse effect of perioperative transfusion is traditionally accounted for by two explanations, that either:-

A) The patients are severely compromised anyway, and that the group is self selected because only the more prognostically challenged patients are likely to require a transfusion.

This is supported from studies upon cancer of the colon, rectum, cervix and prostate, Blumberg concluded that transfusion of whole blood may represent a surrogate marker for advanced or more aggressive clinical disease[35-37].

B) The Transfusion has an immune modulating effect (similar to a graft versus host effect) allowing the tumour to escape host immuno-surveillance.

The first link between transfusion and reduced immunity was proposed by Fischer, since this may also have had an effect upon immuo-surveillance[38]. Blumberg showed that homologous transfusion causes a significant down regulation of immunological function including host defences against malignancy and infection[36, 39]. This immune dys-regulation caused by transfusion is augmented by the effects of haemorrhage, anaesthesia, and surgical stress combine to create an adverse overall effect[40,41]. However the relationship between solid tumour development and the immune system is inconclusive.

It has recently been hypothesised that stored blood may be prognostically deleterious by a 'direct effect' on tumour cells independent of its immuno-modulating effects[42,43] (Fig 1,2).
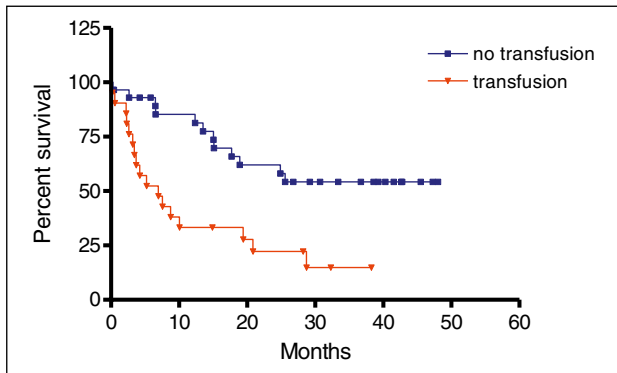
Figure 2: *A 5 year prospective review undertaken at the University College Hospital Head & Neck Unit showing a deleterious effect of perioperative transfusion of leukocyte depleted packed cells on survival in a cohort of 50 patients treated for head and neck squamous cell cancer. Perioperative blood transfusion were found to significantly worsen survival (Kaplan Meir analysis Log Rank Test Chi 2 p<0.005). The preoperative co-morbidity index (Charlson score) was not associated with the need for transfusion (p>0.05).*

Number of units transfused

It has been realised that one unit or more of whole blood perioperative transfusion has universally poor outcomes compared with non-transfused patients (p<0.001). Red blood cell transfusion has progressively worse recurrence and death rates with increasing numbers of transfusion products suggesting a dose effect relationship. Proportional hazard risk analysis showed that transfusion of any whole blood or more than three units of red blood cells was significantly associated with earlier recurrence and death due to cancer[44] (Fig 3) ($\leq$2 units vs > or $\geq$3 units, p<0.0001)[45,46,47]. The effects on recurrence were cumulative[37].

When tumour cell lines are grown in vitro the usual immuno-modulation explanation is to an extent abrogated.
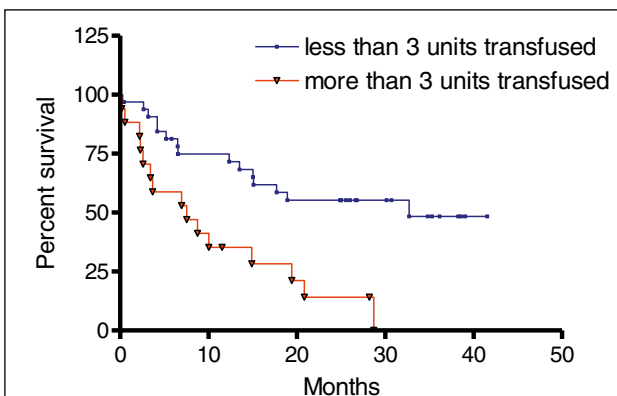
Figure 3: *Showing the negative effect of the perioperative transfusion of 3 or more units of blood in patients with squamous cell carcinoma prospectively followed up for 5 years. the Kaplan Meir curve showed a significantly deleterious effect of peri-operatively receiving 3 units of more of leukocyte depleted packed red blood cell transfusions (Kaplan Meir analysis Log Rank Test Chi 2 p =0.0007 Hazard Ratio 0.3147) in 50 patients with squamous cell carcinoma of the head & neck).*
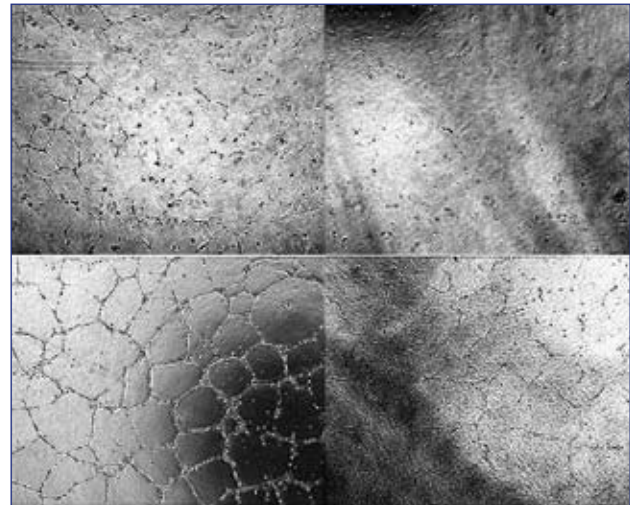

Figure 4: *Showing the effect of the addition of blood product supernatant upon the growth of an endothelial cell line (HUVEC). A, top left represents a control group; B, top right represents the control group with the addition of anti-endothelial growth factor antibody; C, bottom left represents the effect of incubation with blood product supernatant; D , bottom left, represents the effect on HUVEC growth in media supplemented with blood product supernatant pre-incubated with anti endothelial growth factor. This is representative of the direct effects of blood product supernatant upon the cell lines studied. The effect of anti-endothelial growth factor antibodies is similar, i.e. in reducing vascular channel formation. The antibody did not directly reduce growth in the cell line, however there was a significant reduction (Chi squared test _2 p<0.001) in cell line growth caused by transfusion products pre-incubation with anti-endothelial growth factor antibody. There was a significant statistical difference between groups represented by 'A, C and D', but not between groups 'A and B' suggesting there is a direct effect of supplementation with blood product supernatant which is abrogated by the use of anti-endothelial growth factor antibody but no cytotoxic effect of the antibody per-se on the cell lines.*

With the use of supernatant from Group O Rhesus negative blood product on cell lines grown on collagen matrices to determine the direct growth effects of the leached/ accumulated mediators. Other purified blood products such as white blood cells and platelets contain a greater quantity of a range of additional growth and immunological mediators which cause further uncontrolled tumour growth[48,49]. The growth of head & neck squamous cell lines after transfusion is analogous to vacular cell line growth[7,50,51]. The ability of tumours to express vascular mimicry is variable[52] but in general tends to be greater in those tumours whose prognosis is worsened by perioperative transfusion[53].

Direct exposure to transfusion products exaggerates the growth effect. The supernatant of stored blood transfusion products causes increases growth in both control vascular and tumour cell line (χ2, p<0.001) (Fig 4). Cell line migration and invasion was also significantly increased (p<0.001) with increasing age of blood product supernatant (Fig 5).
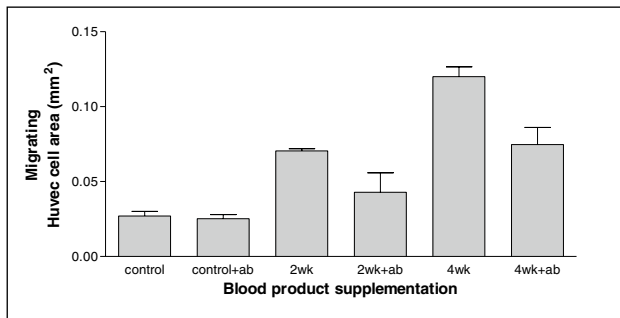
Figure 5: *Showing the stimulatory effects of aging blood product upon the migratory ability of HUVEC cells. The other cell lines studied showed similar trends and statistical differences. The effects upon invasion were similar but appeared in part to reflect the cell size. Leached factors from stored blood products have a significant direct growth effect on the cell lines studied. There is a statistically significant difference (p<0.01) between the growth effects of control, 2 week and 4 week old blood product supplementation as well as the effect of the antibody (p<0.01). This suggests that there is a direct 'growth and vascular mimicry promotion' effect of supplementation with blood product supernatant which is abrogated by the use of anti-endothelial growth factor antibody but no cytotoxic effect of the antibody per-se on the cell lines. This was confirmed by separate growth assay.*

The 'red cell lesion', of ATP depletion and cell membrane dysfunction with age related fragility, has been known for some time[54]. It is also believed that as result of normal physiological aging and metabolic processes with depletion of ATP and reduction of active membrane processes[55], there is leaching of biologically active substances from the cells into stored blood. These leached bioactive substances may have immunomodulatory effects, which may in part explain the increased likelihood of postoperative sepsis and adult respiratory distress syndrome in transfusion recipients[43,56-59]. Given the above, the extra-cellular accumulation of bioactive factors in blood transfusion products could directly cause tumour growth and hence a worsening of prognosis[56-61,62]. Furthermore, one of the main protagonists for this effect may be the VEGF family

which are concerned with neo-angiogensesis, neo-lymphangiogenesis, and direct tumour growth[42,43]. Mynster et al showed that stored blood may have a sVEGF A165 of 97pg/mL which is sufficient to cause angiogenesis[63-66]. There appears a time dependent leaching of VEGF into the supernatant of stored packed cells. (Fig 6). This doesn't exclude the leaching of other growth factors not assayed and which may have an effect. Extrapolating from the results of VEGF levels it may be that a transfusion of 3 or more units is enough to tip the angiogenic balance of residual tumour tissue to promote recurrence and worsen overall prognosis.

Cell contamination

A unit of red cells contains least 106 to 107 white blood cells, monocytes, neutrophils and platelets, some of which contain high concentrations of physiologically and biologically active substances including growth factors[5,42,43,48,49,67-70]. Leaching from these contaminants can cause an acceleration of tumors growth and spread[48,49,67]. Storage of RBCs leads to membrane and metabolic changes[71]. The presence of leukocytes in blood components reduces glucose availability, and leukocyte lysis leads to release of cytokines that reduce overall RBC survival[72], causing release of their bioactive mediators, such as VEGF[43].

This rationale explains the conflicting findings of research to date in this area[53,64] [Table 7]. That red cells should store endothelial reparative growth factors would seem logical, as would the release of any factors as the metabolic processes of the anucleate red cell decline over time. The perioperative status of the cancer may be associated with inflammatory release of factors which may stimulate residual viable tumour cells before or during scar or wound healing ischaemia[73]. These active tumour cells
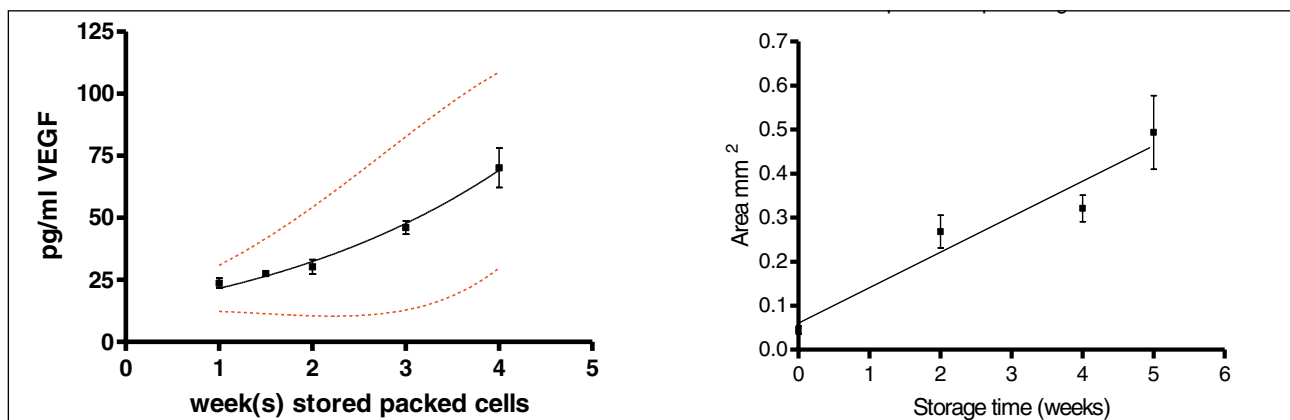

Figure 6: *(Left) Showing the leaching of VEGF A165 from stored packed cells over time. Leaching is significantly correlated to length of storage (weeks) with a non-linear curve fit with approximation to the Gaussian distribution $y=(area/stdv.*(2\pi)1/2)e(-1/2*(X-\mu)/stdv.)2)$ with 95% confidence intervals, (r2= 0.9377, p< 0.001). (Right) showing the in vitro grow stimulatory effects of blood product supernatant stored for increasing periods of time upon HUVEC cells. The curve show a significant correlation of growth with age of blood product used p<0.001.*

Table 7: Showing the deleterious effect of inadvertent white cell transfusion[43]
Definitive
Non-hemolytic febrile transfusion reactions
Transmission of leukocyte-associated viruses
Cytomegalovirus, Epstein-Barr virus, human T cell leukaemia virus type 1
Allo-immunization
Likely
Immuno-modulatory effects
Cancer recurrence
Postoperative infections
Theoretical
Reperfusion injury
Transfusion storage time for red blood cells and platelets
Transfusion-related acute lung injury
Transfusion-associated graft-versus-host disease

(with autocrine or paracrine stimulation[43]) having increased receptors numbers in response, for example, to hypoxia or changed cytoskeleton attachments are then further

Table 8: Shows the suggested changes in practice to ameliorate the deleterious effects of transfusion[43]
Use of revised physiologically based transfusion triggers for peri-operative transfusion.
Use of perfectly matched or autologous blood with
minimal mechanical disruption of the blood
Use of efficient leuko-depletion
Use of antibody filters for white cells, platelets or deleterious growth factors.
Use of washed cells
Use of younger blood (<2 weeks) if possible stored for the minimum amount of time
Use of less units of blood(<3 units)
Use of synthetic blood products
Use of marrow stimulators eg, recombinant erythropoietin (caution in giving cell growth stimulators to cancer patients)
Use of nutritional supplements
Use of surgical technique with an emphasis on haemostasis and atraumatic tumour removal with negative margins
Use of haemodilution to combat haemovolemic insult
Avoid platelet transfusions

stimulated by large amounts of exogenous growth factors delivered through transfusion.

Conclusions

Avoidance of blood transfusions by meticulous technique and haemostasis, along with the use of plasma expansion and oxygenation strategies may benefit patient outcome. Alternatives to the antiquitidated "10/30" transfusion trigger should be sought including the use of synthetic blood analogues and recombinant erythropoietin. If transfusion is inevitable then the minimal necessary amount, to alleviate symptoms with due consideration to the patients pre-morbid cardio-respiratory status, should be given. The use of specific anti-endothelial growth factor antibody filters before transfusion may be suggested, although simple red cell washing before transfusion may be simpler and more cost effective. The easiest solution may be the use of fresher blood stored for the minimal amount of time [Table 8][74].

Future studies

The only available mechanism available to develop data that will unequivocally settle this issue of the deleterious effects of blood transfusion is a randomised controlled trial in which different cohorts of patients receive blood transfusions of different storage durations and some do not.

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Nerve Monitoring in Otolaryngology

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Introduction

Loss of cranial nerve function has a significant, adverse, effect on the quality of life of a patient. An avoidable or unnecessary facial palsy, husky voice or swallowing problems caused by vagal or recurrent laryngeal nerve palsy can be equally devastating for the patient and their surgeon. The only difference is that the patient has to live with it. Intra-operative cranial nerve monitoring was introduced into skull base surgery over 30 years ago and has been accepted as the standard of care for vestibular schwannoma surgery[1]. The same cannot be said for head and neck surgery or indeed routine otology where the risks of permanent damage to the facial, vagus and recurrent laryngeal nerves are significant and ever present. Those committed to modern intra-operative monitoring find it hard to understand why it has yet to gain universal acceptance.

Surgeons have used electrical and mechanical stimulation of nerves during surgery to aid their dissections for many years. They relied on crude stimulating devices and visible or palpable muscular responses. In other words, these techniques were not particularly specific or sensitive and in some circumstances downright traumatic. Modern devices monitor surgically and electrically evoked responses in muscles supplied by the cranial nerve in question. They are extremely sensitive, more specific and, if used properly, not at all traumatic. Today's monitors all work on the same basic principal, they amplify electromyographic responses picked up by needle or surface electrodes and transform them into an auditory signal. By this means, irritation or early damage to a motor nerve can be detected without any visible movement of the muscle it supplies. Like neural stimulators of the past, modern devices can be used to locate nerves that are not immediately apparent within the operative field, but they do so in a far more precise and accurate fashion. Better still, intra-operative monitoring aids atraumatic dissection and helps preserve function.

Monitoring Techniques

A number of monitoring devices are currently marketed worldwide. These include the NIM-Response Nerve Integrity Monitor (NIM-2; Medtronic Xomed, Jacksonville, Fla), the Neurosign series of monitors (Magstim Co., Ltd, Whitland, South West Wales, UK), and the Viking II–EMG System (Nicolet Biomedical, Madison, Wn). Their design follows a standard pattern. Each contains a variable current stimulator and a receiver that consists of EMG needle electrodes, amplifiers and loud speaker circuitry.

Stimulation

Muscle responses can be evoked by electrical and mechanical neural stimulation. The strength and frequency of the stimulating current is critical. A nerve covered by a layer of bone or embedded in dense scar tissue may require a stimulation current of 5mA to evoke a response, while an exposed nerve in the neck requires far less, perhaps just 1-2mA. In the cerebello-pontine angle, where the facial nerve is covered by a glial coat, just 0.05mA is required to evoke a strong response. Over stimulation has the potential to cause neural damage in just the same way as rough handling of the nerve by the surgeon and should be avoided. In some devices there is the option to vary the frequency of the stimulating current. For a completely unparalysed patient, a stimulating current set at 30Hz frequency is appropriate, while 3Hz frequency stimulation will be sufficient for a patient with a partial muscle blockade.

Mechanical neural stimulation can be evoked by the surgical irritation of dissection. Audible responses can even be elicited by irrigation of the wound and often suggest that the irrigating fluid is either too hot or too cold. Simple changes in dissection technique, for example, avoiding tension or stretching, minimises or avoids iatrogenic trauma that should translate into better post-operative function.

Figure 1A: *Bipolar stimulating forceps used in a parotidectom*
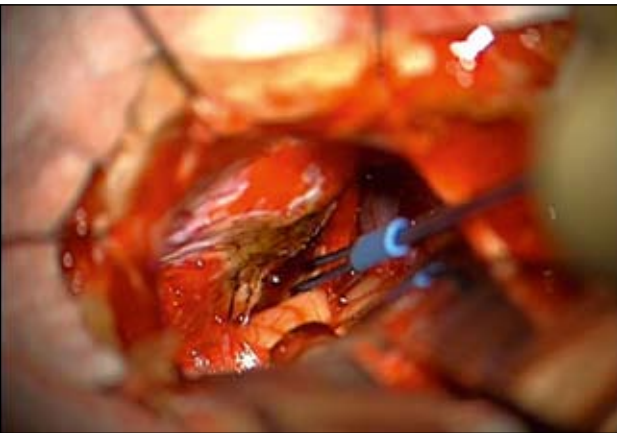

Figure 1B: *A disposable bi-pronged stimulator being used in the cerebello-pontine angle.*

A number of different stimulator handpiece designs are available which suit specific anatomical locations. These range from adapted bipolar forceps for use in the neck to concentric ring probes and off-set bi-pronged devices more suited for work in mastoid or cerebello-pontine angle (Figure 1).

Bipolar stimulating forceps, as used in the neck, are expensive and care must be taken when sterilising them lest their electrical connections become damaged. Stimulator handpieces for use in the temporal bone and cerebello-pontine angle are single use and therefore disposable.

ELECTRODE PLACEMENT

Facial Nerve Monitoring
Paired, sampling, needle electrodes are inserted trans-cutaneously into the ipsilateral muscles of facial expression as also an electrode that acts as an "earth". It is important to place the sampling electrodes close together, but not touching. The "earth" should also be relatively close by, within a few centimetres. So, if monitoring the facial nerve, the sampling electrodes should be placed in the lower lip with an "earth" in the upper lip for the lower division; while for the upper division sampling electrodes should be placed in the forehead with the "earth" in the peri-orbital musculature overlying the nasal bones (Figure 2). It has been suggested that recording from both divisions samples from a greater proportion of the facial nerve fibres and that this may enhance sensitivity[2]. In reality, it increases reliability in the event that one set of electrodes becomes displaced or develops a fault during the operation.

It is extremely important to ensure that the electrodes are secured firmly with adhesive tape and that they are sited some distance from the muscles not innervated by the facial nerve, for example, the masseter. This is particularly important in cerebello-pontine angle surgery. Electrodes placed too far laterally in the buccinator muscle pick up signal from the masseter, which might be provoked by trigeminal stimulation or irritation, and could be easily misinterpreted as facial nerve activity. It is always wise to test the monitoring system before draping the patient. Pre-

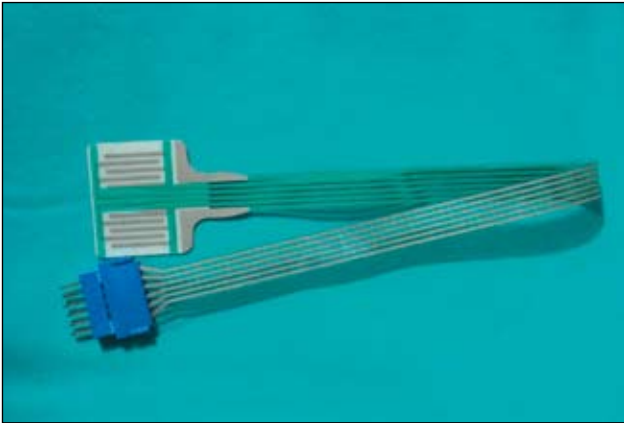**Figure 2:** *Electrode placements for facial nerve monitoring.*

Figure 3: *A adhesive laryngeal electrode.*

operative trans-cutaneous stimulation confirms electrode integrity and monitor function.

Vagus And Recurrent Laryngeal Nerve Monitoring

Sensing electrodes within the larynx are most appropriate for both these nerves. Hook-wire, needle or surface electrodes are available. Hook-wire electrodes are possibly more reliable. They are inserted directly into the vocal cord on the side of the operation. This can be performed either under direct vision through a laryngoscope or placed blindly by insertion through the cricothyroid ligament into the vocal cord. An "earth" electrode placed nearby it also required.

Adhesive surface electrodes can be applied to the endotracheal tube just above the cuff. In this way, they sit in the glottic chink and detect vocal cord activity (Figure 3).

With some devices, it is possible to check the electrode impedence immediately after insertion before continuing the set up. This ensures that they will function adequately. The electrodes are then connected to a pre-amplifier and filtering device positioned relatively close to the operative field. The pre-amplifier pod is connected to the main amplifier, positioned some distance from the patient, and this transforms the EMG response into an audible signal. The separation of the pre-amplifier from the main amplifier ensures that the monitor output is unaffected by extraneous radio frequency interference. "Circuit breaking" devices are also available if required that switch off the monitor when diathermy or bipolar coagulation is being used. However, it is at these times that monitoring might be needed most!

Discussion

There is no substitute for anatomical knowledge and surgical experience. Never-the-less, intra-operative neural monitoring has its place in modern surgery and in some

situations has become established as a standard of care. Many of the surgeons who ridiculed and derided their use many years ago have come to see their advantages and incorporated intra-operative monitoring in their clinical practices. For example, in vestibular schwannoma surgery, intra-operative monitoring can be invaluable to locate the root exit zone of the facial nerve on the brain stem and identification of the nerve as it courses around the capsule of a large tumour. It can alert the surgeon of a nerve that has split into several fascicles, so fine that they have become invisible the eye. Likewise in the neck, intra-operative monitoring can help the surgeon locate the main trunk of facial nerve when displaced by a large tumour, or peripheral branches when a retrograde dissection is more appropriate. For example, when removing a recurrent pleomorphic adenoma that has precluded a direct approach to the main trunk of the facial nerve.

Detailed analysis of electromyographic waveforms has been undertaken in an attempt to identify types of stimulation that translate into post-operative neural deficits. While evoked electromyographic potentials are a sensitive measure of neural irritation, it does not always indicate irreversible damage. But specific sequences of potentials have been identified, "A trains", and these have a direct correlation with post-operative facial nerve paresis[3,4]. An "A train" is a burst of high frequency potentials, up to 210Hz, with maximum amplitudes of 100–200_V. Their duration may be just a few milliseconds but may be far longer, several seconds. The duration of "A train" patterns correlates strongly with a deterioration in post-operative facial nerve function[4].

Facial nerve stimulation thresholds at the conclusion of vestibular schwannoma surgery have predictive utility. In this respect, post operative function has been assessed at least six months after surgery. A threshold of 0.05mA or lower is considered a positive prognostic factor[5]. Increased thresholds have a good positive predictive value also. But, no response whatsoever does not necessarily indicate that there will be a poor final outcome[6]. The precise location of a neural block can be identified as well and, with a partial block, the degree of neural damage can be inferred from the ratio of stimulation thresholds at the root exit zone and the meatal segment within the internal auditory canal[7].

Sadly there has not been widespread support for the use of intra-operative monitoring for parotid surgery. Abnormal EMG responses during surgery have not predicted post-operative facial nerve function reliably[8]. Furthermore, while a significant reduction in operating time can be achieved by the use of monitoring, it is not sufficient to make it cost-effective. A recent review concluded that

studies on the value of monitoring in parotid surgery are limited by a lack of multi-institutional prospective controlled trials with sufficient power to draw worthwhile conclusions[9]. It would seem the most common reasons why surgeons use monitoring in parotid surgery are as an aid in facial nerve identification, for medico-legal reasons and for a perception of increased patient safety[10].

Within the middle ear and temporal bone facial nerve monitoring has been perceived to be sensible for procedures where it might be at significant risk. For example, cochlear implantation, revision surgery or extensive disease, where anatomical landmarks have been lost and if a congenital abnormality might be suspected.

The role of intra-operative recurrent laryngeal nerve monitoring in thyroid and parathyroid surgery has yet to be determined and there would seem to be conflicting evidence in the literature. In the absence of monitoring, the incidence of permanent vocal cord paralysis may be as much as 5%. While intra-operative monitoring is recognised as a useful aid to identify the nerve, this has not translated into observed benefit[11]. Monitoring for revision thyroid surgery has shown no benefit either[12]. Direct stimulation of the vagus has been advocated as a way of checking that the electrode array and monitor are working at the outset of surgery and that the recurrent laryngeal nerve is both intact and functioning at the conclusion[13].

For what and who should use or have intra-operative monitoring? In short, for any surgical intervention in the cerebello-pontine angle. To do otherwise would be negligent. A strong case can be made also for any intervention by experienced surgeons in the proximity of the facial nerve within the temporal bone or neck but this is not been universally accepted. It should certainly be used for any revision mastoid, parotid or thyroid surgery regardless of the experience of the surgeon. Last but not least, any mastoid, parotid or thyroid surgery being undertaken by a surgeon in training. Intra-operative monitoring reduces psychological tension, facilitates gentle handling of nerves and might sharpen the learning curve for this group of surgeons.

With easy access to clinical information available through the internet, patients have become more aware of the use of neuro-physiological monitoring during surgery and many ask if it is going to used during their operative intervention. The knowledge that a nerve monitor was available but not used for a patient left with a facial palsy or incompetent larynx would be hard to accept regardless of the experience and reputation of their surgeon.

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Paragangliomas of the head and neck

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Key Points

1. Paragengliomas are rare, generally benign, but locally aggressive lesions with potential to cause significant morbidity.

2. Recent genetic advances have highlighted the association between paragangliomas and phaeochromocytoma, and have suggested that a significant proportion (20-40%) of paragangliomas are inherited.

3. Treatment should be offered as part of a multi-disciplinary team, with the primary aims being to control tumour growth with minimal cranial nerve morbidity.

Introduction

Recent years have seen interesting developments in our understanding of the pathogenesis and treatment of paragangliomas: genetic studies and advances in surgical and radiotherapy techniques are particularly exciting. This review article will focus upon these advances and will also provide a general overview of the natural history, pathology and management of these rare lesions.

Paraganglial anatomy and physiology

Paragangliomas develop from paraganglia: aggregations of hormone-secreting tissue found throughout the body closely associated with neural and vascular structures with both para- and endocrine roles in maintaining homeostasis, although often their function is poorly understood. Paraganglia are simply classified as either 'head and neck' or 'thoraco-abdominal'; the former associated with the parasympathetic nervous system, the latter with the

sympathetic[1]. The adrenal medulla could be described as the largest paraganglion in the body, and there is an important association between head and neck paragangliomas and phaeochromocytomas (see below: 'Genetics').

In the head and neck, paraganglia are found at multiple sites associated with neurovascular structures: the most significant being the carotid paraganglion ('carotid body'), with other sites reflecting the sites at which paragangliomas are seen (see below). The role of carotid body in the regulation of blood oxygenation is well-understood (and the subject of the Nobel Prize for medicine in 1938): that of other paraganglia in the head and neck is less clear, but these may also play roles in respiratory homeostasis.

Pathology

Nomenclature

The nomenclature of paragangliomas can be confusing: the lesions can be described according to their histological appearance ('glomus' (meaning nest-like, referring to the whorl-like appearance of the tumour) or 'non-chromaffin' (referring to staining characteristics)), their location ('carotid body tumour') or their supposed physiological role ('receptoma' or 'chemodectoma')[2]. The World Health organisation recommends description according to location ('jugulo-tympanic' or 'vagal' paraganglioma)[3].

Epidemiology

Paragangliomas are rare lesions, with an estimated incidence of approximately 1:30000 annually. They affect females more commonly than males, with most tumours

presenting in the 5th decade: in the authors' unit, the sex distribution among patients presenting with paragangliomas is 4:1 F:M. Paragangliomas in children are exceedingly rare, and invariably associated with a genetic paraganglioma syndrome[4].

Histopathology

Paragangliomas are characterised by 'zellballen' ('cell balls') which are densely-packed nests of 'Type I' (catecholamine-producing) cells. These zellballen have a rich capillary network and are surrounded by a dense fibrous tissue. Tumour growth is expansile, with the capacity to infiltrate and erode bone, but tends to be slow (there is an estimated median tumour doubling time of 10 years and an annual growth rate or 0.83mm)[5].

Tumour sub-types in the head and neck

Paragangliomas occur throughout the head and neck, but are found particularly at four sub-sites. The most common location is the carotid body, with the tympanic cavity (arising from Jacobsen's nerve), jugular bulb and vagus nerve following in relative order of frequency. Other sites at which paragangliomas have been described include the larynx (usually the sub-glottis), the sinuses and cranial nerves including the facial and hypoglossal nerves.

Malignancy and functionality

Although generally considered benign, the United States National Cancer Database[6] estimates that some 10% of paragangliomas are prone to loco-regional (and less commonly), distant metastasis. Other series have suggested a lower rate of malignancy, and this would accord with the authors' experience. Approximately 5% are 'functional' (in that they produce clinically significant levels of catecholmines)[7].Both functionality and malignancy are more common in familial paraganglioma syndromes than in sporadic tumours.

Tumour Classification Systems

Shamblin Classification for Carotid Paragangliomas[8]
This classifies carotid lesions with respect to encasement of the carotid artery, and with respect to the adhesion of the tumour to the adventitia of the vessel.

Fisch Classification for Jugulo-Tympanic Tumours[9]
This system embraces both tympanic and jugular lesions. Type A and B are confined to the middle ear or mastoid respectively, while Type C lesions breach the bony covering of the jugular dome . Sub-sets of Type C lesions describe the degree of involvement of the carotid artery. Type D lesions are intra-cranial.

Presenting symptoms and clinical features

The presenting symptoms of different head and neck paragangliomas are clearly dependant upon the site of the lesion. Tympanic lesions typically present with pulsatile tinnitus and a conductive hearing loss, while carotid body tumours usually present as a neck mass. Of interest is the significant number of lesions (predominantly jugular and vagal) that present with cranial nerve palsies: the largest series of vagal paragangliomas reports a rate of 36%,[10] and a large (n. 152) series of jugular paragangliomas[11] found at least one cranial nerve palsy in 46% of patients.

The genetics of paragangliomas

It is estimated that between 20 and 40% of paragangliomas are inherited, and while it has long been recognised that paragangliomas are clustered in families, a detailed understanding of the different paraganglioma syndromes has only recently evolved. In addition, molecular genetic studies have revealed putative mechanisms for paraganglioma formation and have suggested possible therapeutic avenues.

SDHx Paraganglioma Syndromes
Researchers in the Netherlands investigating families known to develop paragangliomas during the 1990's mapped a locus of homozygosity to chromosome[11] ('PGL 1')[12]. Consistent areas of abnormal genetic homogeneity in a large family with a clinically-recognised disease are often the first step in identifying genes responsible for pathology: the identification of a 'locus' (which may contain multiple genes), allows researchers to sequence individual genes in order to decide whether those genes are mutated or disrupted in some way. Subsequent studies identified the abnormal gene as 'SDHD' (succinate-ubiquinone oxidoreductase subunit D), with further research associating other paraganglioma syndromes with 'SDHB' and 'SDHC'.

The SDHx group and putative mechanisms of pathogenesis
Although the SDHx genes responsible for paraganglioma syndromes are found on different chromosomes (11 and 1), they each form a subunit of a tetrameric protein: 'Mitochondrial Complex II' (MCII): a protein that forms part of the electron transport chain in mitochondria. It is postulated that SDHx mutations lead to the generation of a 'pseudohypoxic state' in which a build-up of succinate (due to MCII reduced activity) leads to the stabilisation of hypoxia-induced factors (HIF-1 and HIF-2)[13] and the down-stream up-regulation of growth-promoters such as vascular endothelial growth factor (VEGF) and erythropoietin. Although these mechanisms are not currently exploited in the treatment of paragangliomas, 'biological' chemotherapy agents are currently in use that

Table 1: Clinical characteristics of SDHX syndromes			
	SDHD (n=34)	SDHB (n=32)	SDHC (n=22)
Mean/ median age at diagnosis	31 (mean)	29 (mean)	46 (median)
Penetrance	50% by 31 yrs, 86% by 50 yrs	50% by 35 yrs, 77% by 50 yrs	N/A
N. with multiple tumours	25 (74%)	10 (31%)	2 (9%)
N. with HNPG	27 (79%)	10 (31%)	22 (100%)
N. with phaeochromocytoma	18 (53%)	9 (32%)	0 (0%)
N. with extra-adrenal abdominal paragangliomas	7 (21%)	16 (50%)	0 (0%)
N. with malignant tumours	0 (0%)	11 (34%)	0 (0%)
Carriers with other cancers	1 (3%)a	3 (9%)b	0 (0%)

*Information presented here is derived from information drawn from a studies based upon a central European (Germany and Poland) registry of HNPG (n=121) and phaechromocytomas (n=371), extending to other centres in Europe(6,16). **A** 1 patient (age 26) also showed a papillary carcinoma of the thyroid. **B** 1 patient (age 14) also showed a papillary carcinoma of the thyroid, 2 patients from one family demonstrated clear cell renal carcinoma (age 21 and 26). This Table was originally published in "Clinical Otolaryngology" and is produced with the permission of the Editor.*

modulate VEGF pathways, and it is to be hoped that in due course, these (currently toxic) agents will be appropriate for the treatment of, for example, metastatic or multiple paragangliomas[14].

Differing characteristics of SDHx paraganglioma syndromes

All the SDHx genes are associated with multiple head and neck paragangliomas, and all are inherited in an autosomal dominant manner (thus a child will have a 50% chance of inheriting a copy of a defective allele from a carrier parent). There are also similar penetrance levels: a carrier of an SDHx gene can expect to develop a paraganglioma by the time they are 30 years old in 50% of cases, with the penetrance rising to approximately 80% at age 50.[15,16] In

Figure 1: *Sample family tree in SDHD illustrating how disease can be hidden within families due to maternal imprinting. The susceptibility gene is carried and transmitted by females but only manifests as disease when inherited from a father. This Table was originally published in "Clinical Otolaryngology" and is produced with the permission of the Editor.*

some other respects, however, SDHx syndromes differ in their clinical characteristics (these differences are summarised in Table 1).

SDHD Inheritance

Of particular note is the fact that SDHD families demonstrate 'parent-of-origin' inheritance. Thus, while the genotype is passed in an autosomal dominant manner from either parent, the phenotype is only manifest (i.e. the patient only develops paragangliomas) if the individual inherits the gene from their father. This inheritance can obscure disease within families, with 'silent' genotypes being passed through generations and creating an apparently bland family history (this phenomenon is illustrated in Figure 1).

Screening for SDHx genes

If a paraganglioma syndrome is suspected, then patients should be offered genetic testing (for SDHB, C and D) within the context of a multi-disciplinary clinic offering both clinical genetic and otolaryngological expertise. The authors would recommend offering such screening to the following groups:
- patients with multiple head and neck paragangliomas or paraganglioma and phaeochromocytoma
- patients with a positive family history
- patients with functioning or metastatic tumours
- patients presenting at a relatively young age (currently recommended as <50 years)

As in all genetic screening, informed consent should be taken with appropriate counselling prior to investigation. In patients with positive results, further genetic investigations should be offered to relatives.
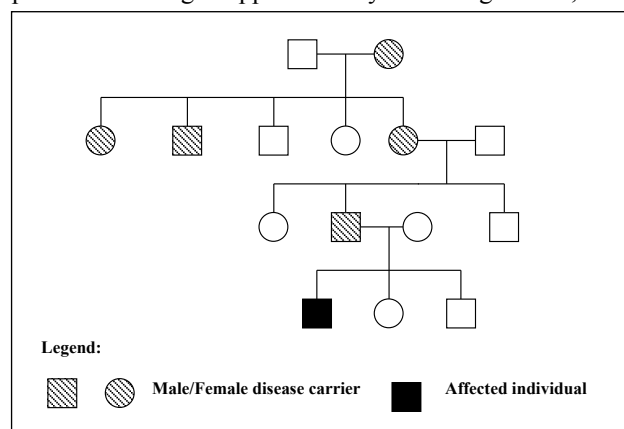
Management of inherited paraganglioma syndromes
Patients carrying SDHx genes will require surveillance in order to identify sub-clinical lesions. Subsequently, treatment is likely to be more conservative than that offered to patients with sporadic lesions due to the risk of significant cranial nerve injuries if bilateral lesions are treated. Clearly, patients with bilateral vagal tumours that are causing cranial nerve deficits present particular clinical challenges, and it may be that challenging patients of this nature would be amenable to the medical treatments discussed above.

Investigation of paragangliomas
Leaving aside the particular genetic investigations discussed above, patients with either sporadic or familial paragangliomas require both biochemical and radiological investigations.

Biochemical investigations
All patients with a paraganglioma should be investigated with 24-hour measurement of urinary catecholamines. A positive result should prompt radiological investigation to rule out a synchronous phaeochromocytoma.

Radiological investigations
A common presenting symptom for jugular and tympanic paragangliomas is pulsatile tinnitus, and this symptom should prompt investigation with magnetic resonance imaging (MRI). This modality will usually be combined with computed tomography (CT) in most cases in order to accurately define bony anatomy. Classically, T2-weighted MR imaging produces a 'salt-and-pepper' appearance[17].

Radionuclide imaging
The biochemical activity of paraganglial tissue (at physiological, rather than pathological levels) renders it suitable for radionuclide imaging techniques. While largely superseded by CT and MR in terms of diagnostic imaging, these techniques offer promise in cases where whole body screening is undertaken, in cases where CT and MR findings are equivocal, or in post-surgical cases identifying recurrent or residual disease when scarring may render traditional anatomical imaging ineffectual. Of particular interest is ^{18}F-DOPA-PET scanning: this new modality is exquisitely sensitive to paraganglial tissue, and in one study has been found to be more sensitive than MR imaging[18].

Management of paragangliomas
Both surgery and radiotherapy are accepted treatment modalities for paragangliomas: both techniques offer similar rates of tumour control (90% approximately). Decisions over treatment are increasingly made in a multi-disciplinary setting and should take into account tumour, patient and institution factors.

Surgery
A full discussion of surgical techniques at the various sites at which paragangliomas can develop is beyond the scope of this article: this review will focus upon surgical principles, areas of controversy and new developments.

Tumour embolisation.
Embolisation (usually on the day before surgery) is standard practise when carrying out surgery on tumours involving the skull base (thus jugular and most vagal paragangliomas: Figure 2 illustrates the exposure of an embolised vagal paraganglioma). It is important to identify all significant feeding vessels to the tumours (these are usually branches of the ascending pharyngeal artery). Patients should be aware of the risk of cerebrovascular accident, which is approximately 1%.

Total vs. subtotal tumour resection with preservation of cranial nerve function.
While total removal of tumour is the aim in some tumours, in larger lesions involving cranial nerves, a sub-total removal allowing cranial nerve preservation is appropriate. Remnant tissue may be monitored and treated with radiotherapy (see below) if there is evidence of further growth. In the authors' experience, the removal of the bulk of tumour is often sufficient to arrest tumour progression. Such an approach may be even more appropriate in familial lesions where lesions may be bilateral. In general, the authors prefer to preserve facial and middle ear function where possible by employing a 'Fallopian Bridge' technique combined with an extended facial recess approach when accessing the hypotympanum and infra-temporal fossa: Figure 3 illustrates the Fallopian Bridge as performed at a later stage of the operation illustrated in Figure 2.

Carotid artery stenting
Perhaps representing a different philosophy to that outlined above, an interesting development in paraganglioma surgery is the use of a vascular stent to allow tumour clearance from the carotid adventitia. This technique, whereby the stent is inserted 2-3 months prior to surgery,
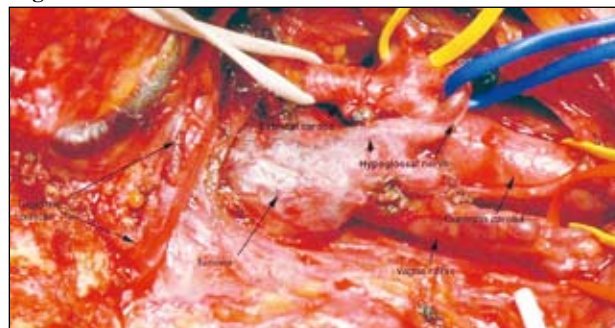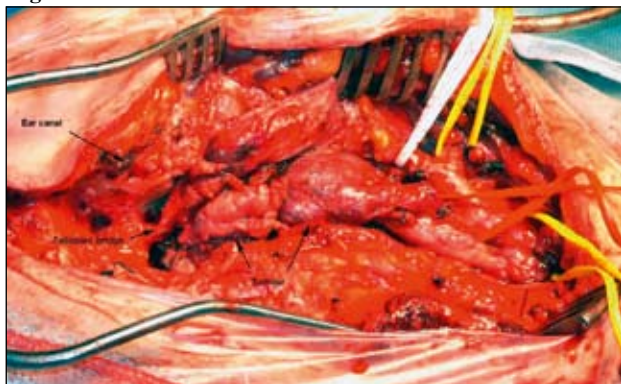
Figure 2

Figure 3

allows the carotid artery with adherent tumour to be stripped away, leaving the stent - upon which a 'neo-intima' has formed – in situ[19]. This allows an attempt at complete tumour removal in cases where carotid artery sacrifice would not be possible due to an inadequate contra-lateral circulation.

Nerve monitoring

In large tumours involving the skull base, cranial nerve monitoring is essential. The VII and Xth nerves are monitored as standard, with additional monitoring of IX, XI and XII as indicated by the location of the tumour.

Radiotherapy

Prior to the introduction of microsurgical techniques, radiotherapy was the mainstay of treatment for paragangliomas. A recent review of long-term results with radiotherapy suggests control rates of approximately 90% (at ten years), with low rates for major complications including osteoradionecrosis (1%), brain necrosis (1%) and an estimated rate of radiation-induced malignancy of between 0.5 and 1%.[20] One significant benefit of radiotherapy over surgery is a reduced morbidity in terms of cranial nerve morbidity: new cranial nerve palsies are rarely described in radiotherapy series, whereas surgical series report rates of new cranial nerve deficits (IX, X, XI and XII) of between 25% and 50%[11,21]. On the other hand, radiotherapy rarely reduces the bulk of the tumour, and will often fail to reduce the volume of troublesome pulsatile tinnitus. The authors would advocate a management strategy that recognises both modalities as useful, often used in combination, reflecting individual patient requirements.

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The Current use of PET-CT in Head and Neck Cancer

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Abstract

Accurate staging at the time of the diagnosis of head and neck squamous cell carcinoma (HNSCC) is critical for selection of the appropriate treatment strategy. PET and PET-CT are nowadays standard imaging techniques for HNSCC patients. These diagnostic techniques may be helpful for the detection of occult primary tumours, but its sensitivity for the detection of occult lymph node metastases is too low. Screening for distant metastases should be performed by FDG-PET-CT.

FDG-PET is probably reliable enough to select patients with suspicion of recurrent laryngeal carcinoma after radiotherapy for direct laryngoscopy under general anaesthesia. The value of FDG-PET to avoid futile routine evaluation by examination under general anaesthesia in oral and oropharyngeal cancer and neck dissection when a residual mass persists in the neck after (chemo)radiation is promising.

Key Words

Head and neck cancer; pretreatment; work-up; imaging; recurrence; PET

Introduction

A variety of therapeutic options are used for treatment of head and neck squamous cell carcinoma HNSCC. Accurate staging at presentation of HNSCC patients is critical for treatment selection: delineation of the primary tumour, assessment of the presence and extent of lymph node metastases and screening for distant metastases. The presence of distant metastases at initial evaluation influences the prognosis and thus treatment selection.

It is of the utmost importance that organ preservation can be carried out without compromising locoregional disease control. Patients should be carefully observed throughout the course of treatment and during follow-up so that surgery can be undertaken as soon as persistent or recurrent disease is detected. However, distinguishing between recurrent carcinoma and radiotherapeutic sequels can be a difficult clinical problem.

Positron emission tomography (PET) imaging with F-18-fluorodeoxyglucose (18FDG) is a functional modality that has been used increasingly for staging head and neck cancer. PET-CT imaging combines both anatomic and functional imaging, potentially providing more accurate diagnosis and improved patient management. The CT scan is used for attenuation correction of the PET images as well as for anatomic localization.

Primary tumour

Sensitivity of FDG-PET is reported to be 98% and of FDG-PET-CT 97% for the detection of primary tumors in patients who had newly diagnosed HNSCC in a large series of 197 patients. These figures were higher than CT (86%) and MRI (88%)[1]. Since physical examination usually shows the primary tumour and PET alone can not delineate the extent of the tumour, the role of FDG-PET is limited to the detection of the occult primary tumours in patients with cervical lymph node metastases in the neck.

Many small retrospective studies have examined the utility of FDG-PET to identify unknown primary tumours [2-4]. A problem with interpretation and comparison of these studies is their lack of uniformity in the inclusion criteria: after physical examination only or after diagnostic imaging by CT and/or MRI and/or endoscopic examination under general anaesthesia with taking of directed biopsies of areas most likely to harbour an occult primary. Moreover, the definition of sensitivity differs between studies. In principle a primary tumor should be present in all patients,

but that in some patients these tumours will not be detected or become manifest due to wide field irradiation. Therefore, all undetected primary tumours in those patients should be considered as false negative. Consequently the real sensitivity is much lower.than the reported sensitivity (70-100%)[3,4]. The detection rate of occult primary tumors is probably a more realistic outcome parameter than sensitivity.Rusthoven et al[3] reviewed 16 studies and analyzed a total of 302 patients after negative conventional work-up. FDG-PET detected the primary tumour in 74 (24.5%) patients.

Lymph node metastases
Kyrzas et al[5] found in a meta-analysis that FDG-PET has a good performance in the overall pre-treatment evaluation of the presence of lymph node metastases in HNSSC patients: pooled sensitivity of 79% and pooled specificity of 86%[5]. Roh et al[1] compared pre-operatively in 167 HNSCC patients PET or PET-CT with CT or MRI for the detection of (occult and evident) lymph node metastases. The sensitivity was 60-67% and 87-90% and the specificity 90-92% and 93-94%, respectively[1].

Detection of occult lymph node metastases is the most important problem. The aforementioned meta-analysis showed that FDG-PET detected only 50% of the occult lymph node metastases, reiterating the inability of imaging test to document microscopic disease[5]. Ng et al[6] showed that for the detection of subclinical lymph node metastases the visual correlation of FDG-PET with CT/MRI has been reported to be more accurate than FDG-PET alone. In 134 patients with oral squamous cell carcinoma they found a sensitivity of 51.4%, which increased to 57.1% after visual correlation with CT/MRI. This increment stemmed from the correction of false-negative FDG-PET results caused by necrotic nodes[6]. Jeong et al [7] showed that PET-CT was more accurate than PET and CT alone for the conducting cervical lymph node evaluation in 47 HNSCC patients who were scheduled for neck dissection(s). Unfortunately, in this study clinically negative as well as clinically positive necks were evaluated together.[7] Although PET and PET-CT have probably the best accuracy for detecting occult cervical lymph node metastases in the clinical N0 neck these techniques are still not reliable enough to avoid elective treatment of the neck.

Detection of distant metastases
Most studies that used FDG-PET in screening for distant metastases lack a fair and controlled comparison between PET and other standard conventional imaging such as chest CT and/or an adequate reference standard such as reasonable follow-up. In a multi-centre prospective study the data of 92 HNSCC patients with high risk factors

(clinically three or more lymph node metastases, bilateral lymph node metastases, lymph node metastases of 6 cm or larger, low jugular lymph node metastases, locoregional recurrence and second primary tumours) who underwent screening for distant metastases by chest CT and whole body FDG-PET and had a follow-up of at least 12 months were analyzed.[8] The incidence of distant metastases was 33%. Pre-treatment screening identified distant metastases in 19 patients (21%). FDG-PET had a higher sensitivity (53% vs. 37%) than CT, potentially resulting in less futile extensive treatments. FDG-PET also had a higher positive predictive value (80% vs. 75%) than CT, resulting in lower risk of withholding patients from curative treatment (although mostly clinical decisions will not be based on a single imaging technique). The combination of CT and FDG-PET had the highest sensitivity (63%)[8]. Ng et al[9] compared the detection of distant malignancies (distant metastases and second primary tumours) by FDG-PET and extended-field multi-detector row CT (MDCT) in 160 newly diagnosed oropharyngeal and hypopharyngeal squamous cell carcinoma patients with negative results from chest radiography, liver ultrasound and bone scanning and a minimum follow-up of 12 months. Twenty-six (16.3%) of these patients had distant malignancies. The percentages of additionally detected distant malignancies of FDG-PET and MDCT were 12.5% and 8.1%, respectively. The sensitivity of FDG-PET was significantly higher (76.9% vs. 50.0%), while its specificity was slightly lower (94.0% vs. 97.8%) than MDCT. Visual correlation of FDG-PET and MDCT improved the sensitivity and specificity up to 80.8% and 98.5%, respectively, leading to alteration of treatment in 13.1% of patients[9].

Both studies do show that the combination of FDG-PET and CT is the best diagnostic work-up for the detection of distant metastases.. Kim et al[10] staged a heterogeneous group of 349 previous untreated head and neck cancer

patients using PET-CT. During a mean follow-up of 15 months the incidence of distant metastases was only 7.4%. Of these 26 patients who developed distant metastases only 8 were detected during pre-treatment diagnostic work-up by PET-CT, resulting in a sensitivity of 30.7%. Initial (pre-treatment) PET/CT detected 10 of the 14 (71.4%) second primary tumours which developed in this

Figure 1. *Coronal whole body FDG-PET image.of a patient with T3N2c oropharyngeal carcinoma and lung metastases.*

period. For the detection of distant metastases and second primary tumours by initial and follow-up (every 6 months) PET-CT scans a sensitivity of 97.5%, specificity of 92.6%, positive predictive value of 62.9%, negative predictive value of 99.7% and accuracy of 93.1% were found. However, in clinical practice the detection of asymptomatic distant metastases during follow-up is of less importance since currently no treatment options with curative intent are available. Unfortunately, comparisons between the accuracy of CT, PET, visual correlation of PET and CT en integrated PET-CT were not made. Gourin et al[11] analyzed retrospectively 27 patients with previously untreated (mainly advanced stage) HNSCC who underwent PET-CT. PET-CT appears to improve the detection of distant metastases compared to chest radiography. PET-CT detected distant metastases in 19%. They reported a sensitivity of 100%, specificity of 96%, positive predictive value of 75% and a negative predictive value of 100%. Unfortunately. the reference standard was the work-up of chest radiography and PET-CT rather than a reasonable follow-up[11].

Locoregional recurrence after (chemo) radiotherapy

FDG-PET is highly reliable in the detection of recurrent or persistent HNSCC after (chemo)radiotherapy. Isles et al[12] found a pooled sensitivity and specificity of PET for detecting residual or recurrent HNSCC were 94% and 82%, respectively. Positive and negative predictive values were 75%, and 95%, respectively[12].

In an attempt to compare PET with CT and/or MRI in the detection of recurrent or residual head and neck cancer after (chemo)radiotherapy Klabbers et al[13] found that data on PET in head and neck tumours are mainly based on small patients groups which are usually heterogeneous with regard to tumour type, treatment, clinical follow-up, proof of diagnosis, and time interval between PET and completion of treatment. To reduce the effects of studies with small study groups and thus provide more reliable estimates of the value of PET and CT or MRI, weighted averages were calculated. The weighted averages for sensitivity and specificity for FDG-PET were 86% and 73%, and for CT and/or MRI 56% and 59%, respectively[13].

Probably the most difficult head and neck sites to differentiate between posttreatment changes and recurrent tumour are the irradiated larynx and hypopharynx. A systematic review on FDG-PET to detect recurrent laryngeal carcinoma found pooled estimates for sensitivity and specificity of 89% and 74%[14].

In a pilot study of 30 patients suspected of recurrent laryngeal carcinoma after radiotherapy conservative

(equivocal analysed as negative) and sensitive (equivocal analysed as positive) assessment strategies were compared to the reference standard (recurrence within 6 months after PET). For the conservative and sensitive strategy the mean sensitivity was 87% and 97%, specificity 81% and 63%, positive predictive value 61% and 46% and negative predictive value 96% and 99%, respectively[15]. It can be anticipated that in clinical practice the sensitive reading is used if FDG-PET have to select patients suspected of recurrent laryngeal carcinoma after radiotherapy for direct laryngoscopy under general anaesthesia. For the physician the risk of missing a recurrence probably outweighs a futile direct laryngoscopy, because early detection of a recurrence can be important for salvage surgery and clinical outcome.

Kitagawa et al[16] reported in a series of 23 patients who underwent chemoradiation for oral and oropharyngeal carcinoma a sensitivity of 100%, a specificity of 89%, a positive predictive value of 67 and a negative predictive value of 100% for the detection of local recurrent disease by serial (before and within 4 weeks after treatment) FDG-PET imaging. In this group of patients these figures were for CT 75%, 59%, 30% and 91% and for MRI 100%, 41%, 23%, and 100%, respectively.

In some patients, surgical treatment of the neck may be an option following complications or failure of chemoradiation therapy., Since distinguishing between residual metastasis and (chemo)radiation sequelae is difficult in most cases with a residual neck mass, the risk of futile neck dissections is present. In some institutes planned neck dissections are performed. Negative predictive values between 14 and 100% are reported in these studies, probably depending on the timing of PET scanning. PET imaging obtained too soon after radiation had been associated with high rate of false positive findings due to post-radiation soft tissue effects, and false negative findings because of the residual viable cancer cells not having sufficient time to repopulate to a level that can be detected by PET. One month after radiation the negative predictive value was only of 14%.[17]

When PET scanning was performed 4-12 weeks after chemoradiation this figure was 73%[18]. When the interval between PET and completion of chemoradiation was 8-12 weeks a negative predictive value of 92% was reported[19]. If the time interval between the end of therapy and PET scanning increases the negative predictive value further improved to 97-100%[20,21]. On the other hand a high sensitivity is warranted to refrain patients from neck dissection. In these studies the sensitivities from 45 to 100% are reported, depending on timing of the scanning. The reported specificity was 65% -94%. A study of 43 head and neck cancer patients with N2 or N3 neck disease

before chemoradiation FDG-PET-CT 2-5 months posttreatment reported a sensitivity of 88%, a specificity of 91%, a positive predictive value of 70% and a negative predictive value of 97%[22].

Conclusions

FDG-PET is helpful for the detection of occult primary tumours and distant metastases. FDG-PET is not reliable enough for the detection of occult lymph node metastases. It seems that FDG-PET is suitable to select patients with suspicion of recurrent laryngeal carcinoma after radiotherapy for direct laryngoscopy under general anaesthesia. In oral and oropharyngeal cancer it may be justified to refrain patients from evaluation by examination under general anaesthesia when FDG-PET is negative after (chemo)radiatiotherapy. The value of FDG-PET to avoid futile neck dissections when a residual mass persists in the neck after (chemo)radiation is promising. However, the optimal time interval between completion of radiation and FDG-PET has still to be assessed.

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Surgical Management of Locally Invasive Thyroid Cancer

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Abstract

Up to 15% of patients with differentiated thyroid cancer present with extra-thyroidal extension and locally invasive disease. Consequently, these patients have poorer outcome with higher mortality rates and higher incidence of disease failure loco-regionally and in distant sites. It is important to recognize this at the outset, as effective primary surgery offers the best possibility of control. A significant proportion of these patients are asymptomatic, hence a strong clinical suspicion together with judicious pre-operative evaluation with imaging and endoscopy are critical in making the diagnosis early. Common sites of invasion include strap muscles, recurrent laryngeal nerve, trachea, esophagus and larynx. Primary surgery should aim to remove all gross tumor, with adjuvant therapy with radioactive iodine. External beam radiation is used for selective indications. While it is important to preserve functioning structures, locally aggressive cancers may warrant more radical resection. This review addresses the salient points associated with diagnosis and surgical management of this scenario.

Introduction

Prognostic factors in differentiated thyroid cancers include patient age, tumor grade and histological subtype, tumor size, presence of distant metastases and extra-thyroidal extension[1, 2]. Extra-thyroidal extension (ETE) is seen in 10-15% of patients and is usually seen in patients with long-standing, untreated tumors, in elderly males and in patients with poor/aggressive histological variants, such as tall-cell, insular or poorly-differentiated thyroid cancers.

ETE reduces 10-year overall survival in half and results in higher treatment failures rates: 48% local recurrence rates, and 41% and 37% of patients with metastasis to regional nodes and distant sites respectively[3]. The extent of extra-thyroidal extension is an important variable in staging thyroid cancer, where tumors with minor ETE into strap muscles or peri-thyroidal tissue are staged as T3, tumors with major invasion of the recurrent laryngeal nerve, larynx, pharynx, esophagus or trachea are staged as T4a and tumors invading the carotid artery, mediastinal great vessels or prevertebral fascia are staged as T4b.

The strap muscles are commonest site of invasion, being involved in approximately half of all patients with ETE. This is followed by invasion of the recurrent laryngeal nerve and trachea, and less commonly esophagus and larynx[4].

Clinical presentation and investigation

Presentation is usually insidious, and patients may be asymptomatic. Rarely, patients may present with hoarseness, dysphagia, odynophagia, hemoptysis, stridor, symptoms of superior vena cava obstruction or a large, fixed mass in the neck. Routine pre-operative evaluation for all patients with differentiated thyroid cancer includes a thyroid and neck ultrasound, fine-needle aspiration biopsy and laryngoscopy to evaluate the vocal cords (fiber-optic or mirror)[5]. In patients with a high index of suspicion for local invasion, detailed cross-sectional imaging is essential to evaluate extent of local disease, and this is easily achieved with a contrast-enhanced CT scan

or MRI scan of the neck[6]. Additional investigations include definitive airway evaluation by examination under anesthesia, direct laryngoscopy and esophagoscopy to evaluate the larynx, trachea, hypopharynx and esophagus

Principles of surgical management

Numerous studies have shown that surgical resection of all gross tumor offers the best outcome in patients with locally aggressive thyroid cancer[7-9]. Hence it is incumbent on the thyroid surgeon to determine the extent of local invasion prior to and during surgery, and make the appropriate intra-operative decision on surgical extent[10]. Best outcome is achieved when the appropriate procedure is performed during the first surgery. The fundamental concepts in the management of locally invasive thyroid cancer are listed in Table 1. The important points to note are as follows. First, all gross tumor should be removed; gross residual disease makes further treatment more difficult, will not respond adequately to adjuvant therapy and result in poorer overall outcomes. Every attempt should be made to preserve functioning (eg nerve) and vital (larynx) structures where possible, without compromising oncologic principles. Invasion of mediatinal vessels and carotid artery may render the tumor inoperable, where heroic surgical measures may result in greater morbidity. It is also important to remember that while surgery is the mainstay of treatment, adjuvant treatment including radioactive iodine and external beam radiation therapy have a role in controlling microscopic disease[11]. The following sections are aimed at specifically addressing the different scenarios encountered in locally invasive thyroid cancer.

Basic surgical principles

Patients undergoing surgery for major extrathyroidal extension should be counseled regarding possible need for more extensive procedures and the complications therein. These include the possibility of hoarseness, dysphagia, need for tracheostomy, prolonged requirement for tube feeding, or possible need for extensive procedures such as a laryngectomy or pharyngolaryngectomy with reconstruction. Patients with suspected extrathyroidal

Table 1: Principles of surgery for locally invasive thyroid cancer
- All gross tumor should be removed
- Preserve functioning structures
- Preserve vital structures
- Balance between tumor control and best functioning results
- Use adjuvant treatment- radioactive iodine, external beam radiotherapy

extension should undergo surgery under general anesthesia. Endotracheal intubation should be performed by a skilled anesthesiologist. Recurrent laryngeal nerve monitoring may be a useful adjunct if the tumor is believed to be closely associated to a normally functioning nerve[12]. It is especially useful to locate and confirm normal function of the contra-lateral nerve, if the ipsilateral nerve needs to be sacrificed due to tumor involvement. A standard 6-cm thyroidectomy incision is fashioned in a cervical skin crease, bearing in mind that this length can be altered to accommodate a lateral neck dissection or laryngectomy, if required.

Anterior extension

Local invasion can be anterior, and the strap muscles are the most common site for tumor extension[2]. Excision of the sternothyroid and sternohyoid muscles is not technically demanding, but requires the surgeon to recognize this possibility, especially in anterior or isthmic tumors. Failure to appreciate may result in leaving tumor behind or violating the tumor during surgical exposure. The strap muscles should be divided at the sternal, thyroid and hyoid attachments, and resected en bloc with the main tumor specimen. This results in minimal additional morbidity, however most patients with strap muscle invasion will require a total thyroidectomy as they will usually undergo adjuvant therapy with radio-active iodine.

Posterior/ extensive local invasion

Recurrent laryngeal nerve

The recurrent laryngeal nerve is the second most frequently involved structure by locally invasive thyroid cancer[4]. Unfortunately, hoarseness is an unreliable indicator of vocal cord paralysis as is only present in one-third of patients with recurrent laryngeal nerve palsy. Hence all patients undergoing thyroid surgery should have their vocal cords evaluated prior to surgery. When recurrent laryngeal nerve invasion is identified in a patient with normal vocal cord function, every attempt should be made to spare the nerve. However, this approach needs to be balanced with a need for oncologic clearance especially in patients with aggressive tumor histology such as Hürthle cell, insular and tall-cell variants of papillary carcinoma, or poorly differentiated carcinomas where radioactive iodine is less effective. If the nerve is non-functioning and grossly invaded by tumor, resection of the nerve en bloc with the main specimen is indicated. In this scenario, careful preservation of the contralateral nerve is mandatory, and this can be achieved with meticulous dissection (with or without the use of nerve monitoring)[13]. Medialization procedures of the paralyzed cord may be delayed, especially in younger patients as they compensate well with unilateral cord paresis, and in most cases the eventual
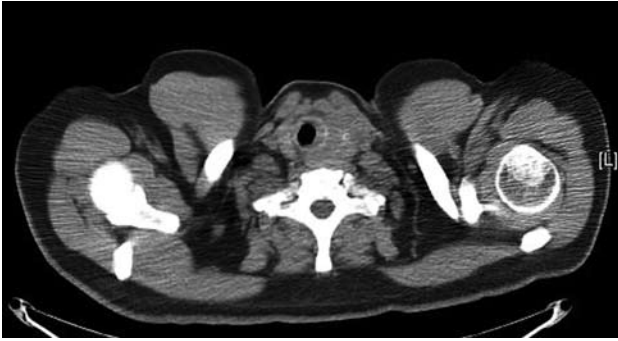
Figure 1: *Scan images showing a large left sided thyroid mass with invasion of the trachea, esophagus and recurrent laryngeal nerve invasion*

resting cord position will not be known in the pre- or intra-operative setting.

Tracheal invasion

Shin et al proposed a staging system to guide surgical decision-making, based on depth of tracheal involvement (Figure 1)[14]. For well-differentiated thyroid cancer with involvement of the tracheal peri-chondrium only, a shave resection is adequate. Any patient with deeper cartilaginous involvement, submucosal extension or extension through the tracheal wall will require full-thickness resection of the airway[11]. The major caveat to this approach is that intra-operative assessment can underestimate the depth of tracheal invasion, and this may only be appreciated when the pathology is reviewed. Furthermore, there is evidence to suggest that patients undergoing shave resection have higher local recurrence and disease-specific mortality rates. Hence some surgeons suggest that all patients should undergo full-thickness tracheal resection at the time of primary surgery[15].

Shave procedure

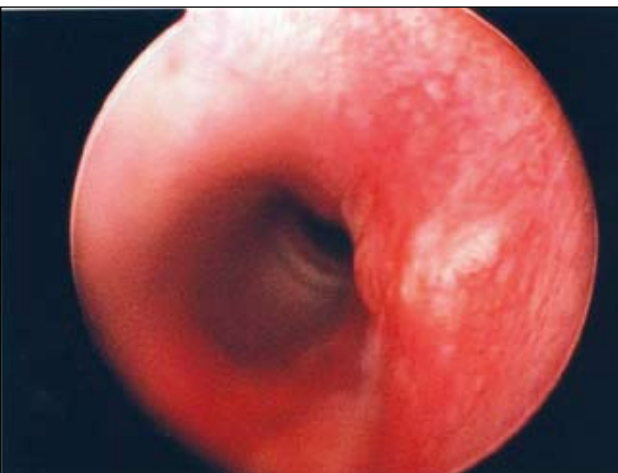This is the procedure of choice when there is minimal

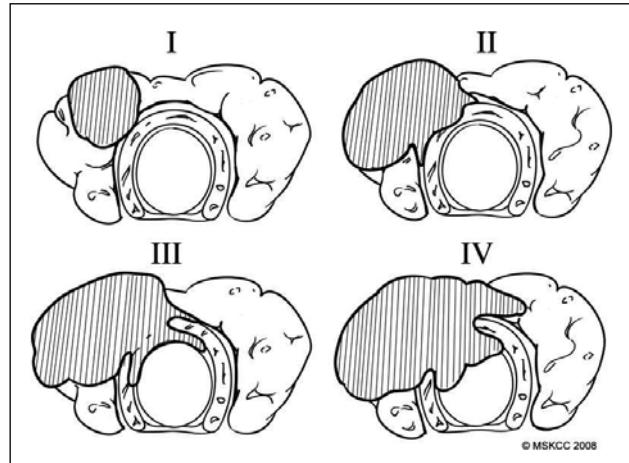**Figure 2:** *Endoscopic images of the same patient in figure 1 showing submucosal disease*

Figure 3: *Classification of tracheal invasion. Stage I involves outer perichondrium only; stage II invades the cartilage; stage III invades through the cartilage with submucosal involvement; and stage IV full-thickness involvement with mucosal disease*

involvement of the perichondrium. The thyroid or residual tumor is dissected leaving it attached at the point of tracheal invasion. Using a fresh scalpel blade the thyroidectomy specimen or tumor together with the attached perichondrium and a portion of underlying cartilage is cut tangentially and removed en bloc. The base of resection examined to ensure no gross residual tumor or a mucosal breach.

Full-thickness airway resection

Isolated involvement of a small portion of the trachea can be managed with a window or wedge resection. The thyroidectomy specimen or tumor is dissected out, leaving the point of tracheal invasion attached. A sharp blade is used to enter the membranous trachea above and below the tracheal ring to be excised, and the incision extended transversely to include the width of invasion. A sharp, curved Metzenbaum or tenotomy scissor is then used to cut across the cartilaginous ring on either side and connect the previous incisions, and the specimen removed. Small window defects can be closed by interposing the strap muscles, or mobilizing and rotating the sternocleidomastoid and suturing it as a buttress to close the defect. Wider defects or wedge resections should be closed primarily placing interrupted absorbable sutures such a Vicryl or Monocryl 2-0. A tracheostomy is best avoided after a window or wedge resection, as it delays healing and is often a source for infections. However, placing a tracheostomy tube in small, unanticipated tracheal defects is a simple solution for the unwary surgeon who is unfamiliar with techniques of tracheal reconstruction

Sleeve resection

Tumor involvement of multiple tracheal rings necessitates a more extensive tracheal resection- a sleeve resection,
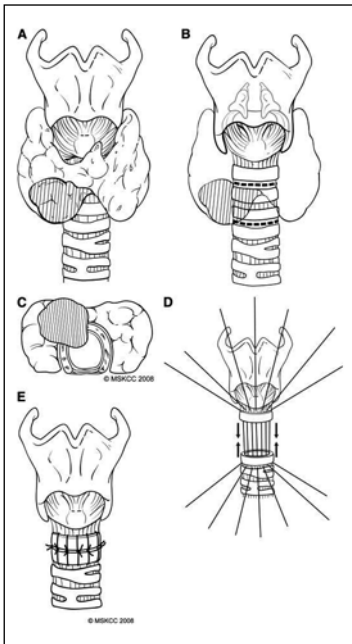
Figure 4: *Sleeve resection step-by-step; A. Thyroid cancer (shaded) with full-thickness (stage IV) tracheal invasion showing anterior and transverse views; B. Dashed lines show extent of sleeve resection; C. Intraluminal extent of disease on transverse section; D. After resection and placement of sutures; E. Sutures tied extraluminally.*

The plane between the trachea and esophagus is initially developed by blunt dissection, taking care not to injure the esophageal musculature or mucosa. Using a sharp blade, the membranous trachea is incised along the superior border of the planned segment of resection. The incision is then extended circumferentially around to the initial point of entry, mobilizing the upper limit of the 'sleeve'. Similarly, the inferior incision should be placed in the membranous trachea, extending across and circumferentially, while ensuring an adequate margin between the tumor and the line of resection. End-to-end tracheal anastomosis should be tension-free and performed with interrupted sutures, usually Monocryl or Vicryl 2-0. If only short tracheal segments (<3 cm) are removed, these can be anastomosed primarily without any mobilization of the trachea or larynx. Segments longer than 3-4 cm require further mobilization as follows. Figure 5 shows the various maneuvers and length of trachea that can be mobilized by each maneuver. Suprahyoid release of the larynx is performed by detaching the muscles attached to the hyoid using electrocautery (mainly the sternohyoid, geniohyoid and myelohyoid). If additional length is required, the hilum may have to be released, and even further mobilization may necessitate bronchial re-implantation, although these are rarely used and excessive mediastinal mobilization may devascularize the trachea. The trachea is then anastomosed using interrupted Monocryl or Vicryl 2-0 suture, starting in the midline posteriorly and working laterally. Occasionally, a segment of cricoid needs to be excised together with the sleeve (Figure 5). In this case, a sharp Mayo scissors may be used to make the cuts across the cricoid. The inferior tracheal stump can then be fashioned to rotate and fit into the cricoid defect like a piece of a puzzle (Figure 6). In these procedures, it is imperative to prevent unwanted injuries to the recurrent laryngeal nerve, especially to avoid damage to the contralateral nerve if the ipsilateral nerve is sacrificed.

which involves removing a circumferential segment of the trachea (Figure 4). Up to 5 tracheal rings may be resected and repaired primarily with suprahyoid release procedures, and this may be technically easier to reconstruct than wide, window resections. If the tumor involves more than 6-7 tracheal rings or extends to the carina, the tumor is inoperable. The upper limit of the resection should also be at least 1 cm below the subglottis for primary tracheal anastomosis. During the thyroidectomy and central compartment clearance, it is important not to devascularize the trachea, by avoiding excessive circumferential dissection[16-17]. The recurrent laryngeal nerves should be retracted laterally from the tracheo-esophageal groove.
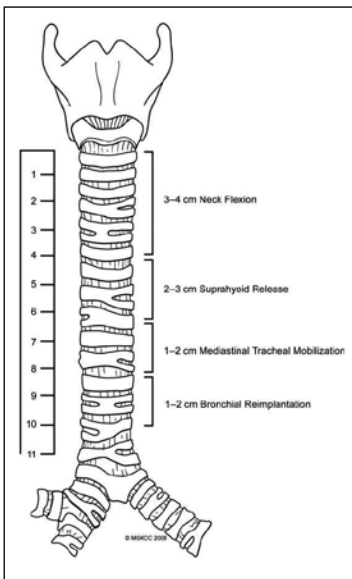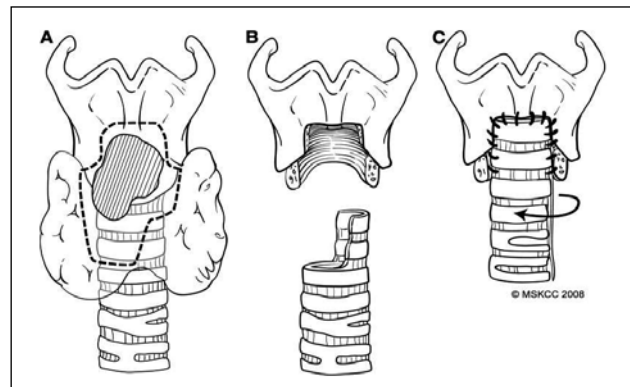

Figure 5: *Tracheal length gained by maneuvers. Neck flexion and suprahyoid release may be performed to close large tracheal defects. Mediastinal mobilization and bronchial re-implantation should be performed with caution in selected cases.*

Figure 6: *Cricotracheal resection with rotation and primary anastomosis. A. Primary disease with cricotracheal invasion with dashed line showing extent of resection. B. Lower segment of trachea fashioned to fit the cricoid defect. C. Lower segment rotated and anastomosis performed to reconstruct cricoid defect*

Laryngeal invasion

Invasion of the larynx occurs in approximately a third of patients with extra thyroid extension, and usually occurs via direct invasion through the thyroid cartilage, through the pyriform sinus via the posterior edge of the thyroid lamina or through the cricothyroid membrane[8,18]. The main options for surgical treatment for laryngeal invasion are shave procedures, partial excision of the framework (thyroid cartilage), partial laryngectomy and total laryngectomy[19]. Shave procedures have limited applications, only used when there is no cartilage invasion beyond the perichondrium. If there is disease extension into the paraglottic space partial or total laryngectomy should be performed. This is usually evident on pre-operative cross-sectional imaging, although occasionally the surgeon may be surprised with this discovery intra-operatively. Submucosal extension may be evident during fiber-optic laryngoscopy, however mucosal ulceration is rare. When laryngeal invasion involves less than 50% of the laryngeal framework, a vertical hemilaryngectomy is the procedure of choice, especially because these tumors tend to be located laterally (Figure 7A and 7B). The need to consider to a total laryngectomy arises when there is significant pharyngeal involvement, contralateral recurrent laryngeal nerve paralysis, or tumor involvement greater than 50% of the larynx or cricoid cartilage. Patient factors also influence the choice of surgery, as older patients with poor pulmonary reserves are less likely to tolerate the aspiration risk that invariably ensues in any patient undergoing partial laryngectomy. More extensive involvement of the pharyngeal and esophageal musculature may even require total pharyngolaryngectomy.

Vertical hemilaryngectomy

Once the tumor specimen has been mobilized and left attached to the larynx, the thyroid perichondrium should be incised and elevated a few millimeters to either side of midline. The larynx is rotated to expose the posterior lamina of the thyroid cartilage on the involved side, and
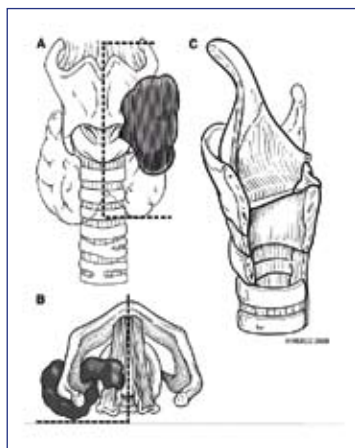
Figure 7: *Vertical partial laryngectomy for thyroid cancer invading the larynx.* **A**. *and* **B**. *Plan of resection incorporating tumor with invaded hemilarynx*
C. *Post-resection defect*

the inner perichondrium and muscular attachments are freed with electrocautery. A thyrotomy can be placed either in the midline, or paramedian so as not to disturb the anterior commissure. The larynx is entered without violating the tumor specimen, and avoiding injury to the uninvolved cord. Once the larynx is entered, the remainder of the specimen can be freed under direct visualization. The thyrohyoid membrane is then divided, extending the incision inferiorly through the piriform sinus along the posterior edge of the thyroid ala. The arytenoid cartilage on the involved side can be frequently saved, which is important to limit scarring of the posterior commisure and reduces the severity of postoperative aspiration. The incision is extended across the cricothyroid membrane, or if cricoid invasion is present, the specimen can then be resected in continuity with the cricoid (Figure 7C). Reconstruction can be achieved with the overlying strap muscles (if not resected) or a sterno-cleidomastoid muscle flap although occasionally a pedicled myofascial or a free flap may be necessary. Complications include wound breakdown, fistula, and poor voice and swallowing function.

If a partial laryngectomy is performed with resection of the paraglottic space and the vocal cord, a separate tracheostomy is required and should be placed through a separate incision below the incision of thyroidectomy. However, a tracheostomy can be avoided if the partial laryngectomy only involves resecting of the framework alone (thyroid lamina) without entering laryngeal mucosa.

Esophageal invasion

Invasion of the esophageal musculature usually occurs with concomitant tracheal invasion, and may be evident on cross-sectional imaging. Patients with suspected tracheal invasion should be evaluated by rigid esophagoscopy to identify the extent of intraluminal involvement.

Invasion of esophageal musculature

More commonly, the tumor extension is confined to the esophageal musculature sparing the mucosa (Figure 8A)[18-20]. In this scenario, retracting the tumor mass away from the esophagus, allows the surgeon to develop a plane between the inner circular layer of esophageal muscle and the submucosa by sharp dissection (Figure 8B). By working carefully in this plane, the tumor can be resected en bloc. With concomitant tracheal invasion, the tracheal resection should precede esophageal dissection, with the tumor resected en bloc with the adjacent structures (Figure 8C).

Intraluminal invasion

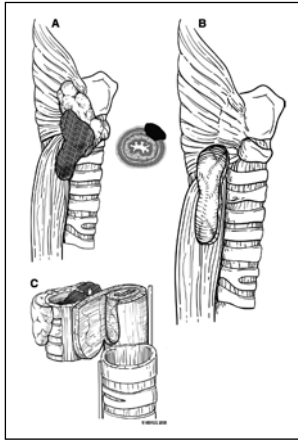Intraluminal involvement requires a partial esophagectomy

Figure 8: *Invasion of esophagus by extra-thyroidal extension from thyroid cancer* **A.** *Invasion of esophageal musculature, with no mucosal and submucosal extension* **B.** *Resection of musculature, sparing submucosa by developing a plane between the two.* **C.** *Invasion into trachea with simultaneous tracheal resection*

and reconstruction with either a regional (pectoralis major) or free flap. After mobilization of the tumor, a plane is developed between the prevertebral fascia and the esophagus, and between the trachea and esophagus, sparing the recurrent laryngeal nerves. The esophagus should be entered inferior to the tumor, and under direct visualization the esophagus is sharply dissected from an inferior to superior direction to remove the entire tumor and attached esophageal segment en bloc. Reconstruction is then carried out over a feeding tube. More extensive invasion may require a total laryngopharyngectomy, segmental or total esophagectomy with a tubed flap. This can be achieved with a tubed free flap (eg antero-lateral thigh), jejunal free flap or gastric pull-up.

Discussion

Thyroid cancer is most effectively treated by surgical resection. Locally invasive thyroid cancers require complete en bloc resection of the primary tumor with adjacent structures. Failure to achieve complete resection results in persistent disease with further functional deficits if left untreated. Salvage surgery in a previously operated or radiated field is difficult. Furthermore, the addition of external beam radiation or radioactive iodine is insufficient to eradicate gross residual disease. In planning aggressive surgery for resection of all gross tumor, a balance must be maintained between complete resection and functional outcome. Postoperative radioactive iodine, and external beam radiation can be used after adequate surgery to control microscopic disease and prevent future locoregional recurrences.

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Nutrition in Head and Neck Cancer

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Abstract
The nutritional management of patients with head and neck cancer is complex. Nutrition is now an accepted fundamental long term prognostic factor in head and neck cancer patients. Prevention of the development of malnutrition is expected to lead to a better response to therapy and fewer, treatment related complications[1]. Nutritional intervention should be recognised as an integral part of cancer therapy to improve clinical outcomes and quality of life[2].

Key Words
Head and neck cancer, malnutrition, nutrition intervention, nutrition support, quality of life.

Introduction
The nutritional management of patients with head and neck cancer is complex. Frequently these patients are at risk of malnutrition as a result of the site of their cancer, the disease process and the treatment[3]. Furthermore patients may have long standing dietary habits and detrimental lifestyle factors such as alcohol misuse that can predispose them to malnutrition[4].

Head and neck cancer is a broad term that includes an assorted group of malignancies that have variable presentation, prognosis and treatment[5]. Head and neck cancer is the 6th most common type of cancer and accounts for approximately 650,000 new cancer cases world wide each year[6]. There are various sites of disease. The mouth, lip and tongue (oral cavity), the oropharynx, hypopharynx and nasopharynx, the glottis and the thyroid represent the majority of head and neck malignancies[7]. Most cancers of the head and neck are squamous cell carcinomas. The main risk factors associated with head and neck malignancies are tobacco and alcohol misuse[8].

Surgery, radiotherapy and chemotherapy are the treatments of choice for curative or palliative management of locally advanced head and neck cancers[8]. The site of disease and associated treatments can cause problems with eating, swallowing, breathing, speech and voice[7].

Malnutrition
The incidence of malnutrition in patients with cancer ranges from 40-80%[9] and has multiple causes. It is often defined as involuntary weight loss of more than 10% in the previous six months, 5% in one month, or 1-2% per week[3,10]. Malnutrition is associated with increased risk of infection, treatment toxicity, poorer quality of life and reduced life expectancy[11-13]. Hammerlid et al[14] (1998) have estimated that over 50% of head and neck cancer patients are malnourished. Ravasco et al[15] (2005) go further, suggesting that up to 75% of newly diagnosed patients are malnourished. Patients with head and neck cancers may present with dysphagia, odynophagia, weight loss and / or anorexia. Nutrition intervention aims to prevent further weight loss, treat existing malnutrition and improve treatment tolerance[16,17].

Nutritional Intervention
Appropriate nutritional intervention is influenced by treatment decisions. Usually stage I or II disease is managed with single modality treatments whilst stage III and IV cancers usually require multi-modality treatment[8].

Surgery
The effect of surgery on a patients' ability to eat depends upon the site of disease and extent of resection[18]. Severe malnutrition is known to be detrimental to surgical outcome[10] and many surgical patients are unable to meet their nutritional needs from normal food alone. Weimann et al[19] (2006) encourage the use of oral nutritional support during the pre-operative period. Furthermore, patients with severe nutritional risk have been shown to benefit from nutritional support for 10-14 days prior to major surgery even if surgery has to be delayed[19].

ESPEN Guidelines19 define severe nutritional risk as:
- Weight loss > 10-15% within 6 months.
- BMI < 18.5 kg/m2
- Subjective Global Assessment Grade C
- Serum albumin < 30g/L
- Inability to maintain intake above 60% of recommended intake for more than 10 days.

Within surgery, interest has been shown in the use of immune modulating enteral nutrition formulae enriched with arginine, omega-3 fatty acids and nucleotides. Trials in both general surgery and gastrointestinal cancer patients suggest that the use of immune modulating formulae has contributed to a reduction in wound healing complications, infections and consequently reduced length of stay[20,21]. However, minimal effects have been demonstrated in patients with head and neck cancer.

Radiotherapy / Chemotherapy

The effect of radiotherapy / chemoradiotherapy on a patient's ability to eat depends upon the radiation prescription and / or the structures within the treatment field[22]. Weight loss can occur as early as the second week of treatment with the greatest decline occurring in weeks three and four[23,24]. Munshi et al[23] (2003) found that 37% of their study population lost more than 5kg during treatment while Larsson et al[24] (2005) reported all patients losing between 2-11% of their weight despite dietetic intervention during radiotherapy. Gosselin et al[25] (2008) suggests that 'patients lose less weight during treatment when aggressive symptom management strategies are implemented using a patient generated subjective global assessment tool and having a dedicated Dietitian on the staff who can facilitate those interventions'.

It is recognised that achieving and maintaining adequate nutrition intake during treatment requires motivated and committed patients. Swallowing problems, loss of appetite, xerostomia and dysgeusia can increase the time and effort required for optimal intake. In addition, for some patients the thought of weight loss may be viewed as a benefit of therapy[26], thus presenting another obstacle. Patients require intensive support both at home and at the hospital to help them maintain nutritional intake during and after treatment.

Nutritional Assessment

All patients with head and neck cancer should undergo a nutritional assessment at diagnosis, and at regular intervals thereafter in light of both the affects of the tumour itself and its associated treatments upon nutritional status. NICE7 (2004) recommends that a Dietitian should be an integral member of the head and neck multidisciplinary team. Early and timely nutritional intervention in patients with head and neck cancer can improve calorie intake, hydration, treatment tolerance and subjective quality of life[27,15]. Assessment at presentation can identify those patients who are at risk of nutritional problems and early interventions can reduce the possibility of developing nutrition related morbidity. Although an improvement in survival due to nutritional interventions has not yet been shown16, the impact of malnutrition upon quality of life and treatment tolerance cannot be underestimated.

A useful assessment tool for assessing nutritional status is the scored patient generated subjective global assessment tool (PG-SGA)[28]. The PG-SGA score can be used as an objective measure to demonstrate the outcome of nutritional intervention. It is accurate in identifying well nourished from malnourished patients[29]. Nutrition assessment pertaining to cancer management should include: anthropometric measures (weight history, height, body mass index, hand grip strength and mid arm circumference), a detailed dietary history, stage of disease, proposed treatment plan and intent, biochemical indices where appropriate, diet and alcohol history, social set up e.g. cooking facilities, social support, employment status and patients views of nutrition status in order to ensure appropriate nutritional intervention[18].

Types of Nutritional Interventions

The principle aim of nutritional intervention with cancer patients is to 'maintain physical strength and optimise nutritional status within the confines of the disease'[2]. 'Nutritional intervention should be tailored to meet the needs of the patient and be realistic for the patient to achieve'[30]. Whilst weight maintenance is not always the primary goal of intervention, numerous studies strongly suggest that substantial weight loss, >10%, leads to adverse consequences including, reduced response to chemotherapy & radiotherapy, increased morbidity, poor quality of life (QoL) and increased mortality rate[10].

Nutritional interventions can include relaxation of previous therapeutic diets in order to minimise further nutritional compromise. Food fortification is often suggested as the first line of nutritional support intervention; however, this may not necessarily be appropriate in this setting due to the intensity of treatment regimens and their side effects. It is important to treat each patient individually, in terms of their specific cancer diagnosis and planned treatment. Patients may require more intensive nutritional support methods from the beginning of treatment over and above traditional food fortification methods with the early use of oral nutrition support e.g. nutritionally complete liquid supplements and enteral nutrition (EN). This can be initiated at any point from diagnosis.

Types of Enteral Nutrition Support

Nutrition support with tube feeding is frequently required. The type and volume of EN will depend upon the patients' symptoms and current intake and is likely to change throughout and following treatment. The choice of feeding route will depend upon local arrangements however, clinical considerations should include: site of tumour, treatment plan, and intent, predicted duration of enteral feeding and patient choice. Gastrostomy insertion is recommended if enteral feeding is expected to be required

for longer than 4 weeks[31,32]. Prophylactic gastrostomy insertion is now often recommended in patients who are expected to need prolonged EN. However, there are currently no formal national patient selection guidelines for gastrostomy insertion in head and neck cancer and this remains a contentious area of practice.

Conclusion

Nutrition has an important role in the management of head and neck cancer and its associated treatment modalities. Comprehensive nutritional assessment is necessary to ensure early recognition of patients who have or are at risk of developing malnutrition to allow timely and appropriate intervention. Nutritional interventions are varied and have an important role throughout the course of the disease, from diagnosis through to terminal care[33]. Their effective implementation should ultimately aim to improve quality of life and enhance the beneficial effects of treatments[34].

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Tuberculosis in The Head And Neck

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Introduction

The WHO report on global tuberculosis (TB) control-2009[1] reported 9.27 million new cases of TB in 2007; a significant increase from the 6.6 million cases in 1990. Asia (55%) and Africa (31%) accounted for most of the new cases, but significant numbers were also recorded from the Eastern Mediterranean region (6%), Europe (5%), and the Americas (3%). 1.37 million of the 9.27 million cases were HIV positive, with 79% of these from Africa. The reemergence of tuberculosis as a public health hazard in non-endemic areas has been attributed to multidrug-resistant organisms, immigration from endemic areas, deteriorating health care infrastructures, and the AIDS epidemic[2]. Further, reports indicate that a higher proportion of cases in re-emergent tuberculosis are extra-pulmonary (22%), and accounted for 29% of the increase[3].

The Head-Neck region accounts for a significant proportion of the extra-pulmonary manifestations of tuberculosis. Cervical tuberculous lymphadenitis is by far the commonest manifestation and accounts for 15% of all extra-pulmonary cases. Other Head-Neck manifestations are much rarer, together accounting for some 1% of extra-pulmonary cases,[2,4] and may never have been encountered by surgeons practicing in non-endemic areas. This is however changing, especially in situations wherein tuberculosis is encountered in the immune-compromised.

This report presents the authors' experience with the various Head-Neck presentations of tuberculosis.

Bacteriology

Mycobacterium Tuberculosis - *The Mycobacterium tuberculosis* (MTB) bacillus is a non motile, obligate aerobe which is ubiquitous in soil and water, and domestic and wild animals[5]. Its obligate aerobic characteristic is said to account for its predilection for the well-aerated upper lobes of the lungs. It is a facultative intracellular parasite especially found in macrophages, and has a slow regeneration time of 15-20 hours; both characteristics which account for its relatively low sensitivity to medical therapy and the necessity of long treatment durations. Laboratory cultures, undertaken on the Lowenstein-Jensen egg based medium or the Middlebrook's agar based medium, too take inordinately long with the growth of MTB colonies becoming apparent only after 6-8 weeks of culture. The cell wall of these organisms is rich in lipids, making the surface hydrophobic and thus resistant to many disinfectants as well as to common laboratory stains. On gram staining, MTB stains a very weak Gram-positive (cells referred to as "ghosts"). Once stained though, the bacilli cannot be decolorized with acid solutions, hence the name acid-fast bacilli.

Non- Tuberculous Mycobacterium - The *M. tuberculosis complex* includes four other genetically related bacteria

including *M. bovis*, *M. africanum*, *M. canetti* and *M. microti.* Mycobacteria other than *M. tuberculosis complex* and *M. lepra* are known as Non-Tuberculous Mycobacteria (NTM) and include many members, prominent among which are the *M. scrofulaceum, M. avium- intracellulare* and *M. fortuitum*[6].

Mycobacterium bovis causes TB in cattle, and milk infected with *M. bovis* was a source of tuberculosis in humans till the introduction of routine pasteurization. The primary inoculation in these instances was believed to be in the tonsil with subsequent spread to the cervical lymph nodes.

Non-tubercular bacteria are more likely to be associated with extra pulmonary infections. They are seen in greater proportion in AIDS related Mycobacterial infections, and are more likely to demonstrate resistance to the first line anti-tubercular drugs.

Diagnosis of Tuberculosis
The diagnosis of extra-pulmonary tuberculosis often has to rest on the composite picture of the patient's history, demographics, physical examination, a Mantoux (PPD) skin test, microbiologic evaluation of fluids, and the FNAC/ biopsy features. A definitive diagnosis is only confirmed on identification of the organism by microbiology or by cytology/ histology, but such isolation of the organism is often not the case, and on occasions treatment has to be commenced based on the other evaluations with the response to treatment itself serving as a presumptive confirmation of the diagnosis.

Tuberculosis of the head-neck has two different patterns of presentations- one a mass lesion e.g. tubercular lymphadenitis or a deep seated granuloma; and second, mucosal/ skin disease presenting as non-healing ulcers

Figure 1: *Typical tubercular ulcer with flat and granular base and undermined mucosal edges.*

with scarring (ulcer with undermined edges and a granular base, or apple-jelly nodules- Figure 1). A history of indolent illness not compatible with acute infective pathology or a malignant disorder is one indicator of tubercular infection. The classical history of evening rise of temperature, night sweats and weight loss may be absent. Travel to endemic areas, contact with cases of open pulmonary tuberculosis, or immune-suppression are pointers. Immigrants from endemic areas have a higher probability of tuberculosis, and in the western literature the reported incidence is higher among ethnic minorities (47.9 per 100,000) with >40% having extra-pulmonary tuberculosis[2]. Routine haematology is usually normal except for an elevated ESR.

A positive Mantoux /PPD skin test is an indicator of either a previous or recent infection, or of sensitization to tubercular antigens (BCG vaccination). Cases with active tuberculosis would be expected to manifest a significant response, and the test is a sensitive though non-specific indicator in the immune-competent (sensitivity 74%to 96%)[2,7] but not in the setting of HIV immune-suppression (sensitivity 20-40%). The criteria for positivity in the immune-competent is taken as induration of >10 mm, but in the immune-compromised a reaction of >5 mm may also be significant.[8] A chest X-ray is statutory and may demonstrate evidence of current or past tuberculous infection in 15-30%[7, 9].

Accessible mass lesions such as lymph nodes may be sampled by Fine-needle aspiration cytology (FNAC) with a reported sensitivity ranging from 77% to 93% and a specificity of 93%[2,7]. It is currently the main diagnostic test for cervical tuberculosis. The FNAC if inconclusive may be repeated, but if the repeat evaluation too is inconclusive a biopsy is then required. The bacilli per se may not be visualized on histology, but other indicators of tuberculosis such as caseation necrosis, epitheloid cell granuloma and Langerhan's cells are usually seen and are on many occasions the only pointer to the diagnosis[10].

It is also essential to evaluate the aspirate / biopsied tissue by microbiology and culture techniques as this not only confirms the diagnosis but also provides the opportunity to undertake sensitivity tests. This becomes especially important in cases with recurrent or treatment unresponsive disease. Smears or tissues are stained for acid-fast bacilli (AFB) by Ziehl-Nielsen, Wade-Fite, or auramine-rhodamine (fluorescent) techniques. Classical cultures techniques on the Lowenstein- Jensen medium may take six to eight weeks, but currently rapid growth and identification within 7 days can be done with help of the "BACTEC" culture method[11].

Current technology using DNA probes and polymerase chain reaction (PCR) can greatly supplement traditional direct detection techniques[12,13]. These newer techniques amplify and detect specific MTB antigens, and detection of AFB is possible at much lower concentrations than was possible with the traditional techniques of AFB staining and microscopic evaluation of slides. Real-time PCR provides the advantages of improved sensitivity and rapidity of diagnosis (results may be available within hours of DNA extraction). On theoretical grounds the technique has lower risks of contamination since both reaction and detection occurs in a single tube, and should provide for a 100% specificity of the diagnosis[14]. A new skill set is however required in the microbiology laboratory to undertake these tests, and the authors' experience has been that in their practice situations the PCR may provide for some false positive results.

Blood based Elisa tests for TB, and commercial blood tests that use T cell based interferon-gamma release assays have recently become available[15]. Newer genotypic approaches are being developed to detect drug resistance[16].

Clinical aspects of Head and neck tuberculosis

Infection by Mycobacterium may be by direct inoculation or caused by haematogenous spread from another focus (usually pulmonary). Most extra-pulmonary tuberculosis is consequent to haematogenous spread, but direct inoculation of bacilli into the upper aero-digestive tract is also possible due to exposure from air borne bacilli or more commonly from the sputum in cases with open pulmonary tuberculosis.

Tuberculous Cervical Lymphadenitis

Enlarged cervical lymph nodes are the most common manifestation of extra-pulmonary tuberculosis in the head-neck. The initial site of infection may well be direct inoculation in the Waldeyer's ring from wherein the bacilli may then traverse to the lymph nodes. The upper deep jugular nodes (Level I and II) are the most commonly affected[7]. Some weight loss and low grade fever may be noted but such symptoms are often absent[7].

Four clinical presentations are described[17,7]- first a single discrete node in the submandibular or carotid triangles and especially seen in young children; second multiple matted lymph nodes with periadenitis and suppuration leading to cold abscesses and sometimes sinus formation; third multiple solitary nodes; and lastly the retropharyngeal abscess secondary to tuberculosis of the cervical vertebrae.

Affected nodes may coalesce and suppurate in about 10% of cases to form a fluctuant abscess which does not routinely display significant pain or redness or signs of acute inflammation ("Cold Abscess", "scrofula"). Since

Figure 2: *Scrofula (Tubercular cervical lymphadenopathy) with healed sinuses.*

most nodes are deep to the investing layer of deep fascia, the abscess too is usually deep and may be localized to the parapharyngeal space or the carotid sheath. In another 5%, the abscess may penetrate the investing layer of deep fascia so as to also manifest with an additional small subcutaneous abscess ("Collar-stud abscess"), which may occasionally progress and ulcerate through the skin to form a sinus which is classically puckered and adherent to the underlying lymph node (Figure 2)[2,8]. The nature of the pus if extruded is characteristic- manifesting as thick, "cheesy", "caseous" debris, or creamy thick pus.

Retropharyngeal abscess in Tuberculosis is anatomically posterior to the pre-vertebral fascia, and presents with dysphagia and a diffuse bulge of the posterior pharyngeal wall which is often imperceptible to clinical evaluation and may only become apparent after radiology (Figure 3a). The abscess is believed to be secondary to suppuration in the

Figure 3a: *X-Ray soft tissue neck demonstrating grossly widened pre-vertebral space secondary to a retropharyngeal abscess.*

cervical vertebrae, though radiologic evidence of the same is not always forthcoming. Nevertheless, a CT/ MR of the cervical spine, immediate cervical immobilization, and an orthopaedic opinion are prudent. In the authors' experience some retropharyngeal abscesses are secondary to involvement of the clivus/ skull base rather than the cervical spine (Figure 3b, 3c)

Aspiration of the abscess- either by an intra-oral or by the trans- cervical route- relieves the dysphagia, and the typical thick creamy pus provides clinical confirmation of the diagnosis.

Figure 3b
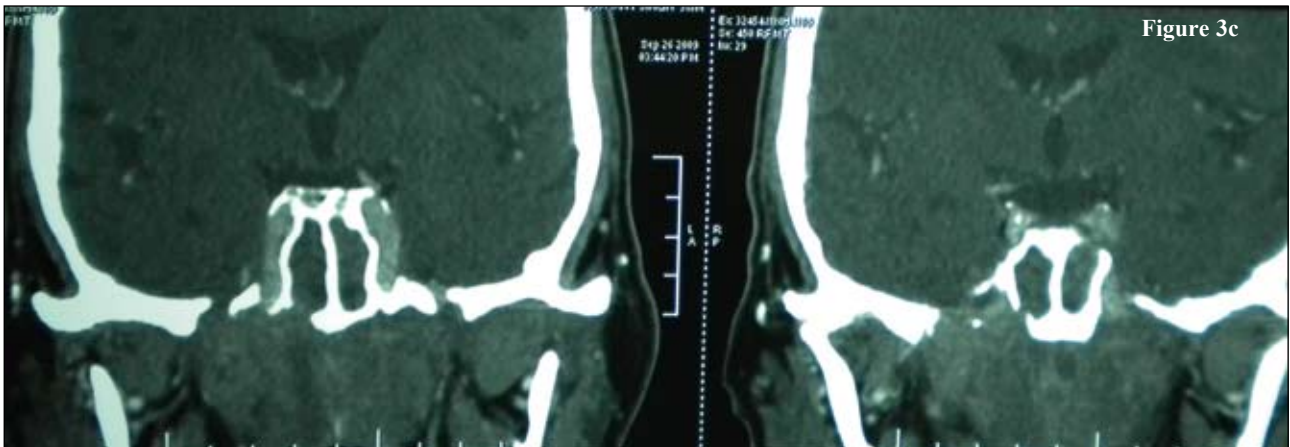
Diagnosis and Treatment- As detailed in the previous section, the diagnosis is usually by FNAC or aspiration of pus, and sometimes by biopsy. The response to the Mantoux test, an elevation of the ESR, and a lack of response to conventional antibiotics may aid the diagnosis.

Medical treatment with multidrug therapy is the standard treatment for tuberculosis at any site in the body. The WHO recommends two types of dosing regimens- daily regimen, and three times per week regimen. The three per week regimen has been designed to facilitate Directly Observed Treatment- Short course (DOTS) in the community wherein doses are taken under the direct observation of a community health worker to ensure compliance; but if compliance is not perceived to be a problem then the daily regimen is usually preferred by most hospital physicians. The first line drugs are Isoniazid, Rifampicin, Pyrazinamide, Ethambutol and Streptomycin administered in doses as in Table 1.

The WHO recommends a standard treatment regimen comprising of 2 months of quadridrug therapy and 4 months of two drug therapy (i.e. 2HREZ+ 4HR). This regimen is now standard for pulmonary tuberculosis, but expert opinion often recommends longer treatment durations for extra-pulmonary tuberculosis (EPTB) with 9-12 months being the usual treatment duration for tuberculosis involvement of the meninges, bones and joints. The authors practice for cervical TB lymphadenitis is to recommend 3 months of HREZ followed by 5-6 months of HR (3HREZ + 6HR).

Some overtreatment is justifiable as partially treated infections, when recurrent, are more likely to demonstrate resistance to the first line drugs (Multi-drug resistant Tuberculosis- MDRTB) and pose very significant management difficulties. Similar difficulties with MDRTB

Figure 3c

Figure 3b & c: *Tubercular involvement of the clivus and skull base leading to bone destruction and a high retropharyngeal abscess.*

Table 1: First line medical treatment for Tuberculosis				
Drug	Daily dosing		3/ week dosing	
	Dose (mg/kg)	Maximum (mg)	Dose (mg/kg)	Maximum (mg)
Isoniazid (H)	5 (4-6)	300	10 (8-12)	900
Rifmapicin (R)	10 (8-12)	600	10 (8-12)	600
Pyrazinamide (Z)	25 (20-30)	-	35 (30-40)	-
Ethambutol (E)	15 (15-20)	-	30 (25-35)	-
Streptomycin (S)	15 (12-18)	-	15 (12-18)	-

can arise in case of inadequate treatment compliance by patients, and patients therefore have to be specially cautioned on this aspect. This is especially relevant as minor side effects such as nausea and malaise are common at the initial initiation of treatment, and patients are prone to discontinue therapy at this stage.

Newer rifamycins such as rifabutin and rifapentine are now available. Rifabutin may be preferred to rifampicin in HIV patients on protease inhibitors. Injectable agents such as kanamycin, amikacin, capreomycin, and streptomycin, and fluoroquinolones (moxifloxacin, gatifloxacin, levofloxacin, and ofloxacin) are used in MDR-TB. Other second line drugs are available orally (ethionamide and prothionamide, cycloserine, terizidone, and p-aminosalicylic acid), but are bacteriostatic rather than bactericidal. In general, second line therapy for MDR-TB is to be based on sensitivity results if available, and best undertaken in conjunction with an infectious disease specialist.

Surgery has a role in two situations-a) to obtain material for biopsy and for microbiology and sensitivity studies; and b) for debridement and surgical clearance of disease not expected to respond to anti-tuberculous therapy (ATT). Small collections of caseous pus may resolve with ATT and do not always require surgical drainage. Large collections are however best evacuated by aspiration with a wide bore needle. There is a theoretical risk of seedling of the needle tract and of sinus formation, and traditional teaching has therefore advocated that aspiration be undertaken with the needle passed along an "anti-gravity" track. If the diagnosis is reasonably certain, then instituting ATT prior to the aspiration is also prudent.

In the situation wherein the lymphadenitis does not resolve significantly with 6-8 weeks of ATT[18], surgical excision may be required to obtain material for culture/ sensitivity and to aid healing. Cases with MDRTB on second line drugs may also need surgical debridement in addition to medical treatment.

Head-Neck Tuberculosis other than cervical tubercular lymphadenitis

Other than cervical tuberculosis, other manifestations of tuberculosis in the Head-Neck are now extremely rare even in endemic areas[19]. Such lesions however are progressive, and may be potentially infective, and familiarity with their presentation is therefore necessary. Previous generations of physicians had granted tuberculosis the epithet of being "a great imitator", and cautioned that the diagnosis be considered in the differential diagnosis of any clinical situation with a slightly unusual manifestation. This continues to be true today.

Laryngeal Tuberculosis

In the era prior to anti-tuberculous therapy, 37% of patients with pulmonary tuberculosis also suffered from laryngeal Tuberculosis[20]. Currently though the incidence is miniscule, and the commonest manifestation is a non-infective laryngitis and hoarseness consequent to the recurrent vocal fold trauma caused by the persistent cough of pulmonary tuberculosis[19]. Recurrent laryngeal nerve paralysis caused by apical pulmonary tuberculosis or mediastinal lymphadenopathy also occurs[20], and may occasionally reverse with anti-tubercular therapy.

Direct involvement of the larynx is often associated with active pulmonary tuberculosis, and 20% are sputum positive[2, 20]. Patients commonly present with hoarseness, odynophagia, otalgia, dysphagia, cough and respiratory distress[20]. The classical presentation is of initial significant edema ("turban epiglottis", "piriform arytenoids"), which progresses to superficial ulceration with pale granulations, (Figure 4) and subsequent perichondritis and scarring.

The lupus vulgaris variant[21] of laryngeal tuberculosis manifests with a minimally symptomatic and non-ulcerative form with significant nodularity, destruction and scarring. These are presumably cases wherein the host immunity is strong and has overwhelmed the infection. It presents with discrete nodules which may coalesce to create a bosselated mass classically on the epiglottis. Lupus runs a very chronic course, with tendency to heal in

Figure 4: *Laryngeal tuberculosis demonstrating some epigottic edema and pale granulations on the left arytenoid.*

areas while activity continues elsewhere[21], consequently leading to considerable scarring. With time the epiglottis may be partially or completely eroded, and significant induration occur in the base of tongue. Clinically, the lesion may be confused with syphilis, or with malignancy, and malignant transformation too has been reported. Histology indicates scar tissue and epitheloid granulomas and Langerhans cells but AFB are unusual. Lympadenopathy is unusual and the tuberculin skin test (Mantoux test) classically shows a significant response.

Tuberculosis of the Ear and the Skull Base

The typical presentation of painless, thin watery ear discharge with multiple tympanic perforations is now extremely rare. Pale and firm granulations should incite clinical suspicion, as should unexplained sensori-neural hearing loss and facial paralysis, or the occasional situation of a bony sequestrum seen on otoscopy[22]. The advent of routine imaging has indicated that many such cases have significant bone invasion and extension to the infra-labyrinthine and petroclival areas (Figure 5a). More extensive involvement of the skull base and the skull vault (Figure 5b) has also been noted, and may present with

Figure 5a: *Right petro-mastoid tuberculosis with extensive bone destruction and bone reaction indicated by hyperostosis.*
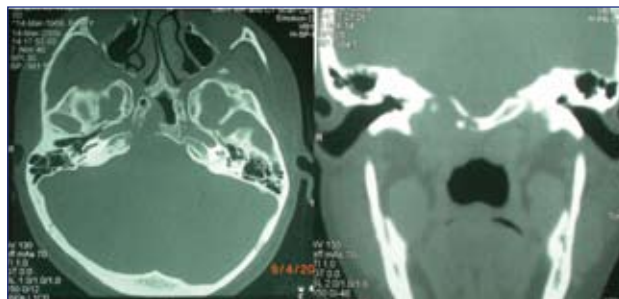

Figure 5b: *Tuberculosis of the skull base medial to the carotid canal in the right petro-clival region.*

deep seated pain, cranial nerve paralysis, mass in the nasopharynx or sphenoid, or with multiple sinuses on the scalp.

The diagnosis is aided by microbiologic evaluation of the ear discharge and by biopsy[22]. A chest X-Ray may indicate a pulmonary lesion and provide a clue to the diagnosis[22,23].

Treatment is by ATT which in the cases with significant skull base involvement may need to be continued for 12-18 months. The perceived risks of extradural abscess and tuberculous meningitis have led towards a more aggressive surgical approach than may be undertaken for osseous tuberculosis elsewhere. Surgery is undertaken under cover of ATT therapy, and can in most instances only provide for a partial debridement. The usual finding is of characteristically pale and tough granulations and a complete debridement may place the facial nerve and the intra-petrous carotid at risk. In the authors' limited experience, a facial nerve decompression is hazardous and the authors have noted facial nerve recovery with ATT alone and no formal surgical decompression. The authors' practice has been to undertake a sub-total debridement through an extended trans-aural skull base approach, and if otherwise appropriate to provide for a good meatoplasty which may drain the nidus and prevent collection of pus, till the time that it responds to medical therapy with ATT.

Nasal, nasopharyngeal & PNS Tuberculosis

Most nasal and nasopharyngeal tuberculosis is by direct inoculation, and may be infective. Three forms have been described[24].

a) lupus vulgaris with skin involvement and scarring which may like its laryngeal counterpart heal without treatment but with scarring;
b) a nodular-ulcerative form with initial mucosal pink and yellow 'apple-jelly' nodules which fail to blanch with topical vasoconstriction, and subsequently ulcerate and may cause a septal perforation with irregular margins and pale granulations; and

c) the sinus or anterior skull base granuloma which presents as diffuse thickening of the mucosa with or without associated osteomyelitis and sinus formation, and is usually noted in the supra-orbital region.

Nasopharyngeal tuberculosis presents with nasal obstruction and discharge and may be associated with aural or petrous involvement. Cervical lymphadenopathy is seen in 70% and may be the only and presenting complaint in 50%[25]. Systemic symptoms are noted in only 30%,[25] and the chest X-ray may show pulmonary disease or hilar lymphadenopathy[26]. Smears may be negative as bacilli are few in the tissues, but the biopsy would indicate to the diagnosis by demonstrating epitheloid granulomas with or without caseation[26].

Treatment is by ATT. Surgery may be required for debridement of bony sequestra or for a skull base granuloma.

Oral & Pharyngeal Tuberculosis

Thompson in 1919 found 6.5% of tonsillectomy specimens showed evidence of tuberculosis[27]. He described pharyngeal tuberculosis to be a slowly progressive disease with chronic nodular irregularity of mucosa which coalesced into raised bosselated epithelium covered with mucinous secretion. The typical presentation of oral tuberculosis is with a painless ulcer with undermined edges, a granular base, and no induration (Figure 1a) and regional lymphadenopathy. Lesions may occur anywhere-common sites being the gum, the tongue, palate, and the floor of mouth[2]. The differential diagnoses include malignancy, syphilis, sarcoidosis and fungal ulcers. Similar to nasal lesions, the diagnosis is more likely to be provided by histology than by microbiology.

Salivary glands Tuberculosis

Involvement of the lymph nodes in substance of / in the vicinity of the parotid or submandibular gland may simulate a chronic parotitis or sub-mandibular adenitis[28]. Facial paralysis may be a feature, but is expected to improve with anti-tubercular therapy. Treatment is on the same lines as for cervical tubercular lymphadenitis.

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The Role of Co-morbidity in Head and Neck Cancer

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Abstract

Background: Comorbidity is defined as the presence of one or more concomitant but unrelated pathological or disease processes. More than half of patients presenting with head and neck cancer harbour conditions that will ultimately define the outcome of treatment in more definitive terms than the actual cancer that they have developed.

Objectives: Comorbidity can be measured relatively easily and there are many scales validated for use in head and neck cancer. It is well recognised that patients with an increased comorbidity burden have increased mortality, decreased disease specific survival and cannot tolerate the same treatment schedules as those patients who have no comorbidity. This article sets out the argument for the prospective collection of comorbidity data by describing the important role that comorbidity plays in various aspects of head and neck oncologic practice.

Conclusions:

The prospective collection of data on comorbidity will enable a more accurate assessment of overall prognosis, compare treatment results across centres and help us to tailor treatment plans to individual patients depending on their comorbid status.

Keywords:

Comorbidity, head and neck cancer, prognosis, survival

Introduction

Comorbidity or the presence of an additional illness unrelated to the tumour has a significant impact on the prognosis of patients with head and neck cancer (HNC). We are all familiar with dealing with patients who present with a multitude of medical problems in addition to their primary cancer. The majority of patients presenting with HNC have a history of alcohol and/or tobacco abuse. This is the primary reason for the high incidence of comorbid conditions in patients with HNC.

The literature suggests that many factors may determine the outcome of treatment in HNC. Performance status, gender[1], race[2], tumour related factors and molecular factors[3] have all been extensively studied. Evidence relating to outcome and comorbidity scores is robust and it is rapidly becoming evident that this may represent one of the most important prognostic indicators.

It is well recognised that patients with significant comorbidities who present with HNC have an increased mortality, decreased disease specific survival and are unable to tolerate the same treatment schedule that patients without these additional issues will manage. When they do undergo treatment, patients with significant comorbidity issues develop more complications and often require a prolonged hospital stay. This is especially true in patients with oral, oropharyngeal, laryngeal and salivary gland malignancies.

If comorbidity represents such a significant factor in patient outcome it seems reasonable to suggest that data on HNC should be collected routinely and published to allow a more informed decision making process when considering treatment options for our patients.

Appendix 1

Cogent comorbid ailment	Grade 3 Severe decompensation	Grade 2 Moderate decompensation	Grade 1 Mild decompensation
Renal System			
End-stage renal disease	• Creatinine > 265m mol/L with multi-organ failure, shock or sepsis • Acute transplant rejection • Acute dialysis	• Chronic Renal Insufficiency with creatinine >265m mol/L • Stable transplant < 6 months • Chronic dialysis	• • Chronic Renal Insufficiency with creatinine 177-265m mol/L • Stable transplant > 6 months ago
Endocrine System (Code the comorbid ailments with the (*) in both the Endocrine system and other organ systems if applicable)			
Diabetes Mellitus	• Hospitalisation < 6 months for DKA • Diabetes causing end-organ failure including retinopathy, neuropathy, nephropathy*, coronary disease* or peripheral arterial disease*	•• IDDM without complications • Poorly controlled AODM	• • AODM controlled by oral agents only
Neurological System			
Stroke	• Acute stroke with significant neurologic deficit	• Old stroke with significant neurologic residual	• Stroke with no residual • Past or recent TIA
Dementia	• Severe dementia requiring full support for activities of daily living	• Moderate dementia (not completely self-sufficient, needs supervising)	• Mild dementia (can take care of self)
Paralysis	• Paraplegia or hemiplegia requiring full support for activities of daily living	• Paraplegia or hemiplegia requiring wheelchair, but able to do some self care	• Paraplegia or hemiplegia but ambulatory and providing most of self care
Neuromuscular	• MS, Parkinson's, Myasthenia Gravis or other chronic neuromuscular disorder and requiring full support for activities of daily living	• MS, Parkinson's, Myasthenia Gravis or other chronic neuromuscular disorder, but able to do some self care	• MS, Parkinson's, Myasthenia Gravis or other chronic neuromuscular disorder, but ambulatory and providing most of self care
Psychiatric			
	• Recent suicidal attempt • Active schizophrenia	• Major depression or bipolar disorder uncontrolled • Schizophrenia controlled w/ meds	• Major depression or bipolar disorder controlled w/ meds
Rheumatologic (including rheumatoid arthritis, systemic lupus, mixed connective tissue disorder, polymyositis, rheumatic polymyositis)			
	• Connective tissue disorder with secondary end-organ failure (renal, cardiac, CNS)	• Connective tissue disorder on steroids or immunosuppressant medications	• Connective tissue disorder on NSAIDS or no treatment
Immunological System			
AIDS	• Fulminant AIDS w/KS, MAI, PCP (AIDS defining illness)	• HIV+ with h/o defining illness CD4+ <200/mL	• Asymptomatic HIV+ patient • HIV+ with h/o AIDS defining illness CD4- >200/mL
Malignancy (excluding cutaneous basal cell Ca., cutaneous SCCA, carcinoma in-situ and intraepithelial neoplasm)			
Solid tumour including melanoma	• Uncontrolled cancer • Newly diagnosed but not yet treated • Metastatic solid tumour	• Any controlled solid tumour without documented metastases, but initially diagnosed and treated within the last 5 years	• Any controlled solid tumour without documented metastases, but initially diagnosed and treated > 5 years ago
Leukaemia or myeloma	• Relapse • Disease out of control	• 1st remission of new dx < 1 year • Chronic suppressive therapy	• H/o leukaemia or myeloma with last Rx > 1 year prior
Lymphoma	• Relapse	• 1st remission of new dx < 1 year • Chronic suppressive therapy	• H/o lymphoma with last Rx > 1 year prior
Substance abuse			
Alcohol	• Delirium tremens	• Active alcohol abuse with social behavioural or medical complications	• H/o alcohol abuse but not presently drinking
Illicit Drugs	• Acute withdrawal syndrome	• Active substance abuse with social behavioural or medical complications	• H/o substance abuse but not presently using
Body weight			
Obesity		• Morbid (i.e., BMI>38)	

OVERALL COMORBIDITY SCORE (Circle one)   0   1   2   3

How is comorbidity assessed?
Multiple validated tools exist to calculate comorbidity burden. Many of these are generic but disease-specific ones also exist. These are based on both the presence of a concomitant disease and use variable scoring techniques that classify comorbid disease burden into ordinal groups. Data can be collected retrospectively from patient notes or electronic databases (e.g. HES data, Medicare) with a good degree of accuracy or the process can be more efficiently performed using self administered questionnaires. It is necessary to collate the data at the time of diagnosis as the comorbidity burden may change after treatment has started and this may affect its prognostic accuracy.

The two most commonly used instruments within head and neck oncologic practice are the Adult Comorbidity Evaluation Index ACE-274 (Appendix 1) and the Charlson Index[5](Appendix 2). ACE-27 has been extensively validated worldwide and is a useful aid in predicting survival[6,7,8], complications[6,9], functional outcome[10], and quality of life[11,12]. Difficulties with this scoring system are based around some of the scores necessitating invasive testing for confirmation e.g. arterial blood gas analysis. It includes 27 different comorbid ailments from different organ systems. Each individual ailment is graded into a three category severity system; none-0, mild-1, moderate-2 and severe-3. The overall score is assigned on the basis of the highest scoring ailment except in the advent of two or more moderate (2) scores in different body systems in which case the overall score is upgraded to severe (3).

The Charlson Index has only twenty-two elements making it simpler. It has also been validated for use in HNC. Its main drawback is that it does not consider the severity of the comorbid condition thus reducing its predictive power. The development of simpler scales that are weighted to improve their accuracy is being investigated. The literature would suggest that all the scales available have similar prognostic performance[13,14,15]. However ACE 27 appears to be the most successful in HNC patients and has a prognostic significance on a par with nodal stage[16].

Performance indicators are not a substitute for comorbidity scores. In their own right they may give limited prognostic information but cannot be consistently reproduced. Functional status does not correlate well with either tumour stage or comorbidity[17].

Prevalence of comorbid conditions
Most studies suggest that around 60% of HNC patients have a concurrent illness with 25% of these being classified as severe. This can be even higher in more elderly patients. The cardiovascular and respiratory

Appendix 2: Charlson index	
Weight	**Condition**
1	Myocardial infarct Congestive heart failure Peripheral vascular disease Cerebrovascular disease Dementia Chronic pulmonary disease Connective tissue disease Ulcer disease Mild liver disease Diabetes
2	Hemiplegia Moderate/severe renal disease Diabetes with end organ damage Any tumour Leukaemia Lymphoma
3	Moderate/severe liver disease
6	Metastatic solid tumour AIDS

systems are most frequently affected. Previous/coexistent malignancy and substance abuse are also common in HNC patients[18].

Comorbidity is less prevalent in the younger age group (<45years) but, if significant comorbidity is present in this population it carries a more important prognostic role independent of other factors[19]. Comorbidity increases with age within the head and neck population and is often cited as the reason for more elderly patients receiving less intensive treatment[20]. Despite its higher prevalence it continues to play a prognostic role even in the older population.

Impact of comorbidity on diagnosis
Patients with comorbid conditions are more likely to seek medical advice than their healthy peers. Despite this, they are no more likely to present with an early stage tumour[21] and often associated with a diagnostic delay. It is thought that this may stem from the frequency of visits and the fact that minor symptoms may be overlooked or assigned to a coexistent problem. Other medical problems present may pose seemingly more important concerns rather than a minor symptom which indicates the presence of an early tumour.

Patients of a lower socioeconomic status are less likely to have access to adequate medical care, as is the case with substance abusers. These patients represent the majority of the population with significant morbidity. It has been shown that these patients with an increased comorbid burden present with more advanced tumours[7].

Comorbidity and treatment selection
Up to a fifth of patients with significant comorbidity may receive reduced (suboptimal) treatment regimens. Consideration of a patient's comorbidity is consistently cited as one of the most important factors when deciding on a treatment plan for HNC patients. Age is not barrier to radical treatment but significant comorbidity can be[22].

Comorbidity and complications
It is well recognised that patients with a significant comorbid burden have a higher complication rate following major surgery[23]. This includes increased severity of complications and increased length of hospital stay. These findings have been confirmed using the ACE 27 scoring system; in addition ACE 27 was also able to identify an increased risk in peri-operative mortality in these patients[24].

Impact of comorbidity on prognosis
Comorbidity inevitably places patients at risk of increased mortality both during treatment and in the first few years following the completion of a comprehensive treatment regimen. There is also and increased mortality amongst inpatients undergoing treatment[25].

Mortality is most apparent in the first two years following treatment; 40% deaths could be attributed to a comorbid condition in one series[26]. Patients who succumb to their comorbidity survive only marginally longer than those who die of disease related problems (1.9 years versus 1.5 years)[27]. The commonest causes of death from comorbid conditions involved either the cardiovascular of respiratory system. This is a very real reminder of the negative impact on survival significant comorbidity can create. An ACE[27] score that is severe (3) has the same negative impact on morbidity and mortality as a T4 tumour or an N2+ neck[28]. Table 1 summarises the increased odds of mortality caused by higher comorbidity in some of the larger published series.

Evidence for the role of comorbidity in individual disease sites within the head and neck also exists. In oral cancer, if comorbidity data and functional status is taken in to account in addition to TNM classification it is a much more valuable prognostic indicator than TNM classification alone[29]. In oral and oropharyngeal cancer patients there is some evidence to suggest comorbidity may be a predictor of overall survival although this is not universally agreed upon. This may be an effect of the decreasing age of oropharyngeal cancer patients, and thus less comorbidity, with evolution of the human papilloma virus (HPV) who have had relatively little exposure to tobacco or alcohol[30].

In laryngeal cancer multiple studies demonstrate a poorer survival rate in patients with significant comorbidity[7, 8, 15, 19, 30, 32].

If we consider those subsites within the head and neck where tumours are not related as strongly to tobacco and alcohol usage such as the salivary glands or the nasopharynx the prevalence of significant comorbidity is less than seen with other subsites. The incidence of severe comorbidity

Table 1: Increased odds of mortality from all causes with higher comorbid burden as seen in large series.				
Authors	**Patient number**	**Index used**	**HR (95% CI) for overall survival**	**Other variables analysed in the same model**
Reid et al.[39]*	9386	CI	Score 1: 1.33 (1.21–1.47) Score ≥2: 1.83 (1.64 –2.05)	age at diagnosis, gender, race, site, stage, treatment, histological grade, marital status, pre-1991 diagnosis, and socioeconomic status
Piccirillo et al.[35]	1086	ACE 27	Moderate: 1.92 (1.50-2.47) Severe: 2.48 (1.77-3.47	age, race, sex, comorbidity level, tumour site, and tumour stage
Datema et al.[28]	1282	ACE 27	Moderate: 1.38 Severe: 2.23	age, gender, stage, prior malignancies and site of primary tumour

is reported to be between 17-19%[33, 34]. It does still play an important prognostic role in both subsites, however the evidence is not as strong as it is for the other head and neck tumour subsites.

How can comorbidity be used in estimating prognosis?

One of the key roles of any staging system used in cancer is that it provides information relevant to the patient's prognosis. An ideal system does not yet exist. As the TNM staging system uses tumour morphology for staging it is recognised that the system has significant drawback in this respect. TNM does not take into consideration tumour and host biological factors or the functional and comorbid status of the patient. All of these may have a prognostic significance[35]. The addition of this data does improve the prognostic value of the TNM classification. The recent edition of the TNM classification incorporates markers of poor prognosis, other than stage, in oesophageal and prostate cancer[36]. In light of the evidence in the literature comorbidity is a potential candidate for inclusion.

Some centres use a 'prognostigram' taking into account demographics, tumour stage, treatment and survival data from large series to more accurately predict outcome in HNC patients[28].

Comorbidity and disease specific survival

There is an easily recognisable connection between comorbidity and its impact on overall survival. Patients with a higher comorbid burden are more likely to die earlier from a concurrent illness than those patients who are otherwise healthy apart from their index tumour.

The role of comorbidity in disease-specific survival is less clear. There is evidence to suggest that patients with a higher degree of comorbidity have an increased risk of disease recurrence[37]. This has been corroborated by a number of studies but remains difficult to explain. It is speculated that additional disease processes in the host may have a negative effect on tumour-host balance in favour of the tumour. This, in turn, leads to a more aggressive disease course. Comorbidity often influences treatment planning and less aggressive (suboptimal) treatment courses may be implemented in order to accommodate the comorbidities of the patient [27, 38].

Comorbidity and quality of life (QoL)

Increased pre-treatment comorbidity scores have a negative effect on post-treatment QoL scores. This appears to be independent of treatment modality[11]. QoL scores prior to treatment may also be adversely affected due to the presence of already significant medical illnesses[21].

So why collect the information?

Analysis of comorbidity data is vitally important in prognostication following any treatment for HNC. It allows comparison between centres treating HNC both nationally and internationally. Pooled data will allow more accurate assessment of the effect of comorbid burden on the complications of treatment as well as the disease specific survival and overall survival. This will also help refine the TNM staging system for head and neck cancer. Comorbidity plays a significant role in defining treatment – how often do we decide a patient is 'not fit'? Data is still required to provide the robust evidence required to aid clinicians in making important treatment decisions in the patients who carry a significant disease burden in conjunction with their HNC.

Comorbidity costs money, and this is well exemplified in the way tariffs are set out in the Health Resource Groups used to identify activity based costing in the NHS. Identifying those patients who will need increased care and thus funding will ensure efficient allocation of monies.

Conclusion

Comorbidity has a significant impact on the complications of treatment, both hard (survival) and soft (QoL) outcomes and probably influences decision making in head and neck oncologic practice. All units involved in the management of HNC should be prospectively collecting data. The National Cancer Intelligence Network recommends that the collection of ACE 27 comorbidity score should be mandated for all adult cancer patients. This will give us a more accurate indication of the true effect that significant comorbidity has on the treatment and outcome for our HNC patients. 'Not fit for a haircut' no longer applies!

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Evaluation and decision making for continued curative treatment in patients who failed chemoradiotherapy for nasopharyngeal carcinoma

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Abstract

Approximately 10% of NPC patients have local failure after primary chemoradiation treatment and 5% have nodal failure. Local failures can be detected with endoscopy or imaging and should be confirmed with biopsy. Small local failures (rT1-rT2) could be treated with surgical resection; the current surgical approach of choice is the maxillary swing approach nasopharyngectomy. Alternatively, re-irradiation by brachytherapy is feasible with small recurrences. Larger local failures required re-irradiation by external beam, which is associated with increased morbidities. External beam re-irradiation for nodal failures has poor control rates and severe complications. Surgery, in the form of radical neck dissection, has a 5-year disease control rate of 68%. Additional brachytherapy in form of after-loading tubes placed during neck dissection is feasible in extensive disease with extra-capsular spread or involvement of the soft tissue of the neck. Current chemotherapy regimens have not shown long-term survival benefit and are regarded as palliative therapeutic options.

Keywords:

Nasopharyngeal carcinoma, Recurrence, Radiotherapy, Surgical salvage

Introduction

Primary radiotherapy has been the established first line treatment of nasopharyngeal carcinoma (NPC), without distant metastasis. Randomized controlled trials have shown that addition of chemotherapy concurrently with radiotherapy has significantly improved the locoregional control of NPC[1-3]. With the advent of stereotactic and intensity modulated radiotherapy (IMRT), locoregional control is further improved with reduction in morbidity of treatment[4-6]. Overall, around 10% of patients will develop local failures within 3 years after treatment[7].

The commonest mode of failure in NPC is distant metastasis, for which the chance of cure is remote and the main treatment target is palliation. Successful salvage is still possible in patients with local, regional or loco-regional failures after chemoradiation for NPC. We present our views on the evaluations and curative treatments options of patients who failed primary chemoradiation for NPC.

Evaluation and assessment of local failures

All NPC patients treated primarily with chemoradiation should have an endoscopy and biopsy 8 to 16 weeks after completion of treatment to confirm the remission of disease. Immediately after radiotherapy, the tumour may not regress spontaneously and early positive post treatment biopsies have high chance of remitting spontaneously[8]. Salvage treatment should not be planned in positive biopsies less than 8 weeks post treatment and should be repeated at 12 weeks.

Radiation therapy may induce inflammation and swelling the nasopharynx and surrounding tissue. These inflammations may take several weeks to subside. Post treatment imaging studies should therefore be postponed until 8 weeks to 12 weeks after the completion of chemoradiotherapy. This point is particularly true in functional imaging studies like PET-CT. The local inflammation after radiotherapy in the nasopharynx will show up as hypermetabolic lesions and mimic persistent diseases when performed too early.

Routine follow up with endoscopy and biopsy of suspicious lesions is mandatory for NPC patients in order to detect recurrences. Opinions are diverse on the use of regular follow up cross-sectional imaging like MRI or CT imaging to detect recurrence. Small mucosal recurrence may not be shown up on cross-sectional imaging. On the other hand, cross sectional imaging may pick up submucosal recurrence which endoscopy may not detect. When new symptoms like cranial nerve palsy or epistaxis develops after treatment, imaging studies to detect recurrence may be warranted.

Radionecrosis in the nasopharynx following radiotherapy mimics recurrenct nasopharyngeal carcinoma and can pose a diagnostic problem to clinician. Radionecrosis is often metabolically active on PET scan[9,10]. Necrosis of the bone as shown in CT or MRI may be confused with recurrence tumour causing bone erosion. Thus before contemplating salvage treatment for recurrent NPC, a histological proof of local recurrence is required.

NPC cells harbour copies of EBV DNA. With advance in molecular technology, we can now quantify the EBV DNA level in peripheral blood. EBV DNA level is now used as a diagnostic marker for primary NPC[11]. Blood plasma EBV DNA level has also shown to be predictive of persistent or recurrent disease[12]. EBV DNA titre has also been employed to monitor the response to chemotherapy[13]. The problem with EBV DNA as a follow up tool is that it is not very sensitive in detecting early recurrences, in which salvage treatments would be most successful[14].

When local failure is detected, additional imaging is required to delineate the extent of the recurrence for decision making on optimum salvage treatment. MRI, with its high soft tissue resolution is the imaging of choice. The addition of PET-CT together with image fusion allows better appreciate of the extent of tumour[15].

Evaluation and assessment of nodal failures

Nodal failure in NPC treated with chemoradiation is not high. A recent review of a large series of patients treated in Hong Kong from 2001-2006 showed the nodal failure rate was 5%[16]. Patients with metastatic lymph nodes that do not resolve 3 months after treatment should consider harbouring residual disease[17] and salvage treatment should be planned. The problem of assessment of nodal failures lies in the detection. Clinical examination is often inaccurate as radiation induced fibrosis make manual palpation of the neck difficult. Lymph nodes with previous metastatic NPC after radiation treatment retain the ultrasonographic features of metastatic lymph node even histologically the lymph nodes do not harbour malignant cells any more[18]. Detection of nodal recurrence would rely on serial increase in size of the lymph node and confirmation with fine needle aspiration cytology. The yield of FNA in lymph nodes after radiotherapy is low, which may limit its usefulness in detection of recurrent nodal disease[19]. Recent studies using PET-CT have shown promising results in detection of nodal recurrence[20, 21]. As positive cytological proof of nodal recurrence may not be easily obtain, nodal failures may need to be determined on clinical grounds and radiological features like positive PET scan or progressive enlargement of the neck lymph nodes. Patients should be warned of the small risk of no viable tumour cells found in the surgical specimen after surgical treatment.

Comparison of curative treatment options for local failures

The options of treatment of locally recurrent NPC are re-irradiation or surgical resection. Re-irradiation can be local brachytherapy or external beam irradiation. Various surgical approaches to the nasopharnx have also been presented. In decision making of the optimal treatment modality for local failures, the pre-requisite is accurate delineation of the extent of the local disease, currently the best imaging of choice is MRI, supplemented by PET-CT. For re-irradiation, the primary treatment planning is also vital in assessing the dosimetry to vital organs.

Re-irradiation

Re-irradiation can either be in the form of external beam fractionated radiotherapy or single dose radiosurgery. The main limiting factor for applying external beam treatment is the radiation dose to the crucial normal structures like brainstem, spinal cord and brain. The advent of 3D radiation techniques like intensity-modulated radiotherapy (IMRT)[22] or stereotactic radiosurgery[23] may avoid excessive radiation to vital organs. A large series of over 100 patients employing conventional 2D radiotherapy techniques to re-irradiate local recurrences had shown poor survival results of 7.6% 5-year survival with significant complications[24]. A recent report of external re-irradiation using IMRT has shown better short-term results in rT1-rT3 diseases[25]. External beam re-irradiation only improves survival in rT1 and rT2 diseases[7]. The main limiting factor in employing external re-irradiation is the significant severe long-term complications to the surrounding normal tissue due to the exposure to 2 courses of high dose radiation.

Brachytherapy re-irradiation delivers high dose radiation locally to the nasopharynx by placing the radioactive source directly in the nasopharynx. The main radioactive source are either iridium 192 (Ir192) or gold 198 (Au198), both emit gamma radiation. Ir192 is afterloaded into tailor made mould fitting the nasopharynx of the patient. The

mold is placed into the nasopharynx via the oral cavity under local anaesthesia[26, 27]. For gold grain implantation, the gold grains are placed into the tumour after the soft palate is split surgically under GA[28]. The soft palate is subsequently repaired. The short half-life of Au198 (2.7 days) does not necessitate the removal of the radioactive source from the patient. Both techniques are only able to irradiate tissue close to the NP and are only efficacious for small rT1 and rT2 diseases with tumour size less than 2cm diameter. The efficacy of both techniques is comparable, with a 5-year survival rates for first local recurrence in the range of 50-60%[26, 29]. The choice of the techniques depends on the local expertise in placing the mold or gold grain and the availability of the radioactive sources. Also, during radioactive gold grain implantation, the surgeon has to be exposed to radiation.

Surgery

Although the nasopharynx is deep seated in the centre of the head, surgical resection of lesions in the nasopharynx is feasible. Nasopharyngectomy can be accomplished by various approaches, including the transmandibular-trans-palatal inferior approach[30], the anterior mid-facial degloving approach[31] and the anterio-lateral maxillary swing approach[32,33]. Recently endoscopic nasopharyngectomy has also been described to removal small tumours in the nasopharynx[34]. The choice of the approach would depend on the size of the lesion and the pathology. NPC are commonly situated in the lateral nasopharynx with extension to parapharyngeal space and involvement of the Eustachian tube cartilages. Anterior mid-facial degloving approach would have difficulty in removing tumour in the paraphrayngeal space. The inferior approach would have difficulty in removing tumour in the roof of nasopharynx and its anterior extension to the nasal cavity. The current surgical approach of choice is the maxillary swing approach. In maxillary swing operation, the ipslateral maxilla is removed similar in radical maxillectomy but the attachment the cheek skin is preserved. The nasopharynx and the ipslateral parapharyngeal space would be adequately exposed after the maxilla is swing laterally. After resection of the nasopharynx, the maxilla is returned to normal position and fix with plates. 5-year overall survival after maxillary swing operation is in the region of 40-60%[32, 35-37]. Maxillary swing approach has been shown to be superior in local control and overall survival compare to the anterior mid-facial degloving approach[38].

Decision for nasopharyngectomy depends on the local tumour factor and the general condition of the patient. Patient should be fit for general anaesthesia for a 5-hour operation. Tumours that encases the carotid artery or with extensive skull base involvement or intracranial extensions could not be removed completely without significant perioperative morbidity. The results for removal of large T3 recurrence are poor[35], and alternative treatment like reirradiation should be considered.

The choice between surgery and brachytherapy in small recurrent disease depends on the availability of the expertise and the location of the tumour. When the tumour extends 2 cm beyond the surface of the nasopharynx and yet the carotid artery is not involved, or in cases with anterior extension to the paranasal sinus or nasal cavity, nasopharyngectomy should be employed. Overall, the local control rate of brachytherapy and nasopharynectomy in small residual or recurrent diseases are comparable[7].

Chemotherapy

Chemotherapy as a sole modality for salvage has not been successful in NPC. Overall complete response rate to various single agents are less than 50% and with combination of agents, the complete response rate can be increased to 70%[24]. Poor results in the literature maybe skewed towards patients with extensive diseases not suitable for radiotherapy or surgery. Newer agents, especially targeted therapies are undergoing clinical trials. At present, chemotherapy should be reserved for patients who are not suitable for re-irradiation or surgical treatment.

Treatment of nodal failures

Radiotherapy for residual or recurrent nodal disease in NPC has a poor efficacy of less than 20% 5-year survival[39]. Together with increased toxicity of re-irradiation to a previously highly radiated tissue, re-irradiation for nodal failures is not recommended. The definitive curative treatment for nodal failures in NPC is neck dissection. Study has shown that nodal recurrence in NPC shown extensive subclinical involvement of the lymph nodes with 70% extracapsular spread. There was also propensity for spreading to posterior triangle along the spinal accessory nerve[40]. Radical neck dissection and not less extensive surgery should be the surgical treatment of choice. Due to post radiation fibrosis of the neck skin, clinical assessment of nodal recurrence can be inaccurate. It is advisable that cross sectional imaging to be included as part of the work up for neck dissection. Special attention should be paid note the presence of carotid artery encasement by tumour, tumour invasion to the brachial plexus or deep muscle of the neck and any extention of tumour to skin. Patient with tumours that completely encased the carotid artery or lymph nodes extending beyond the neck may not be salvaged by surgery; alternative means of palliation should be discussed with the patient.

As the neck skin has been extensively irradiated, it is advisable to avoid a 3-point junction in the neck incision and employ the parallel MacFee incisions. If the neck skin is suspected to be involved by tumour, the suspicious part of the skin should be resected together with the neck dissection and the skin defect repaired by a locoregional flap like deltopectorial flap or pectorialis major myocutaneous flap[17]. If during the operation, microscopic tumour is found be to attached to vital structures like carotid artery, vagus nerve or brachial plexus etc, instead of sacrificing these structures to achieve complete tumour clearance, the site of microscopic tumour should be marked with metal clips. Brachytherapy tubes are then place over the region for post-operative brachytherapy. The overlying skin should be resected and a loco-regional flap then raised to cover the defect to avoid radiation necrosis of the skin41. The overall control of control rate of the nodal disease after neck dissection is 66% with a 5-year actuarial survival rate of 38%[19].

Conclusion

With improvement in chemoradiation technologies in treating primary NPC, the incidence of local or nodal failures has decreased. Still we occasionally see patients presented with local or nodal failures. Careful assessment of the size and location of failure, together with consideration of previous treatment strategies will allow us to formulate a plan for salvage while minimizing morbidity from salvage treatment. Long term survival after salvage is not uncommon.

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Prescribing Information
(Please refer to the full Summary of Product Characteristics before prescribing)

Avamys®▼ Nasal Spray Suspension (fluticasone furoate 27.5 micrograms /metered spray) Uses: Treatment of symptoms of allergic rhinitis in adults and children aged 6 years and over. **Dosage and Administration:** For intranasal use only. *Adults:* Two sprays per nostril once daily (total daily dose, 110 micrograms). Once symptoms controlled, use maintenance dose of one spray per nostril once daily (total daily dose, 55 micrograms). Reduce to lowest dose at which effective control of symptoms is maintained. *Children aged 6 to 11 years:* One spray per nostril once daily (total daily dose, 55 micrograms). If patient is not adequately responding, increase daily dose to 110 micrograms (two sprays per nostril, once daily) and reduce back down to 55 microgram daily dose once control is achieved. **Contraindication:** Hypersensitivity to active substance or excipients. **Side Effects:** Systemic effects of nasal corticosteroids may occur, particularly when prescribed at high doses for prolonged periods. *Very common:* epistaxis. Epistaxis was generally mild to moderate, with incidences in adults and adolescents higher in longer-term use (more than 6 weeks). *Common:* nasal ulceration. *Rare:* hypersensitivity reactions including anaphylaxis, angioedema, rash, and urticaria. **Precautions:** Treatment with higher than recommended doses of nasal corticosteroids may result in clinically significant adrenal suppression. Consider additional systemic corticosteroid cover during periods of stress or elective surgery. Caution when prescribing concurrently with other corticosteroids. Growth retardation has been reported in children receiving some nasal corticosteroids at licensed doses. Monitor height of children. Consider referring to a paediatric specialist. May cause irritation of the nasal mucosa. Caution when treating patients with severe liver disease, systemic exposure likely to be increased. Nasal and inhaled corticosteroids may result in the development of glaucoma and/or cataracts. Close monitoring is warranted in patients with a change in vision or with a history of

increased intraocular pressure, glaucoma and/or cataracts. **Pregnancy and Lactation:** No adequate data available. Recommended nasal doses result in minimal systemic exposure. It is unknown if fluticasone furoate nasal spray is excreted in breast milk. Only use if the expected benefits to the mother outweigh the possible risks to the foetus or child. **Drug interactions:** Caution is recommended when co-administering with inhibitors of the cytochrome P450 3A4 system, e.g. ketoconazole and ritonavir. **Presentation and Basic NHS cost:** Avamys Nasal Spray Suspension: 120 sprays: £6.44 **Marketing Authorisation Number:** EU/1/07/434/003 **Legal category:** POM. **PL holder:** Glaxo Group Ltd, Greenford, Middlesex, UB6 0NN, United Kingdom. **Last date of revision:** January 2010

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