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ENT MASTERCLASS®

Year Book 2009

Volume 2 Number 1

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JOURNAL OF ENT MASTERCLASS®

Welcome to Volume 2 Issue 1 of Journal of ENT Masterclass®!

The ENT Masterclass has established itself as a well-recognized training event.

Each year for the past 2 years the courses have expanded to not only include doctor or medical tuition, but also nursing staff. There are currently four fixed annual events and during 2009 these were; January the 5th Annual National ENT Masterclass, May the 2nd Tracheostomy Masterclass, June the 2nd Thyroid and Salivary Masterclass, and September the 3rd National Nursing Masterclass. Each of these Masterclass' are a success not only to Shahed Quraishi, the Founder and Organiser of the Masterclass concept, but thanks also go to the dedication of the Faculty in giving-up their valuable time, the support of Doncaster & Bassetlaw NHS Foundation Trust, sponsorship and the volunteers who help with the logistics allowing to keep these courses completely free of cost to the attendees.

An extension or expansion of ENT Masterclass was the launch of The Journal of ENT Masterclass in January 2009 with 21 review articles on current ENT topics from national and international authors. This year, Volume 2 Issue 1, we have continued along the same lines expanding the contents with 26 invited articles, with topics divided into Head and Neck, Nose and Sinuses, Pediatrics and Otology and Neuro-otology. Feed-back had suggested that a contribution from International Experts was a "novel idea", this issue is fortunate to have increased these contributions from 2 to 10, which will probably be our "ceiling" for future Journal Issues. Again we are indebted to the many "locals" who have willingly contributed, some for the second time, to the Journal's success.

During the 5th National ENT Masterclass Mr Barney Harrison, President-Elect of the British Association of Endocrine and Thyroid Surgeons, Consultant Surgeon from Sheffield gave the Second ENT Masterclass Lecture 2008 on "Evaluation and Management of Thyroid Nodules". His lecture was given with eloquence with his usual confidence, didactic and demonstrating his life-time experience with the management of thyroid diseases.

The Editorial Board has undergone change, with the loss of Professor A Wright and Mr David Pothier. We would like to thank them for their help and support. The Board has been expanded to reflect the wider curriculum, to reflect the distribution and internationalisation of The Journal. Accepting the invitation and coming "on board" are Mr Alec Blayney, Ireland, Professor Greg Weinstein, USA, Professor Simon Carney, Australia, Mr Derek Skinner, Shrewsbury, Mr Ken McKenzie, Glasgow.

Again, The Journal welcomes suggestions and comments on how to better the Masterclass concept! Most current sources and information can be obtained on the website, as well making direct contact to the Editor and the Chairman of the Editorial Board!

The Journal and Masterclass continue to thank each and everybody for their involvement, for their continued support and remain in your debt!

Professor Patrick J Bradley, MBA, FRCS
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November 2009.

Editorial: Revalidation

Following a series of high profile scandals involving independent reports (Bristol, Ledward, Alder Hey) the political climate in Britain changed and the medical profession was warned by the Chief Medical Officer that some kind of regular 'MoT' certificate would be required. These scandals were like manna from heaven for politicians who were keen to take doctors down a peg or two. However, his initial proposals were thrown into disarray when Dame Janet Smith severely criticized these proposals in her final report into the activities of the mass murderer Harold Shipman. Many observers feel she went well beyond her brief in making these comments but the CMO was forced to go back to the drawing board. This then led to a White paper in 2007: Trust Assurance and Safety.

This White paper introduced two concepts: relicensing and recertification, together called revalidation. All doctors on the GMC register would now require a formal Licence to Practise and this has in fact already been introduced (Nov 2009) and that every five years all doctors would be subject to revalidation of this licence via relicensing.

In addition to relicensing, all doctors on the Specialist register would also have to be recertified as specialists every 5 years. In practice the two parts to revalidation would run as one. The medical Royal Colleges have been charged with describing the standards that specialists should meet and the RCS has worked closely with ENT-UK to set these standards for us. Maurice Hawthorn has been leading on this for our specialty.

"Recertification, like relicensure, will be a positive affirmation of the doctor's entitlement to practise, not simply an absence of concerns."

The stated purpose is thus to further ensure patient safety and to facilitate improvement in clinical practice (i.e. to stop a future Shipman).

How revalidation can be achieved is also a source of massive effort. It is expected that specialists will have to undergo a more robust annual appraisal (now known as strengthened appraisal) every year and that the 5 yearly revalidation event will be a formal review of the preceding 5 years of strengthened appraisals. It therefore follows that we will all have to provide a great deal of data about our practice in a number of different domains. These include:

- outcomes data
- evidence of participation in any relevant national audits
- attendance at M&M and MDT meetings
- CPD which will have to be carefully logged

All doctors must be the subject of a multi-source feedback exercise (often known as 360 degree assessment) and, where appropriate, patient surveys. However, despite some pilot work, this process is not yet validated as a means of assessing professionals such as doctors. Dr Shipman would have received glowing reports from his patients! It therefore follows that such evidence cannot be considered alone but as part of a wider assessment.

Much of this will come as an unpleasant surprise to established consultants but younger colleagues (and trainees) will be quite familiar with this approach. RCS and RCS Ed are currently developing electronic portals to help Fellows collect and store this information.

The entire process is the statutory responsibility of the GMC not the DH and so crosses all four home nations. The Deptartment of Health in England . has set up a Revalidation Support Team to support the process but of course each health department may yet take a different view in each nation. Currently the start date for revalidation has moved from 2010 to mid 2011. As there are over 60 different specialties in medicine a staggered start is expected - taking perhaps 5 years. So by around 2016 all specialists will be embroiled in this process. However, no financial modelling has taken place and so no realistic estimate of the costs can be made. Employers will be key to the annual process and yet they have not been closely involved in developing these ideas. In addition, the role of the Colleges in providing quality assurance of the process has not been defined. All ENT-UK members must expect a fair and transparent process - especially if problems are identified which might threaten your place on the specialist register. I have grave concerns that appraisal inside a Trust often focuses on how well you are meeting targets etc. But this is a separate issue from the key one of whether you are fit to remain on the specialist register.

A further problem arises in the case of those carrying out independent (private) practice. Currently appraisal is supposed to be of your whole practice. Often it is not. Under revalidation this will have to change and private hospitals will be obliged to involve themselves in the process.

As I write this there are expectations that the UK will have a new Government in 2010. They are expected to face severe financial problems following on from the banking crisis of 2008/9 and I would not be too surprised if the timetable for introducing revalidation slips further. The most likely side effect of this legislation is that the huge increase in bureaucracy will encourage many specialists to take early retirement in the years leading to 2016. While this will open up job opportunities for trainees, the loss of a huge swathe of experienced specialists aged 60 and over will be a great loss for the Health Service and a sad unwanted consequence. The Law of Unintended Consequences still applies.

And as any medical director will tell you privately, this process will not prevent another Shipman: which of course continues to leave a deficit in the regulation of doctors in the UK.

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HPV as an Aetiological and Prognostic Factor in H&N Cancer

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Introduction

Head and neck squamous cell carcinomas (HNSCC) arise from the mucosa of the upper digestive tract. Taken together they have an annual incidence, world-standardised, of 25/100,000 and 4/100,00 in European men and women, respectively, with significant variations among the European regions[1].

Head and neck cancers are subcategorized according to their site of origin due to different etiology, management and outcome. Strong carcinogenic and epidemiologic evidences support an etiopathogenetic role of tobacco and alcohol; in fact, about 90% of cases is due to them. Recently, oncogenic human papilloma viruses (HPV) have been associated with a subset of HNSCC[2]. HPV DNA is present in the tumor, more frequently in those arising in the oropharynx, although it has rarely been detected also in oral cavity, larynx and hyopharynx. HPV positive testing varies across countries in different series, ranging from 20 to 72%, depending also on the detection techniques[3]. In general, more recent studies tend to report an increase in HPV tumor positivity[4]. Moreover, a relative rising number of oropharyngeal cancer, together with a declining incidence of oral cavity, larynx and hypopharyngeal cancer, has been reported in the United States and Europe[5-8]. In Sweden the proportion of HPV positive tonsillar cancers had significantly increased since 1970s with 93% of positivity in 2006-2007, thus suggesting a virus induced carcinoma epidemic with the virus presence in virtually all tonsillar cancers, similar to cervical tumor[9].

HPV as aetiological factor

Similarly to cervical cancer, high risk sexual behaviours, exposure and infection have been correlated with oropharyngeal cancer in a case control study[10].

Sexual behaviours increasing the risk of developing HPV oropharyngeal associated cancer have been defined as having more than 6 lifetime vaginal partners, having oral sex, anal sex, never or rarely using condoms and having sexual partners with a history of HPV related cancers.

When just infection is taken into account, then oral sex and open mouth kissing are associated with an increased probability of oral HPV infection. The infection prevalence in a college aged men's cohort is 3%, while that in a non selected general outpatient clinic population is 5%[11].

In the HIV positive population HPV related cancers are statistically significantly higher than in the general population[12]. However, in contrast to the high risk of other HPV associated cancers, the risk to develop oropharyngeal cancer was only modestly increased and, paradoxically, the onset of oropharyngeal tumors was more frequently in AIDS patients with a relatively higher CD4 T - cell count. Nevertheless, HIV positive patients treated with active antiretroviral therapy are expected to live longer, thus increasing their risk to develop HPV oropharyngeal cancer[13].

Markers of exposure and infection, such as HPV16 viral capsid (L1) serologic status, HPV 16 oral infection, any HPV oral infection, E6 and E7 HPV 16 oncogenes

serologic status, have been found to be significantly associated with the risk of developing an oropharyngeal cancer. This risk seems to be independent of alcohol and tobacco use. In particular, in HPV16 seropositive patients the risk was not affected by alcohol and smoking increasing consumption[14]. On the contrary, in seronegative patients this risk significantly increases with increased alcohol intake and smoking. In general, HPV16 seropositivity was associated with a 10-fold increased risk of pharyngeal cancer after adjusting for alcohol and tobacco use. Among patients drinking less than 3 drinks/week or among never–smoker patients, HPV seropositivity was associated with a 30-fold increased risk of developing a pharyngeal cancer.

Interestingly, smoking habits can have a modulating impact on the favourable prognostic outcome of HPV positive patients, as it has been recently demonstrated[15].

HPV oral infection through oral rinse serial analysis could be also exploited to detect not only subjects at risk to develop tumors, but also to provide earlier evidence of tumor recurrence after therapy. It has been shown that in the majority of cases the HPV variant sequence is of the same type of the index tumor. Its presence has been shown for as long as 5 years. Moreover, the prevalence of HR HPV infections other than HPV 16 is common in patients with HPV16 positive tumors before and after treatment16. In some rinses a different HPV variant was detected, suggesting the possibility of a different infection. According to the present study no correlation was found between HPV persistency and development of tumor recurrence and/or second tumors. However, numbers were small and follow up still brief to conclude that this marker is useless in the clinic. In another small case series the presence of HPV16 E6 and E7 in convalescent salivary rinses turned out to predict tumor recurrence or metastasis[17], Contrary to cervical infection, the time course of oral infections is still unknown. Similarly to cervical cancer, genetic variants, such as HLA class and chemokines may influence viral oral clearance, but individual predisposition of HPV oral infection has to be further investigated. Interestingly, familial clustering of HPV related cancers, including oropharyngeal tumor site, has been described by the Swedish data base. The study could not allow to understand whether the observation was due to shared environmental or genetic factors[18]. Genetic susceptibility of developing HPV related head and neck cancers has been reported to be represented by p53 codon 72 polymorphism and with a variant vitamin C transpoter SLC23A2[19,20].

A biological causal relationship has been postulated on the basis of the integration of HPV DNA, particularly HPV 16 and the expression of oncogenic viral genes, such as E6 and E7, high viral load that has been consistently found in oropharyngeal carcinomas[21]. Indeed, this has been less rigorously demonstrated for other head and neck subsites. It is possible that oropharynx offers a facilitated access to the mucosal basal cell layer in the tonsillar crypts, similarly to what happens in the cervical transformation zone. HPV16 is the most common type identified in all head and neck cancers, in less than 10% of cases other high risk types (18, 31, 33 and 35) have been detected. Corollary evidence is provided by the presence of antibodies directed against HPV16 E6 and E7 oncoproteins, HPV seropositivity and oral HPV in patients with HPV positive oropharyngeal cancers.

Molecular alterations, including those occurring at p53, cyclin D1, p16, pRB in tumors induced by HPV are tipically different as compared to HPV negative squamous head and neck carcinoma, supporting the existence of two distinct carcinogenetic pathways. Other markers, such as EGFR expression, have been found to be inversely correlated with HPV positivity[22]. Interestingly, hypoxia markers were not found to be correlated with HPV positivity, thus suggesting that this may not be the mechanism responsible of radiosensitivity of HPV positive tumors (see below)[23].

Genetic patterns are also different in head and neck cancer, either containing or lacking transcriptionally active HPV. HPV positive tumors are characterised by occasional chromosomal loss, on the contrary in HPV negative tumor cells there are gross chromosomal deletions tipically seen in the early phase of tumor development[24,25]. In a recent study chromosomal alterations among HPV positive cancer cells of cervical and oropharyngeal origin has been shown to be organ site specific[26].

HPV as prognostic factor

Survival of patients with HPV head and neck tumors has been analysed in a study metanalysis, which showed a lower risk of dying (HR 0.85) and a lower risk of recurrence (HR 0.62) in HPV positive tumors. Interestingly, this seems to be a site specific effect since, for example, OS was not different among HPV positive oropharyngeal versus non oropharyngeal tumors[27]. Different reasons of favourable survival outcome have been hypothesized to be intact apoptotic machinery in response to radiation and possibly chemotherapy, absence of field cancerization and immune system activation by viral specific tumor associated antigens. They are all based on the recognition of a separate and specific biologic profile of HPV positive tumors that justify its distinct behaviour[15,21,28]. Interestingly, a better outcome has been seen for patients undergoing primarily surgery for oropharyngeal cancer, as well

suggesting the possibility of a less aggressive tumor[29]. This observation is also corroborated by the reduced incidence of distant metastases that were observed in a retrospective evaluation of patients enrolled in a phase III study conducted in Italy on oropahryngeal cancer[30].

Prospective studies including HPV positive tumors also showed a statistical improvement of response rates, as well as organ preservation data, disease free survival and better survival[31,32]. One of these studies pointed out that response rate to induction chemotherapy correlates with HPV16 gene copies quantified in the single tumor. The same observation was done by considering p16 tumor staining that is now recognised as an effective and reliable marker of HPV positivity in head and neck cancer[33]. Indeed, p16 immunohistochemical expression has been strongly correlated with in situ hybridisation and HPV gene expression through PCR analysis[15,34].

Smoke status, categorised as never smoker, past smoker and current smoker or per pack/year, has been associated with the outcome of patients with HPV positive oropharyngeal cancer[15,33]. For some still unclear reasons current and past smoking negatively affects the cure probability of HPV positive tumors. An inverse correlation between EGFR expression and smoking has been also observed, possibly suggesting a role of EGFR pathway in determining prognosis. To date studies that correlate HPV positivity and tumor response to EGFR inhibitors have not been reported. Given the absence of any correlation between EGFR status and tumor response to cetuximab[35], if HPV positivity is associated with a better outcome with EGFR inhibitors, then the reason should not be attributed to the more preserved EGFR status correlated with tumor HPV infection.

In conclusion, HPV positive tumor patients display an epidemiologic, biological and outcome profile that has paved the way for considering it a separate tumor entity which deserves special attention and also special care in the future. The research strategies for HPV positive tumor are now concentrated in studying prospectively whether a treatment de-escalation to avoid unnecessary acute and late toxicity is foreseeable, for example by reducing radiation both in terms of total dose and irradiation volumes or by skipping concomitant chemotherapy or by using biological therapy instead of chemotherapy. By separating those patients clinical research in head and neck cancer will have to focus on more aggressive tumors, for which biology will have a prominent role in designing future studies.

It has to be recognised that HPV infection is sexually transmitted and any high-risk sexual behaviour is associated with oral HPV infection[10]. In this context strategies of primary prevention to reduce high-risk sexual behaviours among adolescents and the young population must be considered in public health. Vaccination of adolescents and young adults to hasten the reduction of HPV-16 prevalence has been claimed although its efficacy at population level has not yet been demonstrated.

Acknowledgment

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Robotic Surgery For Head And Neck Tumors

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Abstract
Minimally invasive surgery has been increasing in multiple specialties as a means of reducing patient morbidity and mortality; the surgical robot has add three-dimensional visualization and significant technical advantages to these approaches. Transoral Robotic Surgery (TORS) in Head and Neck area presented major advances in neoplasms of the larynx and pharynx, with clinical trials assessing large series of patients with adequate follow-up for oncological, morbidity and mortality results. Preclinical studies have also demonstrated the feasibility of TORS in areas as the skull base, nasopharynx, parapharyngeal space, and neck surgery. In some anatomic sites it may also shift the paradigm away from non-surgical approaches and back to primary surgery.

Key Words
Robotic, minimally invasive surgery, transoral robotic surgery, head and neck cancer

Introduction
Minimally invasive surgery has been increasing in multiple specialties as a means of reducing patient morbidity and mortality. The commercially available da Vinci surgical robot (Intutive Surgical,Inc, Sunnyvale, CA, USA) provides three-dimensional visualization and significant technical advantages, allowing procedures to be performed through a minimally invasive route, diminishing surgeon tremor and fatigue. Since the introduction of the surgical robot in the 1990's, robot-assisted cardiac, gynecologic, pediatric and urologic procedures have become widely accepted internationally. In urologic surgery, approximately 60% of the patients underwent radical robot assisted radical prostatectomy in the United States in 2007[1]. Head and neck tumors fequently requires a transcervical approach, and sometimes jaw-splitting, and may result in poor cosmesis and dysfunctional speech and swallowing[2]. Experimental studies using canine and cadaver models demonstrated the technical feasibility of transoral robotic surgery (TORS)[3,4]. Complimentary studies in patients have demonstrated both the feasibility and the safety of robot-assisted resection of upper aerodigestive tract neoplasms, with limited surgical morbidity, reduced hospitalization, and enhanced visualization over traditional techniques[5-7].

The Robotic System
The da Vinci Surgical Robot (Intuitive Surgical, Inc., Sunnyvale, CA) is made up of three primary components: a surgical cart, a vision cart, and a surgeon's console (**Figure 1**). The surgical cart is equipped with a robotic manipulator and three mounted arms: one arm holds the camera and the other two hold 5 mm or 8-mm instruments(**Figure 2**) . The vision cart is equipped with two three-chip cameras mounted within one integrated, three-dimensional 12-mm stereoscopic endoscope with two separate optical channels. The surgeon's console, positioned a distance (approximately 5 to 10 feet) from the patient acts as an operating microscope, displaying stereoscopic images obtained by the double endoscopic cameras. At this console the surgeon controls the instrument

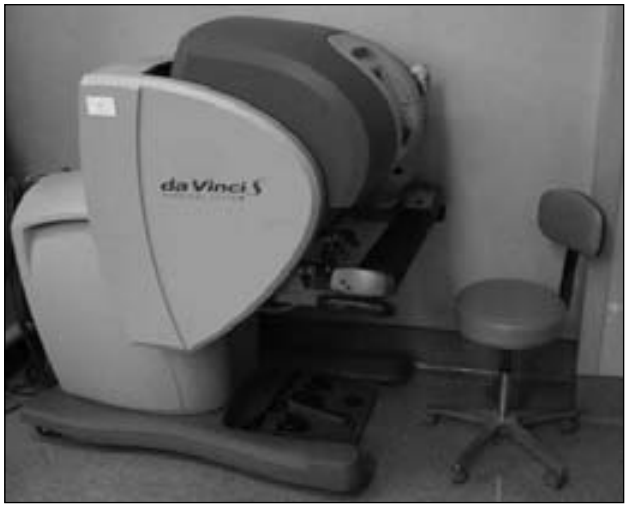

Figure 1 – *da Vinci surgical robot (Intutive Surgical,Inc, Sunnyvale, CA, USA) Robotic Console.*

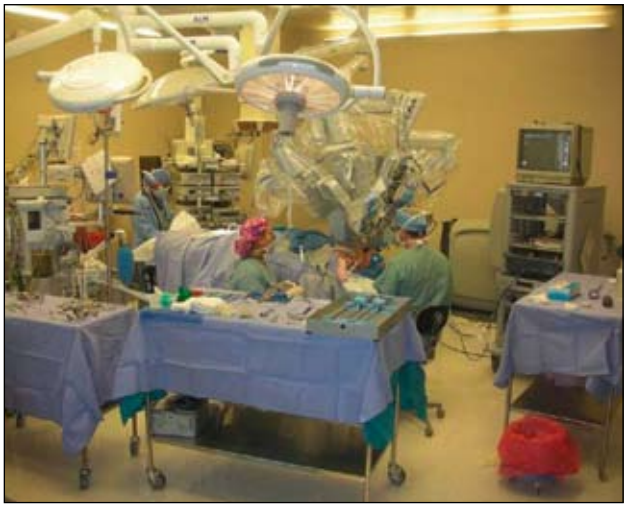

Figure 2 – *da Vinci surgical robot (Intutive Surgical,Inc, Sunnyvale, CA, USA) Robotic bedside cart.*

arms and camera by maneuvering the robotic manipulators (**Figure 3**). Instrument tips are electronically aligned with the instrument controllers to provide optimal eye-hand orientation and natural operative capability. The robotic arm is designed to hold surgical instruments that are "wristed" and are completely controlled by the surgeon's movement of the handles in the console and precisely duplicate the motion of the surgeons hands while providing motion scaling of the hand movements to accomadate for the miniaturized instruments on the robotic cart (**Figure 4**). The advantages of this system are: realistic 3-D imaging, motion scaling, 6° of motion around the "wrists" of the instruments and physiologic tremor filtration.

Robotic-Assisted Surgeries

To the date, several uses for the robot-assisted surgery in Head and Neck area have been described both in preclinical set-ups with animals and cadaveric models, and on clinical trials. Major advances occurred in neoplasms of the oropharynx and larynx, with clinical trials assessing large series of patients with adequate follow-up for oncological and morbidity and mortality results. Although preclinical studies have demonstrated the feasibility of TORS in areas as the skull base, nasopharynx, parapharyngeal space, have, there remains a lack of large number of patients and late follow-up in clinical trials of these anatomic sites.

Figure 3 – *da Vinci surgical robot (Intutive Surgical,Inc, Sunnyvale, CA, USA) Robotic Console manipulators.*

Oropharynx

Oropharynx neoplasms comprises primarily of tonsil and tongue base malignancies. Lately, there have been increasing reports of the use of primary radiation or combined chemotherapy and radiation for tongue base and tonsil neoplasms 8. The key factor driving this movement away from primary surgery was the reported morbidity of such surgical procedures[9]. Cervical incisions and dissections with mandibulotomy or pharyngotomy were typically required to remove base of tongue neoplasms even in the early stages[10]. These approaches left the

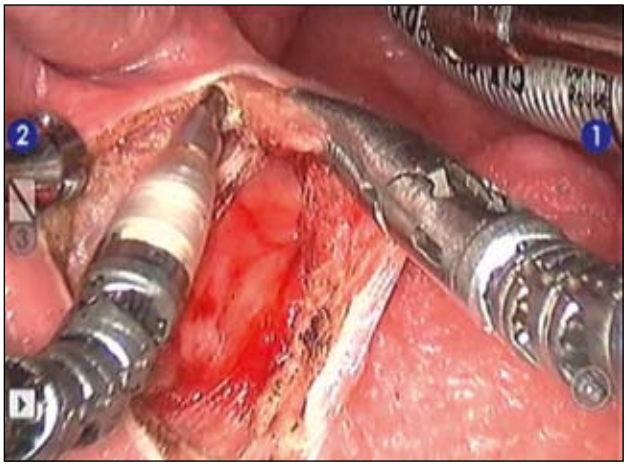

Figure 4 - *Surgeon's view of instruments via the viewing port on the da Vinci surgical robot (Intutive Surgical,Inc, Sunnyvale, CA, USA) Robotic Console.*

patient with various levels of significant speech and swallowing dysfunction as well as cosmetic deformity depending on the size and location of the tumor and extent of resection. TORS eliminates the need for mandibulotomy with a lip split or visor flap or transpharyngeal approaches that adversely affect mastication, swallowing and speech function, and cosmesis. In addition, we believe that TORS tongue base resections and radical tonsillectomies can be performed safely without tracheostomy, which is typically used for open approaches. The techniques of robotic tongue base resection and robotic radical tonsillectomy have been well described[6].

Larynx and Hypopharynx

Larynx and hypopharynx surgeries encompasses both benign vocal fold pathologies and neoplasms, the surgical approaches vary from radical open surgery as total laryngectomy to open partial laryngectomies and microsurgical techniques. The microsurgery of the larynx is performed via a narrow field approach due to the use of tube-shaped laryngoscopes. This narrow field approach has numerous technical limitations based on the physical properties of the laryngoscope and the distance created from the surgeon's hand to the endolarynx. In addition, when performed in conjunction with an operating microscope, the field of view is also limited by the size and position of the laryngoscope. As the microscope is positioned "outside the patient," the operative field is static and dependent on a straight line of site between the lens of the microscope and the tissues at the surgical site, which are over 12 inches apart. The final surgical limitation, which is inherent in standard microlaryngoscopy is the long distance between the surgeon's hands and the working ends of the instruments. These limitations, which are inherent in both endoscopic and laparoscopic surgery, have been found to negatively impact the learning curve for novice surgeons. The feasibility of TORS was demonstrated in both the mannequin and the cadaver models, as well as in the canine model 3,4,11. Among the advantages noted in the robotic supraglottic resections were: wide exposure with oral mouth gag system and no laryngoscope, multiplanar transection of tissues, and a three-dimensional view provided by the integrated high-resolution endoscope. Furthermore, the surgeon may repeatedly and instantaneously reposition the robotically controlled endoscope and instruments to change viewpoint during the procedure rather than reposition a laryngoscope or microscope to change the view.

Parapharyngeal Space

The neoplasms of the parapharyngeal space and infratemporal fossa in the majority of cases use a cervical, transparotid, approach that may be associated with mandibulotomy and the related postoperatory problems in cosmesis, mastication and swallowing disorders. TORS holds potential for parapharyngeal and infratemporal fossa neoplasms as the 30° angled high- magnification 3-dimensional camera optics permitted tremendous visualization, which then allowed careful identification and dissection of the carotid artery, jugular vein, and cranial nerves to their entry points at the middle skull base. With respect to technical limitations and challenges for this TORS approach, the bony skull base cannot be resected, and intracranial work cannot be performed given the technical limitations of the existing robotic instruments and lack of robotic drills and burrs. Also, dissection below the level of the carotid artery bifurcation cannot be readily performed; thus, a transoral formal neck dissection for cervical metastases is not presently feasible. Subsequent to the preclinical investigations, we have demonstrated the successful application of TORS to the skull base in a human patient with a parapharyngeal to infratemporal fossa benign cystic neoplasm[12].

Nasopharynx

The nasopharynx is one of the most challenging areas of the head and neck to reach and resect. For this reason, the nasopharynx had been thought of as an inoperable site in the past. Approaches described in the last few decades were complicated, with high morbidity[13,14]. Very recently, a few case series with a limited number of patients showed the feasibility of minimally invasive endoscopic approaches for nasopharyngectomy[15]. Recently the use of transoral robotic assisted surgery for nasopharyngeal approaches has been described in a cadaveric model[16].

Skull Base

Transnasal endoscopic techniques have been increasingly used for surgical access and treatment of neoplastic and nonneoplastic lesions of the anterior and central skull base. The increasing popularity of these endoscopic skull base approaches may be attributed to a larger trend toward more minimally invasive techniques across all surgical disciplines. The main advantage of transnasal endoscopic skull base approaches is providing more direct access to the anterior and central skull base while avoiding craniofacial incisions and extensive bone removal commonly used in open surgical approaches. Also, the wider angle of vision and angled lenses increases the range of the endoscopic visual surgical field compared with the "line of sight" visual field gained by surgical loupes or microscopes. One major disadvantage of transnasal endoscopic approaches is the inability to provide watertight dural closure and reconstruction. Current techniques of endoscopic skull base reconstruction, such as tissue grafts, mucosal flaps provides reconstruction of

limited skull base defects[17]. The difficulty to secures large dural deffects led to the exploration of the feasibility of robotic-assisted endoscopic surgery and repair of the anterior and central skull base. The preclinical studies showed that further instrument development and continued investigation are warranted before this approach can be touted as an exciting alternative to present surgical techniques and standard approaches[12,18].

Neck Surgery

Neck surgeries encompass salivary glands resections, neck dissections, congenital cysts and thyroid and parathyroid surgery among others. Currently, patients are much more interested not only in treatment of the disease but also in postoperative quality of life, which includes such considerations as operative scar, degree of pain, and ability to return rapidly to the work. These interests have focused on the cosmetic result and the noninvasiveness of the operation, resulting in the development of minimally invasive surgical techniques. Since the first report of endoscopic parathyroid surgeries in 1996[19], various techniques of endoscopic thyroid surgery have been introduced during the past decade[20,21]. Recently, different services of head and neck worldwide reported robot-assisted thyroid and others neck surgeries, in order to diminish the scars in the neck and to avoid the common complications of the traditional approaches[22-24]. The follow-up results and the morbidity outcomes need further evaluation, in addition the reproducibility of the different techniques described must also be confirmed by numerous teams prior to adoption of these techniques.

Final Comments

Robotic-assisted head and neck surgery provides high-magnification and three-dimensional optics that allows careful dissection, with en bloc resection, allnd allows for identification of nerves and vessels before transection or inadvertent injury. Hemostasis is achieved with either monopolar or bipolar cautery robotic instrumentation and the use of small-sized hemoclips. The robotic instrumentation furthermore offers at least 360 degrees of freedom of movement, varied levels of scaled movement, and hand tremor buffering that greatly enhances the precision by which the procedures can be performed. Robotic-assisted head and neck surgery provides technical feasibility of accessing and performing resections without requiring transcervical or transmandibular approaches. Robotic surgery in the head and neck region holds promise for human clinical application and may prove valuable as a minimally invasive and low morbidity primary therapy for varied benign and malignant head and neck lesions. In some anatomic sites may also shift the paradigm back to primary surgery with or without radiation for the management of head and neck cancers.

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Head and Neck Melanoma: Current Surgical Practices

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Abstract
The incidence of head and neck melanoma has steadily risen over the past thirty years. Local and regional disease control remains the critical determinant of head and neck melanoma outcomes, and therefore surgery remains the key treatment modality for malignant melanoma of the head and neck. Multi-center, prospective studies have redefined the surgical decision making in regards to the extent of surgical margins and the critical role of sentinel lymph node biopsy. Furthermore, newer technologies in sentinel node localization and adjuvant therapies have aided the prognosis, management, and treatment of head and neck melanoma. These advances have improved the ability of head and neck surgeons to maximize loco-regional disease control by optimal and thoughtful surgical planning.

Introduction
The incidence of malignant melanoma is increasing at a rapid rate. The National Cancer Institute's SEER data has tracked the steady increase in melanoma incidence in the United States from 7.9 to 21.1 per 100,000 over the past thirty years. Mortality rates, in contrast, have remained relatively stable at 2.7 per 100,000[1]. In this same time frame, the management of melanoma has undergone significant changes and improvements. In this review, we address the current management of head and neck malignant melanoma and summarize the key clinical research which has established the rationale for surgical margins, sentinel lymph node biopsy, technological advances in sentinel lymph node localization, and use of radiation therapy for head and neck melanoma.

Surgical Margins for Primary Melanoma Excision
Complete surgical excision has been and remains the treatment standard of care for primary melanoma. The rationale for the size of the surgical margins is based on melanoma's ability to migrate from primary tumors through cutaneous lymphatics to regional lymph nodes. Traditionally, larger margins of surgical excision were advocated as a means to prevent lymphatic spread. The concept of 5 cm margins was challenged by Breslow and Macht[2], and subsequent randomized, prospective trials demonstrated that narrower margins were, indeed, equally curative.

Three landmark prospective, randomized studies established the extent of margins necessary to control local disease and constitute the current surgical treatment paradigm. Veronesi et al. in a multi-center international trial compared 1cm and 3cm margins for thin melanoma measuring up to 2 mm Breslow depth[3,4]. They demonstrated in their primary report and in their subsequent publication that the there was no statistically significant difference between the narrower margin and the wider margin in local recurrence rates (LRR), disease free survival (DFS) and overall survival (OS). Unfortunately, Veronesi's study did not specifically address nor did it include head and neck melanoma subjects. The subsequent study, by Balch et al., included a patient population of trunk, extremity, and head and neck melanoma, but it addressed intermediate size lesions, specifically Breslow depths of 1-4 mm[5, 6]. Their data also did not demonstrate any statistical difference between OS and LRR, thus establishing a recommendation for 2cm margins for intermediate size

lesions. The studies of Veronesi and Balch were validated by a third prospective randomized study. Ringborg et al looked at thin and intermediate lesions (0.8 mm to 2 mm) comparing surgical margins of 2 cm and 5 cm[7, 8]. Although no randomized study has prospectively studied margins necessary for local control in only head and neck melanomas, the extrapolated data from these studies support a 1 cm margin for thin melanomas, up to 1 mm depth, and a 2 cm margin for intermediate depth lesions. More recently, the United Kingdom Melanoma Study group, in a randomized, prospective study, examined surgical margins necessary for thicker melanomas, greater than 2 mm Breslow depth[9]. Their results demonstrated an increased LRR in patients with 1 cm margins, but no difference in melanoma specific survival and OS. This UK study did not include head and neck melanomas nor did it address differences between 2 and 3 cm margins for thicker melanomas. Finally, the thickest of melanomas, >4mm Breslow depth, have not been studied prospectively, but a retrospective review did not support the use of surgical margins greater than 2 cm[10]. While not settled definitively, thick lesions in head and neck melanoma patients should be treated with 2 cm margins. Attempting larger margins in head and neck melanoma frequently is limited by the proximity of critical facial structures.

Lymph Node Involvement

The evaluation and treatment of lymph node metastases in melanoma has evolved significantly over the past 30 years. Therapeutic lymph node dissections (TLND) have been and remain the standard of care for clinically involved lymph node basins[11]. However, there has been debate about the most appropriate treatment for the clinically negative nodal basins in melanoma, especially for intermediate thickness tumors measuring 1 mm to 4 mm. Elective lymph node dissections (ELND) historically were the standard of treatment for intermediate and thick melanomas of the head and neck. Yet, multiple trials were performed in hopes of demonstrating an overall survival benefit in patients who underwent ELND instead of observation and TLND for progressive disease[12-15]. These studies failed to demonstrate any benefit for patients undergoing ELND. As a result and prior to the advent of sentinel lymph node biopsy (SLNB), surgeons trended to observe the lymph node basins after wide local excision of intermediate thickness melanomas and reserved TLND for clinically involved lymph node basins.

Lymph node status has been recognized as the most important prognostic factor of survival for melanoma[12, 16-18]. Morton's landmark study discussed SLNB as a method of identifying risk of lymph nodal involvement by tumor[19]. SLNB in head and neck melanoma quickly replaced prior strategies as the standard of care for nodal basin evaluation and treatment. Indeed, 15-20% of patients diagnosed with head and neck melanoma will present initially with nodal metastasis [20-22]. Thus, SLNB identifies the subpopulation of microscopic nodal positive patients while shielding the remaining 80-85% nodal negative patients from a larger staging surgery, ELND. Appropriate patient selection, however, for SLNB is critical for accurate application of prognostic data. Thus, patients with positive nodal basins or distant metastases and patients with altered lymphatic drainage from prior surgery, neck dissections, or radiation do not benefit from SLNB.

The most convincing prospective, randomized trial published to date on the role of SLNB for melanoma is the Multi-center Selective Lymphadenectomy Trial I (MSLT-I)[23]. Morton et al compared wide local excision and observation with subsequent lymphadenectomy (TLND) for clinically positive lymph node involvement to wide local excision and SLNB with completion lymphadenectomy (CLND) for positive SLNB in intermediate thickness melanomas. This study confirmed the prognostic role of SLNB, but it also demonstrated a clinical advantage of DFS after SLNB. While there was no OS difference, the 5 year DFS rates were significantly higher in the SLNB group in comparison to the observation group, 78.3% vs. 71.3% respectively. The primary utility of SLNB is as a prognosticator of outcomes, as evidenced by the higher 5-year survival rates of patients with negative SLNs (90.2%) in contrast to those with positive SLNs (72.3%; $P < .001$). Most importantly, MSLT-1 demonstrated a survival advantage between immediate lymphadenectomy in patients with subclinical sentinel-node metastases (72.3%) and patients with delayed lymphadenectomy for clinically detected nodal relapse. (52.4%; $P = 0.004$)[23]. Thus, SLNB is critical for staging and prognostic value in patients with intermediate-thickness melanoma, and has survival advantage in patients with positive SLNB who undergo immediate completion lymphadenectomy.

Technical Considerations of Sentinel Lymph Node Biopsy

SLNB, however, is not without its challenges. Nuclear medicine imaging provides a lymphoscintigraphic map which is used preoperatively for surgical planning. However, the complex and rich lymphatic drainage of the head and neck region can obscure accurate identification of the true SLN. Indeed, head and neck melanomas frequently are mapped to multiple lymph node basins with multiple lymph nodes identified in each basin[20, 24]. This fact may explain the higher rate of false negative SLNB in head and neck melanoma in comparison to truncal and extremity melanoma[20]. Imaging by planar

lymphoscintigraphy is also limited by the complexity of the lymphatic drainage of the head and neck. Because of the smaller size of the lymph nodes and their close proximity in a compressed space, multiple lymph nodes are potentially indistinguishable on preoperative imaging, leading to possible surgical sampling error[25,26]. Furthermore, the primary tumor and the injected tracer may be in very close proximity to the SLN. The signal from the tracer injection can completely obscure the true SLN, thus leading to a false negative biopsy of a secondary draining lymph node[26]. Finally, conventional planar lymphoscintigraphy, especially in the head and neck, is limited by the lack of anatomic references[26].

In contrast, the hybrid single photon emission computed tomography camera with integrated computed tomography (SPECT/CT) combines tomographic lymphoscintigrams with CT images and has only recently been developed. This combined imaging modality has a significant advantage of demonstrating an anatomical relationship between the SLN and the surrounding structures[27]. SPECT/CT also can detect additional drainage basins and improved anatomical localization, especially in patients with inconclusive conventional lymphoscintigrams[26, 27]. This technology has not changed the indications for and benefits derived from SLB, but it has certainly improved the peri-operative planning required for a successful SLB. Ultimately, more experience needs to be accumulated and reviewed in order to confirm the initial impressions that SPECT/CT imaging enhances surgical exploration and may improve melanoma staging with a decrease in false negative rates.

The Role of Radiation Therapy in Melanoma

Melanoma has been generally perceived as radio-resistant tumor, thus external beam radiotherapy as adjunctive treatment never came to widespread use for melanoma[28]. The clinical efficacy and postoperative use of radiation therapy has been widely debated and remains controversial[14]. Furthermore, postoperative adjuvant radiation therapy has not been shown to prolong survival[29]. The rationale, however, for adjuvant radiation therapy in melanoma is based on the reduction and control of residual microscopic disease, thereby reducing the morbidity caused by regional recurrences and risk reduction associated with repeat surgical procedures[30, 31]. Retrospective studies examining the pattern and frequency of regional lymph node recurrence have identified certain clinical and pathologic features which increase loco-regional recurrence rates. Lymph node extra-capsular spread, large number nodal disease, and/or large volume nodal disease have been associated with significantly increased regional recurrences[32-34]. Consequently, multiple retrospective studies have attempted to address the benefit of postoperative radiotherapy for patients with such clinical and pathologic characteristics predisposing to regional recurrence.

Many authors have demonstrated regional control rates of 90% and greater with postoperative radiation therapy after wide local excision and lymphadenectomy[35-38]. These regimens use mostly large dose, hypofractionated radiation. Patients with significant co-morbid conditions or contraindications to TLND benefit from elective radiation therapy. Indeed, Ballo et al achieved a 93% regional control rate with a 5.3 year follow-up using a hypofractionated regimen in patients with significant co-morbid conditions who had excision of primary tumor and palpable nodal disease, but not TLND[38]. Yet, other authors do not support the use of postoperative adjunctive radiotherapy because their reported regional recurrence rates are essentially unchanged in comparison to only surgical treatment[34, 39]. Certainly, there is no argument that surgical management is the standard of care for cervical node metastases from metastatic melanoma. At our institution, we believe there is sufficient evidence of loco-regional control to recommend radiation therapy to patients with bulky nodal tumor involvement, extracapsular nodal involvement, or significant co-morbidities.

Summary

Although there have been significant advances in chemotherapy and immunotherapy, loco-regional control remains the critical determinant of head and neck melanoma outcomes. Consequently, surgery remains the key treatment modality for melanoma, and the role of head and neck surgeons is to maximize loco-regional disease control by optimal and thoughtful surgical planning. Innovative strategies such as SLNB and contributions from multidisciplinary efforts have aided the prognosis, management, and treatment of head and neck melanoma. Most importantly, new knowledge from large, multi-institutional studies has in the past and continues to refine our understanding and management of head and neck melanoma.

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Sentinel Node in Head and Neck Cancer

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Introduction

Squamous cell carcinomas are the most common tumors of the upper aerodigestive tract. The presence of cervical lymph node metastases is one of the most important prognostic factors for patients with head and neck carcinomas. Lymph node metastases are associated with a decrease in the survival rate of up to 50% in this patient group[1]. Imaging modalities such as ultrasonography, magnetic resonance imaging (MRI) and positron emission tomography (PET) have facilitated detection of distant metastases and can identify suspicious regional nodes, but they can not identify smallest metastases within these nodes. Current publications report on a sensitivity rate of about 70-80% for the detection of cervical metastases by sonography, magnet resonance imaging (MRI), computed tomography (CT) and 18F-fluordesoxyglucose (FDG)-positron emission tomography (PET) as well as PET/CT[2-6]. The incidence of clinically occult metastases for patients with carcinomas of the upper aerodigestive tract still amounts to 20%[7-9].

Currently, the extent of neck dissection is based predominately on histological type, stage of primary tumor, and the preoperative knowledge of lymph node involvement. If occult metastases are detected in the neck specimen, adjuvant radiotherapy will usually be indicated while in case of a neck without lymph node metastases there are no therapeutic consequences. Moreover, several studies have shown that the status of lymph nodes is the most important prognostic indicator of survival and the risk of recurrence in patients with clinically involved lymph nodes. For this reason, removal and histologic examination of lymph nodes is considered the most accurate method for assessing spread of disease to the lymph nodes, offers the ability to optimally plan adjuvant therapy and seems to be the only effective therapeutic option for local control and potential cure. The procedure of neck dissection is associated with a risk for functional disability and aesthetic deformity after operation[10]. For this reason the routine use of neck dissection especially in cases of N0 neck is discussed.

The Sentinel Node (SN) concept

The SN concept was first postulated by Gould in 1960[11] and Cabanas in 1977[12]. In 1990 it was introduced for diagnosing melanoma lymph node metastases. The usefulness as a prognostic indicator of metastases in melanomas led to an expanded application for breast, colon, gastric, thyroid, oesophageal, lung as well as head and neck cancer. Since 1996 trials studying SN biopsy in HNSCC were initiated, primarily analyzing oral cancer as it is the most accessible mucosal site. The place of SN biopsy in staging and management of HNSCC is still an ongoing debate. Until now it has not achieved the status of standard of care for the treatment of HNSCC patients. However, a large number of studies have been published in the literature on different aspects of this technique.

The concept of SN biopsy is based on the fact that the first lymph node in a lymphatic chain (the sentinel node) will be the first affected by metastasis and that metastases only subsequently travel to the remaining regional lymph nodes. Therefore, if the sentinel node can be shown to be negative, it is highly unlikely that other lymph nodes are affected.

The lymphatic mapping is done by passage of a marking dye or radioactive substance, injected by a tumoral or peritumoral injection. Several techniques have been reported to identify the sentinel nodes. When a radiotracer is injected at several sites around the tumor the location of SN is depicted by a gamma camera in the department of nuclear medicine or by a gamma probe in the operation room.

The problem of blue dye is that it stains the area around the primary tumor which complicates the resection of the primary tumor and may alter the absorption of laser energy which is often used to resect tumors of the upper aerodigestive tract[13]. Moreover the blue dye often extravasates into the tissue[14]. Therefore most groups prefer a radioactive tracer without using blue dye.

All methods had reliable results in experienced hands. Though theoretically the sentinel node should be one node, in practice there is often more than one lymph node which is positive by either blue dye method or radiotracer method and they are labelled as sentinel node. Since most of the time, there is more than one sentinel node, false negative rates fall if multiple nodes were removed instead of one single node.

Therefore one topic that is widely discussed around SN biopsy is how many lymph nodes should be removed. The principle of SN biopsy is to find the node into which is the greatest lymph flow from the tumor. Therefore, the key to SN mapping is to find the route of lymph flow from the tumor. One complicating aspect in neck surgery is that the lymphatic drainage pathways are quite intricate. Therefore the use of SN biopsy is still debated since there is a variability of the mucosal lymphatic drainage from different mucosal sites and the direction of the lymphatic drainage is not always predictable.

SN in head and neck cancer

Depending on their localization, carcinomas of the upper aerodigestive tract drain to different lymph node levels in the neck. Oropharyngeal cancer initially metastasizes most frequently to levels II and III and less frequently to levels I, IV and V. Levels I-III are at greatest risk for nodal metastases from carcinomas of the oral cavity. The metastases of laryngeal and hypopharyngeal tumors are most often located in level II-IV. Metastases in levels I to V are rare and usually associated with metastases in lymph nodes along the jugular vein. The nodes of level VI were included in tumors of the glottic/subglottic larynx, pyriform fossa apex and the postcricoid region.

The advantages of SN may are a more accurate loco-regional lymph node staging and an identification of lymph node metastases outside the typical metastatic pattern allowing for a more accurate planning of surgical excision. This approach will avoid the morbidity associated with a more extensive neck dissection for HNSCC patients. Sentinel Node biopsy offers the chance to stage the neck with less morbidity than a selective neck dissection. The failure rate of selective neck dissection is between 1.9% and 5%. Common complications and morbidities after neck dissection include numbness and/or burning sensation in parts of the neck or ear, neck pain, shoulder discomfort, lymphedema, neck tightness, and aesthetic disfigurement.

The aim of SN biopsy is to preserve the quality of life without risking the oncologic result. Analyzing the quality of life after sentinel node biopsy and selective neck dissection it could be shown that the functional outcome after sentinel node biopsy is significantly better[15]. Performing a metaanalysis Paleri et al.[16] showed that the cumulative payoff for the sentinel node biopsy arm was lower than that for the elective neck dissection arm by about 1%. However, the problem is that a tumor in the head and neck region will eventually show more than one isolated lymph node[17].

If several lymph nodes have to be removed, the advantage of SN biopsy over selective neck dissection is questionable. Especially the biopsy of multiple sentinel nodes in two or more levels seems to offer only few advantages over selective neck dissection for patients with HNSCC. Dünne et al.[18] defined SN as the most radioactive lymph nodes identified by gamma probe and 1-3 SN per patient were removed. One single SN was removed by Stoeckli et al.[19]. They used dynamic lymphoscintigraphy to identify the lymph node which was first affected by the radiotracer. In most studies between 0-6 SNs were removed. Anuli et al.[20] analyzed how many lymph nodes should be harvested to accurately stage the neck. They contributed that all patients would have been staged accurately if only the hottest three nodes had been retrieved. These results stress that several lymph node have to be resected to avoid false-negative results[21]. Remembering that lymphatic structures are very dense in the head and neck area and altogether about 300 lymph nodes are situated in the cervicofacial area this observation is not surprising.

Although according to the sentinel node hypothesis the metastasis in the first node draining the tumor is identified, this is not always the case. There are many cases which cause sentinel node procedure to give false negative results, or where sentinel node cannot be identified. Hornstra et al.[22] investigated factors for failure to identify sentinel nodes in HNSCC. Patients with a negative preoperative lymphoscintigraphy and patients with tumors in the anterior tongue and floor of mouth were found more likely to have an unsuccessful SN procedure as patients with clinically advanced disease or clinical N+ neck. Even other authors have been reported that in floor of mouth tumors there is a great risk of failure and that the sensitivity of SN biopsy is not as good as in tumors of other oral

locations[23]. Especially sentinel nodes in level I are easily missed on lymphoscintigraphy due to close proximity of the sentinel node to the injection side. This affects tumors of the anterior tongue and floor of mouth predomiantely. Moreover the study of Hornstra et al.[22] demonstrates a correlation between tumor classification and the likelihood of failure to identify the SN. The primary tumor site seems to have an important influence on the success of SN procedure since a larger primary tumor site is more difficult to inject with the radiotracer or the dye.

Among head and neck cancer there were many reports regarding SN biopsy in oral and oropharyngeal cancer. Most of the authors concluded that accurancy rate of the SN concept for these lesions ranged from 93-100%. The first multicenter trial for SN biopsy in oral and oropharyngeal squamous cell carcinomas revealed a sensitivity rate of 93% which is comparable with that of a selective neck dissection[23]. Recently Burns et al.[24] recommended the use of SN biopsy in cases of oral and oropharyngeal cancer. Performing a metaanalysis Paleri et al.[16] found sentinel node biopsy in squamous cell carcinoma of the oral cavity and pharynx to have high sensitivity rates and to be reliable and reproducible. The prognostic impact of positive sentinel nodes was proven by Kovacs et al.[25]. Patients with oral or oropharyngeal cancer that have positive sentinel nodes had statistically significantly higher rates of locoregional recurrences, second primary tumors, tumor-related deaths and a worse overall and disease-free survival[25].

Only few studies of SN biopsy in laryngeal and hypopharyngeal cancer have been published because it is difficult to access these lesions[21,26,27]. The tracer injection to the larynx and hypopharynx can be performed via rigid endoscopy at the beginning of the operation under general anaesthesia[26] or on the day before surgery with a laryngohypopharyngeal endoscope[27]. Werner et al.[26] found an accurancy rate of 97% in laryngeal and hypopharyngeal cancer. Tomifuji et al.[27] reported very similar results showing concordance between the status of the SN and the final results in the regional lymph nodes in 95% of the patients with clinically N0 laryngeal and hypopharyngeal cancer. Therefore it also seems to be a reliable strategy to determine the correct lymph node status in laryngeal and hypopharyngeal cancer.

Many authors recommended that patients who had received a prior radiotherapy or neck surgery should not be treated with sentinel node biopsy since the metastatic patterns may differ from those in untreated necks. In 2008, the feasibility of SN biopsy in patients with HNSCC which were previously treated with surgery or radiation therapy was investigated by Hart et al.[28]. This study demonstrates that SN biopsy can be successfully used in previously treated patients to reliable predict metastases in the remainder of the neck with a negative predictive value of 91%. SN biopsy was shown to be as effective as in previously untreated patients according to published reports. This study therefore may expand the patient population that benefit from SN biopsy.

Since SN biopsy is proven to be a sensitive method and is more and more used in the clinical routine for head and neck cancer, the debate about the best surgical approach to the SNs becomes more intensive. One single small skin incision that could be extended for a successive neck dissection incision seems to be the optimal approach. Multiple incisions on the neck should be avoided. Among other surgical techniques the usefulness of endoscopic surgery in the SN concept is discussed. Endoscopic SN biopsy is a minimally invasive technique which is especially useful in cases in which deep levels of the neck that are distant from the skin incision have to be dissected[29].

However, there are some limitations of sentinel node biopsy. The primary tumor must be accessible to injections, which practically limits the use of SN biopsy. Allergic reaction to blue dye and radiocolloid are rare but have been reported. Furthermore one has to keep in mind the radiation exposure to the patient and staff involved in this technique[30]. However, the radiation risks to the administered doses are lower relative to many other imaging modalities. It is becoming apparent that SN is appropriate in a variety of settings.

But the clinical application of this potentially valuable procedure as a sole diagnostic tool to stage the nodal status requires its standardization at each hospital, because results vary according to the scanning method, the materials for localization and the method of histopathological examination. Especially, it is necessary to establish standards in histopathological examination to identify micrometastases. Frozen section examination is not recommended since the sensivity for micrometastases in low[31]. Studies revealed that an intensive sectioning and haematoxylin eosin as well as immunohistochemical staining will detect more metastases than standard single-block examination of lymph nodes[32]. Step serial examination of the entire sentinel lymph node with 150μm intervals is the standard method[33]. Therefore an intensive and profound patho- and immunohistochemical analysis is necessary.

Conclusion

The role of sentinel node biopsy has been controversially discussed in the fields of otolaryngological oncology but

it seems to be a remarkably safe and successful multidisciplinary diagnostic procedure. Several retrospective studies have demonstrated that SN biopsy is an adaequate diagnostic and therapeutic procedure for N0 neck disease for HNSCC. Tumors staged T1 and T2 seem to be optimal for sentinel node biopsy since larger tumors are more difficult to inject with the radiotracer. The results of SN biopsy are promising with an overall sensitivity of over 90%. Therefore it is now believed that SN biopsy is an oncologically sound concept. In consideration of the tendency towards minimally invasive strategies, SN biopsy seems to be optimal since it is minimally invasive, minimizes radicalness, and individualizes the treatment. The principal disadvantages of neck dissection are the removal of an intact lymph system, the morbidity, and the prolonged operation time. SN biopsy has the potential to decrease the need for neck dissection in cases of N0 neck thereby improving functional results and reducing costs. Therefore SN biopsy appears to be a method to be concentrated on and developed as an alternative to selective neck dissection which will replace selective neck dissection in at least some cases.

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Management of Medullary Thyroid Carcinoma

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Abstract
Medullary thyroid cancer (MTC) is rare, it arises in children and adults, and in 25% of cases is genetically determined.

The serum calcitonin level prior to surgery, in addition to findings on clinical examination and imaging will predict outcome and guide the extent of surgery. The minimum recommended intervention in most patients with palpable MTC is total thyroidectomy, central neck node dissection, lateral selective neck dissection (levels IIa-Vb) is required for patients with N1 disease. In gene positive children, risk reduction thyroidectomy is required to prevent the onset or spread of MTC.

Postoperative normalisation of serum calcitonin is associated with >95% chance of cure, 10-year survival rates vary from 56%-87%. A calcitonin doubling time of <6-12 months indicates a worse prognosis.

The detection of early stage MTC by the use of routine calcitonin screening in patients with thyroid disease and the use of biological therapies in patients with advanced MTC are potential therapeutic 'advances'

Key Words
medullary thyroid cancer – calcitonin – multiple endocrine neoplasia type 2

Introduction
Medullary thyroid cancer (MTC) arises from the calcitonin secreting para-follicular C-cells of the thyroid, it is rare (approximately 5% of all thyroid malignancies), there are an estimated 20 -25 new cases per year in the UK. The reported prevalence of MTC among patients with thyroid nodules is 0.26–1.30%, typically, the diagnosis of MTC is made on the basis of preoperative thyroid cytology or after diagnostic thyroid surgery.

25% of cases MTC arises as a consequence of an autosomal dominant, genetically determined disorder (MEN 2A, MEN 2B, FMTC) - **TABLE 1** associated with a germ line mutation of the RET proto-oncogene on chromosome 10[1]. The remainder of patients with MTC have sporadic disease. When MTC is confirmed, it is essential to take a family history, exclude phaeochromocytoma even in the absence of 'symptoms' (measure plasma nor/metanephrines or 24 hour urinary metanephrines and catecholamines) and in conjunction with clinical genetics perform RET mutation analysis to exclude /confirm hereditary disease. A positive gene test mandates that other family members are offered genetic and clinical screening. Prior to surgery a patient suspected of or confirmed with MTC requires evaluation of basal calcitonin and serum calcium levels and neck ultrasound. If there is evidence of cervical lymphadenopathy, CT chest and liver MRI should be performed.

TABLE 1

Clinical Features of Multiple Endocrine Neoplasia Type 2	
MEN 2A (85%)	Medullary Thyroid Cancer Phaeochromocytoma Hyperparathyroidism Cutaneous Lichen Amyloidosis Hirschsprung disease
FMTC (5-15%)	Medullary Thyroid Cancer
MEN 2B (5%)	Medullary Thyroid Cancer Phaeochromocytoma Marfanoid habitus & musculoskeletal disorders Mucosal neuromas and intestinal ganglioneuromas Failure to thrive Constipation

This article is an update on recent developments in the investigation and treatment of patients with sporadic and familial MTC.

Calcitonin Screening in Patients with Thyroid Nodules

Calcitonin and carcinoembryonic antigen (CEA) are elevated in most but not all patients with MTC[2]. Basal calcitonin levels are a more sensitive indicator of MTC than FNA, and there is current controversy about the role of routine calcitonin measurement in patients who present to secondary care with nodular thyroid disease in order to diagnose smaller tumours and obtain a better outcome[3, 4]. The positive predictive value of an elevated calcitonin (>10ng/l) is approximately 10%, a basal calcitonin of >100ng/l is generally regarded as an indication for surgery. The use of pentagastrin stimulation tests for patients with basal calcitonin of <100ng/l improves the specificity of calcitonin screening, a stimulated calcitonin value of >1000ng/l has a PPV for MTC of 100%. Although calcitonin screening may result in an earlier diagnosis of MTC and improved outcome, there is at present no evidence that the incidence of advanced tumours has decreased because of calcitonin screening, or knowledge that small sporadic MTC identified on calcitonin screening progress to clinically significant disease.

Preoperative Calcitonin Levels in Patients with MTC

The preoperative basal calcitonin level indicates the extent of disease and correlates with tumour diameter[5]. Lymph node metastases are found in patients with calcitonin levels as low as 10-40ng/l, this justifies the practice of routine node dissection in patients with MTC. In node positive patients, extrathyroidal disease and distant metastases appear with calcitonin values of 150-400ng/l [6].

Therapeutic Surgery for Patients with MTC

The aim of surgery for MTC is loco regional control and biochemical / clinical cure. There is evidence that patients with established MTC are frequently treated by a less than adequate surgical procedure[7, 8], this confirms the need for referral of patients with MTC to a designated cancer centre for surgical treatment[9]. The minimum operation to be performed is total thyroidectomy and levels VI and VII node dissection (central compartment).

The British Thyroid Association[9] guideline for the treatment of pT2-4 MTC with radiologically abnormal/ palpable nodes in the central / lateral neck is bilateral selective neck dissection - levels IIa-Vb. Despite the finding that ipsilateral and contralateral lateral compartment neck nodes are frequently involved when central compartment nodes are positive[10] - **TABLE 2**, the American Thyroid Association recommendations for patients with clinically N0 / N1 lateral neck are neither clearly stated or agreed on by all members of the Task Force group[11]. Patients with limited distant metastases should undergo total thyroidectomy, central and therapeutic lateral neck node dissection.

TABLE 2

Frequency of Lateral Compartment Lymph Node Involvement in Patients with MTC from Machens et al.[10]

Number of +ve central compartment nodes	+ve nodes in ipsilateral lateral compartment	Number of +ve central compartment nodes	+ve nodes in contralateral lateral compartment
0	10%	0	5%
1-3	77%	1-9	38%
>4	98%	>10	77%

Approximately 10% of patients with microMTC (<1cm) will have lymph node metastases in the central compartment. In the absence of any preoperative test to accurately discriminate node positive from node negative disease, total thyroidectomy and central compartment node dissection has been recommended for these patients[12].

Patients with mediastinal node involvement inferior to the brachiocephalic vein should be considered for lymphadenectomy via a transternal approach to reduce the risks from subsequent aerodigestive compression/ invasion.

Outcome of Patients with MTC

Less than 5% of patients with postoperative biochemical 'cure' will relapse[13]. Basal calcitonin will be undetectable in 60-90% node negative and less than 20% node positive patients after surgery. Patients with tumours more than 4cm in diameter, or with preoperative calcitonin >3000ng/l, or with more than 10 positive nodes or involvement of more than 2 node compartments do not achieve biochemical cure. The overall disease specific 10-year survival of MTC patients is approximately 75%, although a recent Japanese group describe 10-year and 20-year cause-specific survival rates of 96.6% and 91.7% respectively[14]. Patients with distant metastases have 5-year and 10-year survival of 25% and 10% respectively, more than 50% of patients with MTC will die of their disease. Calcitonin (and CEA) doubling times (assessed by at least 4 measurements) correlate with MTC progression[15] and survival[16] - **TABLE 3.** Sporadic MTC patients with somatic RET mutations (approximately

TABLE 3

The impact of calcitonin doubling time on prognosis of patients treated for MTC – from Barbet et al (2005)[16]		
Calcitonin Doubling Time	**5 year survival**	**10 year survival**
< 6 months	25%	8%
6-24 months	92%	37%

A calcitonin doubling time of more than 24 months was associated with stable disease

50%) in exons 15 and 16 have a high incidence of lymph node metastases, a higher risk of persistent disease and lower survival rates[17, 18].

The Patient with Recurrent MTC / Rising Calcitonin Levels

It is important to distinguish loco-regional recurrence amenable to surgery, from distant metastases. When initial neck surgery was less than optimal, further surgery should be considered even when cross sectional imaging fails to identify disease in the neck. Reoperation in selected patients can result in biochemical cure in approximately one third of patients[19, 20].

An increase in calcitonin of more than 20-100% is an indication for repeat diagnostic imaging studies. A systematic approach to cross sectional imaging (neck ultrasound/chest CT/liver MRI), bone scintiscan or MRI, is appropriate[21]. Distant metastases are best detectable when calcitonin levels are more than 500ng/l[21, 22].

Non surgical treatment of MTC

Adjuvant external beam radiotherapy has not been shown to produce a survival benefit but appears to improve locoregional control in patients with MTC at high risk of locoregional relapse[23]. The current and 'future' palliative treatment options for patients with symptomatic distant metastases include chemotherapy, novel biological therapies directed against angiogenesis and other molecular targets (*RET* kinases, signal transduction pathways). This subject is well reviewed in two recent articles[11, 24].

Risk reduction surgery

RET gene positive children and young adults are at risk of MTC and should be offered prophylactic thyroid surgery prior to the genetically determined neoplastic transformation of C-cell hyperplasia to MTC with subsequent nodal metastasis. In ideal circumstances surgery should be performed prior to the onset of MTC, the reality is that young patients may present when MTC has already developed. The timing and extent of surgery (thyroidectomy ± lymph node dissection) is based on the codon mutation, the age of the patient and the level of calcitonin. This

TABLE 4

Summary of recommendations as to at what age 'Risk Reduction' thyroidectomy and lymph node dissection (central compartment) should be performed according to 'Risk Category / Codon Mutation' in patients with *RET* mutations		
Risk Category (Codon Mutation)	**Age for Prophylactic Thyroidectomy**	**Age for Lymph Node Surgery**
Highest (918,883)	1st 6 months of life	At the time of thyroid surgery
High (634, 611,618,620,630)	Before 5 years of age	After 5 years of age
Least High (768,790,791,804,891)	Before 10 years of age	After 20 years of age

subject is well reviewed in recent publications[11, 25] and is summarised here in **TABLE 4**.

It is important to recognise that young gene carriers identified with overt MTC on the basis of preoperative basal calcitonin levels and ultrasound scan should undergo a 'therapeutic' rather than prophylactic intervention.

Conclusions

An experienced multidisciplinary team within a cancer centre should treat adult and paediatric patients with, or at risk of MTC. All patients with proven or suspected MTC should undergo biochemical tests prior to any surgery to exclude phaeochromocytoma. Patients with confirmed MTC should undergo genetic testing to identify familial MTC. A distinction should be made between therapeutic and prophylactic surgery in terms of the timing and extent of surgery. The standard operation for MTC is total thyroidectomy and central compartment node dissection with many patients requiring bilateral selective lateral neck dissection (levels IIa-Vb).

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Current surgical management of unilateral vocal fold paralysis

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Abstract
Numerous methods have been described to manage patients with unilateral vocal fold paralysis. This article explores some of these techniques.

Key words
vocal fold paralysis; medialisation thyroplasty; vocal fold augmentation

Introduction
A range of surgical procedures is available for the management of a patient with unilateral vocal fold paralysis. The aim of all procedures is to allow contact with the opposite cord during phonation and swallowing, and to improve the patient's ability to cough. In many cases where the phonatory gap is less than 1mm, the non-paralysed cord will compensate sufficiently with speech therapy such that surgery is not required.

The procedures can be divided into static and dynamic methods:

1. Static
In most instances, injecting or implanting a material will augment and medialise the paralysed vocal fold to facilitate contact. In the last few years, numerous materials have been used in vocal fold augmentation, many of them originally used as cosmetic facial fillers.

Injectable materials:
An ideal injection material would have the following properties

- Lack of antigenic response
- Resistant to migration or resorption
- Have similar visco-elastic properties as the vocal fold itself
- Require minimal preparation
- Be easy to inject with precise control of location and volume of injection

Teflon [permanent]
Widely used for vocal fold augmentation in the 1960s, 70s and 80s, Teflon has now fallen out of favour as an injection material, largely because of significant complications of material migration and granuloma formation but is of historical interest.

Collagen [temporary – 3 to 6 months]
Autologous collagen was developed to remove the possibility of hypersensitivity reactions. However, the material takes several weeks to prepare, and it is prohibitively expensive. Bovine collagen [Zyplast][1] is widely available and can be used after an initial test dose to the forearm (6 weeks prior to laryngeal injection). As an alternative, Cymetra®, which is cadaveric micronized acellular dermis, is very useful. It is freeze-dried into a powder, which is then reconstituted in the clinic. Results suggest that long-term improvement is not achieved, but long-term results are often not the aim of therapy in this group of patients who may simply need a palliative procedure. This material is suitable for transcutaneous or per-oral injection or injection as it is low density and can be used in a simple pre-packed syringe[2].

Hyaluronic acid (Rofilan) [temporary]
This material has several properties that make it useful as in injection material for vocal fold augmentation: it is similar in physical properties to the superficial layer of the lamina propria and gives excellent biocompatibility. Over time, it is entirely resorbed and no foreign body reactions have been described[3].

Polyacrylamide gel (PAAG, Aquamid®) [non-absorbable]
Developed as facial filler, PAAG has recently been used as a percutaneous injection material for vocal fold augmentation. Initial results are encouraging, showing a long-lasting improvement in vocal parameters[4].

Radiesse® (Calcium hydroxylapatite) [temporary – lasts up to 2 years]

This has been used increasingly as in injection material for glottic insufficiency[5, 6] and consists of calcium hydroxylapatite spheres suspended in a gel carrier (glycerine and water). The gel is reabsorbed and eventually replaced by soft tissue in-growth but this can be variable. This material is suitable for transcutaneous or per-oral injection as it is of low density and comes in a Luer- Lok syringe.

Vox® (formerly known as Bioplastique®) [permanent]

Vox is a mixture of Polyvinylpyrrolidone (PVP) hydrogel and Polydimethylsiloxane (PDMS). This material is of high density and requires a thick (20G) needle and pressure gun injection device, making it unsuitable for transcutaneous injection. It is not absorbed, so if any recovery of function of the vocal fold is anticipated, this is not the preferred implant substance. Recent studies shows good long-term results following Vox injection[7, 8].

Autologous fat [temporary]

Since the early 1990s, autologous fat has been proposed as a useful injection material. It has clear inherent advantages: there is no antigenicity; it is readily available; it has similar visco-elastic properties to the vocal fold; and once it has been prepared, it is easy to inject. It does, however, require a skin incision to harvest the fat. Furthermore, it is very readily absorbed and may require repeat injections[9-12].

Injection technique

In the awake patient, the vocal fold may be injected perorally (using a curved needle), transnasally (using a flexible nasendoscope with a side channel) or percutaneously.

The 2 most commonly used techniques in the UK are:

Percutaneous injection

Percutaneous injection of material into the vocal fold remains a popular choice in patients who have limited life expectancy and who are too unwell to tolerate general anaesthesia or sedation. A trans-cricothyroid membrane, a trans-thyrohyoid membrane or trans-thyroid cartilage approach may be used. A nasendoscopic camera allows visual feedback as to the correct position of the needle.

The trans-cricothyroid approach is probably the easiest of the three, and will be familiar to many as it is similar to the technique used in botulinum toxin injection. Having sterilised the skin and injected local anaesthetic into the subglottic area, the needle is inserted just off the midline. The needle is angled supero-laterally towards the main body of the vocal fold. The aim is to inject deeply into the body of the vocal fold – the thyroarytenoid muscle – to medialise and allow contact. Both visual and auditory feedback assists the surgeon to achieve the best possible result [13].

Per-oral injection under general anaesthetic

Under general anaesthetic, suspension laryngoscopy is used to access the larynx. The injection is directed into the muscle of the vocal cord. The most common error in this technique is to inject too superficially into the superficial lamina propria resulting in scarring and consequent poor mucosal wave. Over-injection may result in airway compromise that will only become apparent when the patient is extubated.

Laryngeal framework surgery:

Medialisation thyroplasty

Widely considered to be the gold standard procedure, medialisation thyroplasty is performed in many centres. The technique was refined by Isshiki[14]. Although it involves a skin incision, it has significant advantages over injection medialisation: it is possible to enlarge or reduce the size of the implanted material, according to voice or airway symptoms; it is reversible; and it may be performed in conjunction with other procedures.

Under local anaesthetic and sedation, the thyroid cartilage is exposed through a transverse skin incision. A window is cut in the thyroid cartilage and the inner perichondrium is elevated off the cartilage. A second surgeon uses a nasendoscope (connected to a video screen) to inspect the larynx and confirm the position of the elevator at the level of the vocal cord and the degree of medialisation required for contact. An appropriately designed and sized implant is then placed in the para-glottic space and its position confirmed.

The choice of implant is at the discretion of the surgeon. Most commonly, a silastic shim, cut to the required dimensions, is inserted but more recently, Gore-Tex® (expanded polytetrafluoroethylene) has been used. Placing the implant into the vocal fold, this ribbon-like material can be manipulated into the exact shape required[15]. In the Friedrich thyroplasty system[16], different sized metallic implants are ready prepared and in the Montgomery system[17] there are similarly preprepared silastic implants of varying sizes. Having made the window in the thyroid cartilage, trial implants of differing sizes can be inserted and the patient phonates to check for improvement in voice.

Arytenoid procedures

Although medialisation of the paralysed vocal fold corrects the lateralisation of the cord, it does not address the fact that the denervated fold is flaccid and can be at a higher vertical plane. Isshiki[18] originally proposed arytenoid adduction for patients with a wide posterior glottic gap and a modification of this procedure has been developed by Zeitels[19]. A further refinement was the introduction of the cricothyroid subluxation to give tension to the paralysed cord [20]. These procedures are technically very demanding but are very effective in improving laryngeal competence.

2. Dynamic

Dynamic procedures aim to restore co-ordinated movement and tone to the vocal fold but are performed in relatively few centres worldwide. A lack of stimulation of the vocal fold inherent to paralysis can also lead to long-term muscular atrophy from disuse.

Re-innervation procedures

The recurrent laryngeal nerve has no topographical orientation until it reaches the cricoarytenoid joint. Only around 9% of cases have complete atrophy and most have some degree of innervation although this will be random for both adductors and abductors [synkinesis] Reinnervation procedures with either the ansa cervicalis or a partial hypoglossal nerve donor may replace this with a more favourable coordinated muscle tone and return some tone in the atrophic cases but results in both animals and humans can be variable. Further work on selective reinnervation may provide optimal results for both coordinated movement and muscle tone[21].

Pacing

Dynamic rehabilitation using a functional electrical stimulus has concentrated on opening of bilateral paralysis for breathing and glottic closure for unilateral paralysis. Implantable devices using recurrent laryngeal nerve stimulation were able to produce vocal fold adduction in the canine and external controlled devices have been used in human patients. There have been problems with electrochemical corrosion and long-term stimulation of muscle but further refinements and the encouraging laboratory results suggest these may have a real future especially for bilateral vocal cord paralysis in post-CVA patients with aspiration[22-24].

Comparisons of results of different techniques

Few studies comparing different treatment modalities exist in the literature, and these studies are all limited in size. In their 2007 paper, Hamilton et al.[7] retrospectively compared the results of Bioplastique injections with medialisation thyroplasty and demonstrated similar levels of vocal improvement. In a recent study, Umeno and colleagues[25] compared thyroplasty with fat injection augmentation. On a limited range of parameters, fat augmentation was found to be more efficacious than type I thyroplasty. However, there was no observer-rated evaluation of voices, and no patient-rated evaluation. Other studies suffer from significant heterogeneity of patient inclusion, and hence do not allow for realistic comparison of treatment groups[26].

Conclusions

There is a wide choice of treatments available for unilateral vocal fold paralysis and the choice of management is, to a large extent, a matter of personal preference and local practice. In idiopathic cases, it is generally accepted that a period of voice therapy is helpful as spontaneous return of function may occur or compensation from the contralateral vocal fold may negate the need for surgical intervention[27]. An injection of a temporary material whilst waiting for recovery can reduce the symptoms and laryngeal EMG may give prognostic readings suggesting spontaneous recovery.

In cases of patients with terminal malignancy in whom general anaesthesia or even sedation is contra-indicated, transcutaneous or trans-nasal (via flexible nasendoscope) injection of material may be undertaken in the outpatient department.

In cases of long-term glottic insufficiency due to vocal fold paralysis, many surgeons prefer injection of a permanent material into the vocal fold trans-orally under general anaesthetic because of its technical ease and generally good results. For long term results however the gold standard procedure is laryngeal framework surgery, in the form of type I thyroplasty with or without arytenoid adduction. This is preferred because of its reversibility and the ability to fine-tune the degree of medialisation intra-operatively.

Current dynamic methods are still not producing results as good as the static conventional methods. Laryngeal reinnervation is exciting and can give muscle tone (synkinesis) but there are few results of return of full and coordinated movement. Further trials are required with implantable devices although animal experimentation results are encouraging.

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Infections and Neoplasms of the Parapharyngeal Space

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Abstract:
The parapharyngeal space (PPS) is a potential space inferior to the skull base, postero-medial to the body of the mandible, and anteriorly reaches the hyoid, and posteriorly contains the carotid complex and thus communicates with the mediastinum. In clinical practice, PPS only presents when infected or involved in a benign or malignant tumour process. Clinical symptoms and signs may present acutely, chronic or slow progression, depending on the nature of the disease process. Suspicion is the key to early diagnosis, the diagnosis most often being confirmed by radiological imaging using CT +/- MRI. Surgery is the treatment of choice and the majority of patients will suffer minimal or no complications or sequelae. However when patients are poorly selected for surgical treatment, the results may be serious, cosmetically and functionally disastrous and occasionally fatal.

Key words:
Parapharyngeal space, infection, abscess, benign tumours, malignant tumours, surgery

Introduction
Many names have been used to describe the parapharyngeal space, which is now the preferred term. In the past terms such as "lateral pharyngeal", "perimandibular", "pharyngopharyngeal", "pterygomandibular" and "pharyngomasticator" space have all been used. Each of these names previously used, gave anatomic location and emphasis of this deep neck space of the upper neck, below the lateral skull base, medial to the body of the mandible and lateral and deep to the tonsil. When a mass or lesion involves or invades this space, and becomes large, it displaces the lateral pharyngeal wall and pharyngeal tonsil medially towards the midline, as well as causing later displacement of the parotid gland. With the advent of modern imaging, CT and MRI, many of these when initially small would remain undetected for months or even years, before manifesting clinically as a swelling in the oropharyngeal or upper neck area.

Anatomy of the Parapharyngeal Space
The parapharyngeal space (PPS) is a potential space located bilaterally in the upper cervical region. The PPS is not readily accessible to routine clinical examination and remains silent until affected by pathological processes such as infections or tumours[1]. The potential wide spectrum of benign and malignant neoplasms encountered in this complex deep anatomic region contributes to the challenge of surgical treatment.

Boundaries
The PPS is described as an inverted pyramid with its base at the skull base and the apex at the greater cornu of the hyoid bone.

The ***superior boundary*** is a small area of the temporal and sphenoid bones, which includes the carotid canal, the jugular foramen, and the hypoglossal foramen. The fascia covering the medial pterygoid muscle borders this region of the skull base laterally medially is the attachment of the pharyngobasilar fascia and posterior the prevertebral fascia. Anteriorly the medial and lateral borders converge.

The ***inferior boundary*** is formed by the greater horn of the hyoid and the facial attachments of the posterior belly of the digastric muscle and the sheath of the submandibular gland.

The ***posterior boundary*** is the prevertebral fascia.

The ***medial boundary*** is formed by the pharyngobasilar fascia overlying the superior constrictor muscle. Medially the facial layer is the tonsil.

The ***lateral boundary:*** a) in the upper part of the PPS from before backwards is the ramus of the mandible, the fascia of the medial pterygoid muscle and the retromandibular portion of the deep lobe of the parotid gland; and b) below the mandible the lateral boundary is the fascia overlying the posterior belly of the digastric muscle.

The ***anterior boundary*** is the pterygomandibular raphe and below is the submandibular space.

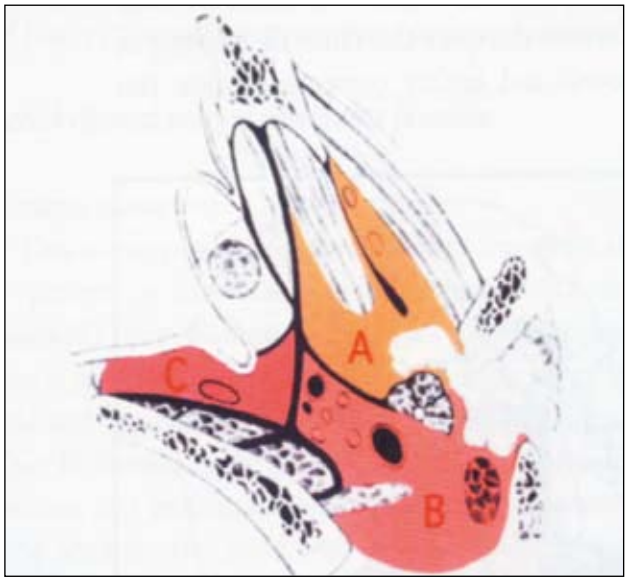


Figure 1: *Location of the prestyloid (A), poststyloid or retrostyloid (B) and retropharyngeal space (C)*

Spaces or Compartments within the PPS

The PPS is divided into two compartments by the tensor veli palatine muscle and fascia - the prestyloid space or the anterior space of the PPS, whereas the retrostyloid space or the posterior space contains the carotid complex **[Figure 1]**. The tensor veli palatine muscle and fascia extends from the styloid process to the fascia covering the tensor veli palatine muscle and crosses posterior into the parapharyngeal fat **[Figure 2]**.

Table 1: Contents of the compartments of the parapharyngeal space

Structure	Prestyloid Compartment	Poststyloid Compartment
Arteries	Internal Maxillary Ascending Pharyngeal	Internal carotid
Veins		Internal Jugular
Nerves	Auriculotemporal	IX, X, XI, XII Cervical Sympathetic
Lymph Nodes		Present
Glomus Body		Present
Parotid Gland	Deep lobe	

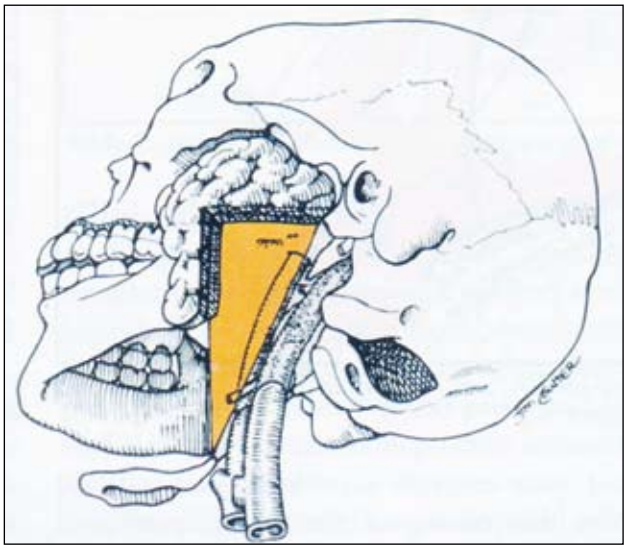


Figure 2: *The prestyloid space*

The prestyloid space extends superiorly into a blind pouch formed by the joining of the medial pterygoid fascia to the tensor veli palatine fascia. Most of the space is occupied by fat. It contains the inferior alveolar, lingual and auriculotemporal nerves and maxillary artery – resulting in neoplasm's that are limited to salivary gland, lipomas and rarely neurogenic **[Table 1]**.

The retrostyloid or poststyloid space contains the carotid artery with the internal jugular vein related to the posterolateral part of the artery at the skull base. Cranial nerves XI, X, XI, and XII and the sympathetic chain also occupy this space. The vagus nerve lies between the artery and vein, the glossopharyngeal nerve crosses the carotid laterally and the accessory nerve crosses the internal jugular vein from medial to lateral. The hypoglossal nerve ends its vertical course outside the PPS. Lymph nodes and glomus "cells" are also found in this region. A thin ineffectual membrane separates the retrostyloid part of the PPS from the retropharyngeal space, allowing easy access and spread of infection and tumours from one area to another.

The PPS has numerous lymphatics that drain the paranasal sinuses, the oropharynx, the oral cavity and a portion of the thyroid gland. These nodes have connection with the node of Rouviere in the retropharyngeal space, which drains the nasopharynx, upper oropharynx and sinuses.

The roof of the parapharyngeal space or skull base has been best described and recommendations are made to separate this space into anteromedial and posterolateral[2]. The PPS roof is bordered laterally by the medial pterygoid fascia and medially by the pharyngobasilar fascia. The tensor veli palatine fascia (TVPF) partitions this roof into an

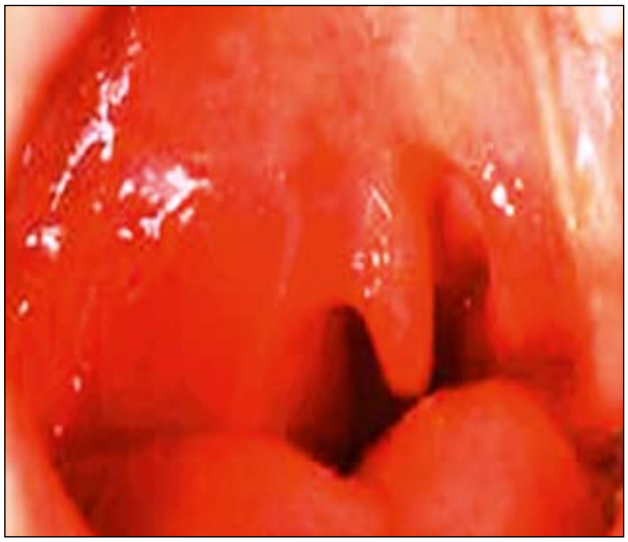


Figure 3: *Distortion of the right lateral pharyngeal wall (Note no trismus!)*

anterolateral compartment containing fat and part of the deep lobe of the parotid gland, and a posteromedial compartment containing the cartilaginous part of the Eustachian tube, internal carotid artery, internal jugular vein, and cranial nerves IX through XII. The PPS roof has 3 important bony landmarks (scaphoid fossa, styloid process and sphenoid spine); 3 important fasciae (medial pterygoid fascia, TVPF, and pharyngobasilar fascia); and 2 compartments, which are anterolateral and posteromedial to the TVPF.

Clinical Manifestation
Infections;

Parapharyngeal infections have many courses because of the sheer number of neighbouring deep neck compartments, which include the submandibular, retropharyngeal, parotid and masticator spaces. Common causes include pharyngitis, tonsillitis, otitis, mastoiditis, parotiditis and cervical lymphadenitis. Odontogenic infections also contribute by way of indirect spread from adjacent deep neck spaces. Infection of the pre-styloid compartment often presents clinically with fever, chills, neck pain, and trismus and anterolateral displacement of the ipsilateral palatine tonsil. Infection of the post-styloid compartment has been known to cause little or no pain, trismus, or obvious swelling; however, involvement of the carotid sheath contents can lead to complications such as septicaemia, Lemierre's syndrome – an infective internal jugular vein thrombosis, or carotid artery aneurysm[3] or rupture, ipsilateral Horner's syndrome, and cranial nerve IX – XII palsies.

Neoplasms

Parapharyngeal space neoplasms more often present with subtle symptoms and signs because of the occult location, and typical slow growth. Early detection requires a high

Table 2: Tumours of the Parapharyngeal Space

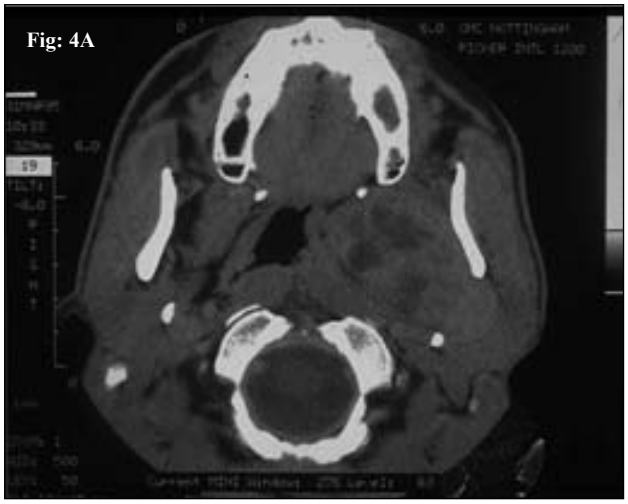
Primary lesions:
Direct extension from adjacent structures
Mandible
Maxilla
Nasopharynx
Neck
Oral cavity
Oropharynx
Temporal bone
Metastatic lesions:
Thyroid cancer
Osteogenic sarcoma
Squamous cell carcinoma

index of suspicion Symptoms are often not present until the lesion is greater than 2.5 cm in size and are related to mass effect. Pain, trismus and cranial nerve deficits may be an indication of malignancy. Symptoms of catecholamine excess may be present because paragangliomas of the PPS secrete bioactive amines. A history of palpitations, headaches, hypertension, tremor, flushing, and nausea is sought when evaluating patients with suspected PPS neoplasm. Up to 80% of PPS tumours will present as an asymptomatic neck or oropharyngeal mass that has caused medial displacement of the lateral pharyngeal wall, ipsilateral tonsil, and/or soft palate **[Figure 3]**.

Neoplasms of the PPS account for 0.5% of all head and neck tumours and are separated into three categories; 1) primary neoplasms which originate from structures within the PPS; 2) tumours that invade the PPS by extension from adjacent spaces; and 3) metastatic lesions[4] **(Table 2)**. The majority of primary PPS lesions are salivary or neurogenic in origin, and most are benign affecting mainly adults, but children have also been reported[5]. Other tumours are unusual and may demonstrate diverse histopathologic types reflecting the anatomic contents of the spaces. Overall 80% primary PPS tumours are benign and 20% malignant. Many large series have been published consistently supporting these facts – one large series[6] recently from China reports 162 patients, salivary gland 74 cases (45.6%), neurogenic tumours 68 cases (41.98%) and 22 patients (13.58%) presenting with malignant disease.

Salivary Neoplasms

Salivary neoplasms account for 50% or more of PPS lesions, and are mainly located in the prestyloid space. They may originate from the deep lobe itself, from ectopic



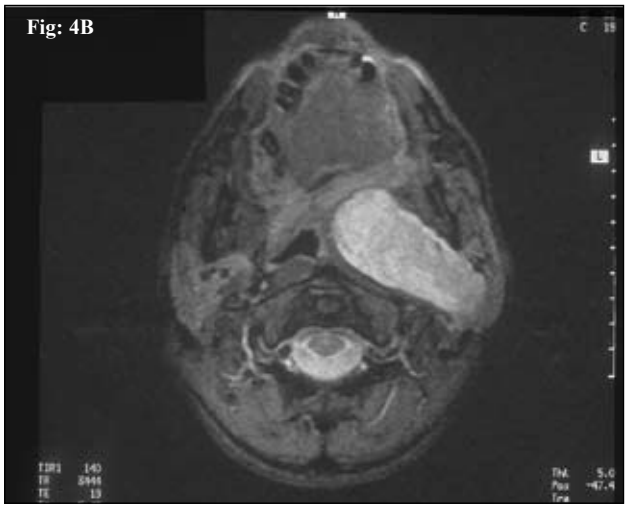
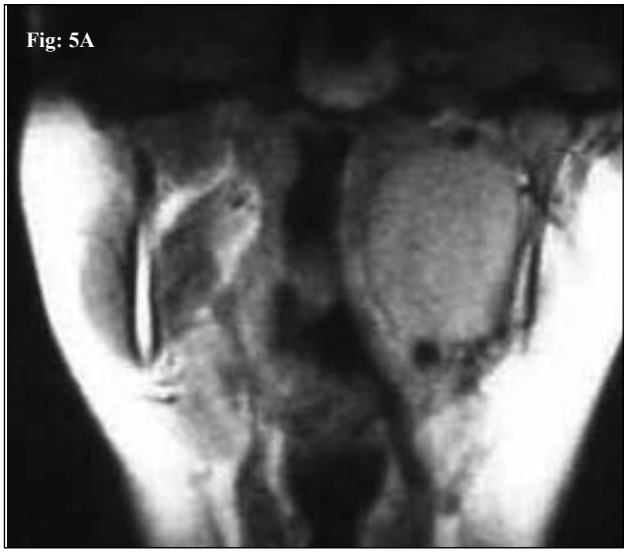


Figure 4: *Pleomorphic adenoma: CT scan (a) and MRI (b).*



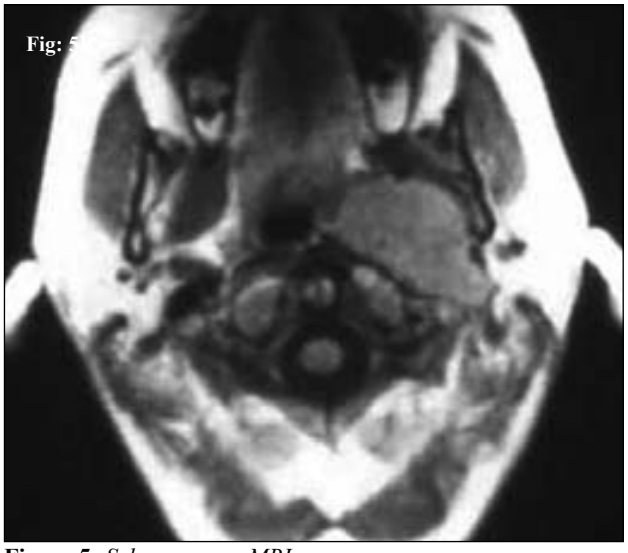


Figure 5: *Schwannoma: MRI scans.*

salivary rests, or from minor salivary glands in the pharyngeal wall. The most common is the pleomorphic adenoma and represents 80 – 90% in most reported series **[Figure 4a & 4b]**. Other salivary lesions, benign and malignant have been reported. Other lesions reported in the prestyloid space include lipomas and neurogenic tumours.

Neurogenic Lesions

Neurogenic lesions are the most frequently located in the poststyloid space accounting for 20 – 30% of PPS lesions. The neural structures include the lower cranial nerves, sympathetic chain, and paraganglia are the sites for schwannomas **[Figure 5]**, paragangliomas **[Figure 6a & 6b]** and neurofibromas.

Lymphoreticular Lesions

Occasionally small lesions, including enlarged lymph nodes, 1 – 2 cm may be identified on imaging for other local symptoms and will thus require investigation. All should have FNAB performed, as well as excluding primary tumours that may metastasise to that area. Remember that more than 30% of lymphomas present initially in the head and neck region. The most common malignant process occurring in the PPS is lymphoma **[Figure 7]**.

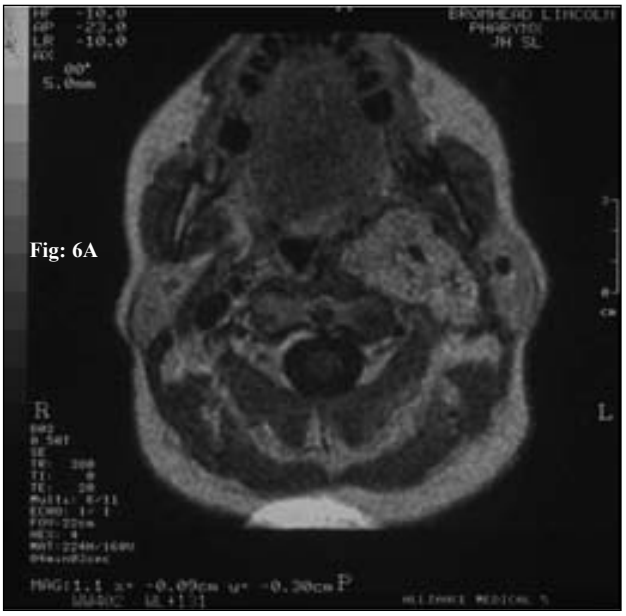
Metastatic Lesions

Primary lesions from other sites metastasise to the PPS and may be the initial presentation of thyroid cancer, sarcoma or meningioma.

Investigation

Imaging

Radiological imaging of patients with clinical symptoms or signs suggesting a possible diagnosis of PPS neoplasm



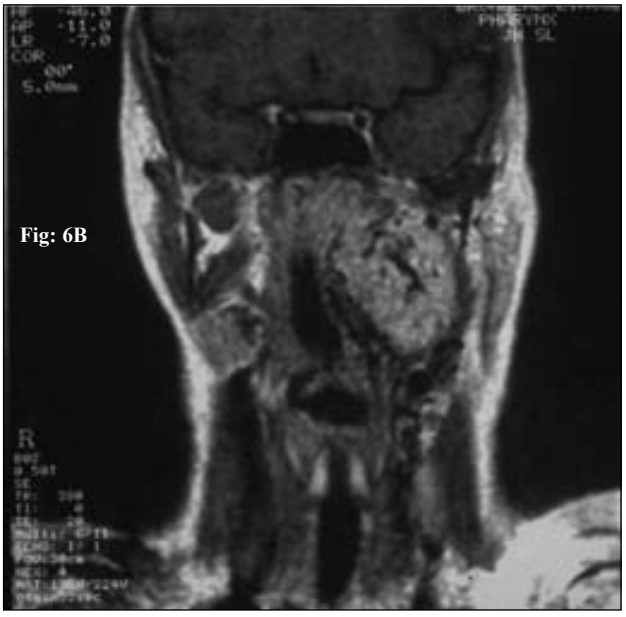


Figure 6: *Paraganglioma: Axial (a) and Coronal (b) CT scans.*

Table 3: Radiographic assessment of parapharyngeal space lesions

Prestyloid vs poststyloid
Relationship to great vessels
Relationship to parapharyngeal fat pad
Relationship to parotid salivary gland
Soft tissue characteristics: Solid / cystic / vascular Homogeneous / heterogeneous Borders: well demarcated / invasive

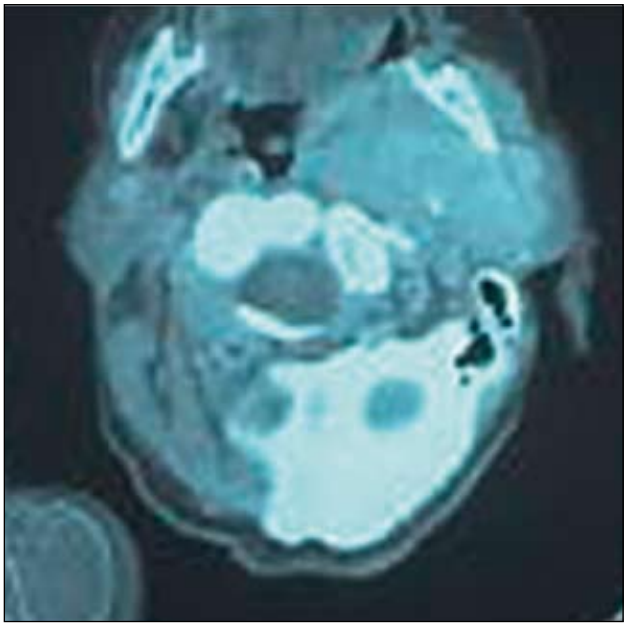


Figure 7: *Lymphoma of the Parapharynx; CT*

or infection is essential as the symptoms and signs elicited be clinical examination are non-specific and limited. The introduction of high resolution computed tomography (CT) and magnetic imaging (MRI) has dramatically improved anatomic accuracy and aided with the surgical patient management planning. Angiography is only necessary for very selected cases.

MRI is the radiographic study of choice for the initial evaluation of PPS processes[7]. The advantage of MR includes multiplanar imaging, excellent soft tissue and vascular resolution, and no patient exposure to ionizing radiation. MR accurately predicts the diagnosis preoperatively in about 95% of PPS lesions. Imaging can determine in which direction the mass has displaced the parapharyngeal fat pad. Prestyloid lesions typically push the parapharyngeal fat pad medially and anterior

Table 4: MRI Characteristics of common parapharyngeal space neoplasms

Tumour histology	T1 signal intensity	T2 signal intensity	Comment
Salivary Gland	low to moderate	moderate to high	
Schwannoma	intermediate	high	enhances w/Gd
Paragangioma	intermediate	moderate to high	focal signal voids
Lymphoma	intermediate	moderate to high	homogeneous

and medial to the great vessels. Poststyloid lesions displace the parapharyngeal fat pad anteriorly and laterally. The relationship of the lesion to the parotid gland and to the great vessels is also an important part of the radiographic assessment **(Table 3)**. T1 and T2-weighted MR images depict the soft tissue characteristics of the lesion **(Table 4)**.

The important distinction for poststyloid lesions is between a schwannoma and a paragangliomas[8]. Paragangliomas show intermediate-intensity images on T1-weighted images and moderately high-intensity images on T2-weighted images. The typical appearance of a paragangliomas is described as "salt and pepper": the "salt" is the enhancing tumour stroma (T1 with contrast) or tumour stroma (T2), and the "pepper" represents the signal voids of many small tumour vessels. This characteristic light and dark appearance of paragangliomas may not always present on MR, especially for lesions <1.5 cm. Schwannomas and neurofibromas have intermediate-intensity signal on T1-weighted images and high T2 signal intensity. They may be homogeneous or heterogeneous, but they lack the many flow voids typical of paragangloma.

Fine-needle aspiration cytology (FNAC)

The use of FNAC may help guide the approach to lesions with atypical MR characteristics and/or suspected malignancy. The biopsy may require guidance by CT or ultrasound when not palpable in the neck, though transoral biopsy has been used! Should the lesion suggest a vascular lesion then FNAC will not usually add any useful information. A recent report on the role of FNAC suggests its usefulness is 90% in benign lesions, and 75% in lesions considered to be malignant, but even this information may help the surgeon and patient to plan for treatment accordingly[9].

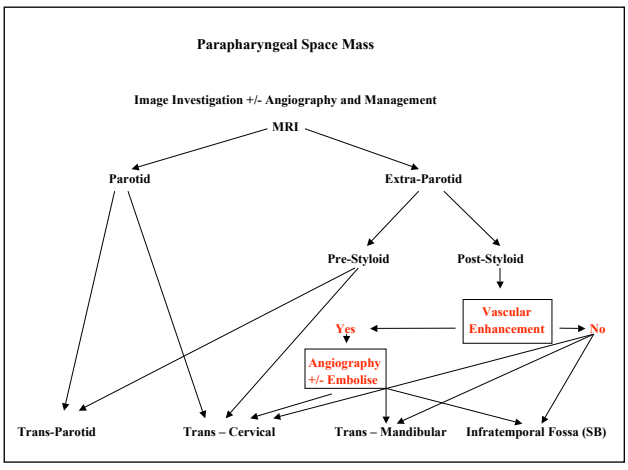


Figure 8: *Imaging and angiography, Management*

MR Angiography

MR angiography allows a non-invasive mapping of blood vessels without exposing the patient to irradiation or contrast agents. The clinical applications of MRA include the pre-operative evaluation of glomus tumours, diagnosis of aneurysm and venous thrombosis, providing a detailed vascular map of PPs neoplasms, and assessing the patency of the vessels postoperatively **[Figure 8]**.

Treatment of PPS Infections

Suspicion and confirmation of diagnosis is mandatory before commencing treatment[10]. Extension of abscess or infection beyond the PPS should alert clinicians of the potential increased risk of airway compromise and steps to observe and anticipate airway intervention must be instigated. Poststyloid infections are more common in children, and usually respond to 48 hours of antibiotics. Infection of the prestyloid space is common in all ages and is most frequently associated with dental and pharyngeal infections. An abscess situated in the prestyloid area should be treated promptly with surgical drainage to avoid complications of from the rapid spread of pus into the adjacent deep neck spaces. Traditionally, access to the PPS space in an abscess situation has been via an external approach, more recently with more accurate location and confirmation, a trans-oral approach to the prestyloid space has resulted in less invasive with improved and more rapid resolution of the infection[11]. Abscesses that spread into adjacent other deep neck spaces and those that involve the poststyloid compartment are more likely to require and external cervical approach to incision and drainage[12].

Treatment of PPS Tumours

Surgery

The treatment of choice for most PPS neoplastic lesions is diagnostic and therapeutic surgical excision[1]. The outcome for most patients with PPS lesions who are treated surgically is favourable. Surgical excision of lesions that

Table 5: Surgical approaches used to excise tumours of PPS

Trans-oral
Trans-cervical
Trans-parotid
Via a mandibulotomy
Infratemporal fossa
Skull base techniques
Singly or in combination

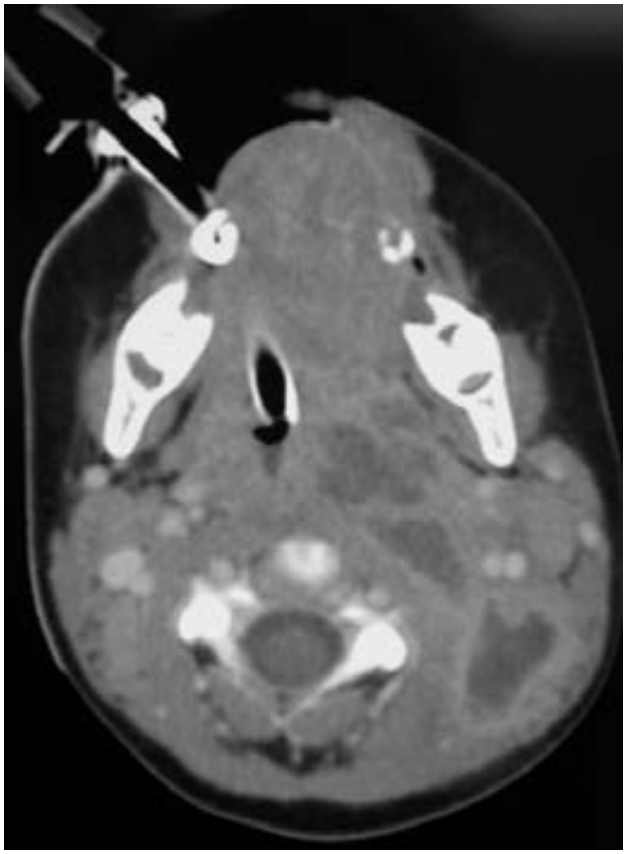


Figure 9: *Parapharyngeal space abscess.*

are relatively small is associated with reduced overall morbidity because of better chance of preservation of cranial nerve function. However surgeons must be cognisant of alternative treatment options for patients who present with complex management situations, such as bilateral or multiple paraganglionomas or elderly patients with large tumours. Surgical excision of lesions in these patients has the potential to create paralysis of multiple cranial nerves resulting in deficits in speech and swallowing which are not compatible with meaningful quality of life postoperatively. The treatment of malignant lesions may require multimodal therapy, including surgery and chemo-radiotherapy. The need to sacrifice the carotid artery needs to be evaluated separately and will depend upon the diagnosis, surgical approach and age of patient.

Surgical approaches for use depends on the location, as well as the size and vascular status of the lesion under consideration, and the clinician's suspicion of possible malignancy. The optimum procedure provides adequate exposure and vascular control for complete excision of the lesion with minimal morbidity **(Table 5)**. Most PPS masses can be excised by the transcervical approach[13], but knowledge and expertise is required by the surgical team when planning a surgical approach[14-16].

Table 6: Surgical approaches to benign parapharyngeal space tumours

Approach	Location	Size
Skull base	Skull base	
Skull base + Infratemporal fossa (ITF)	Superior	
ITF + Trans-parotid (TP)	Middle, anterior, posterior	
TP	Middle, Inferior	
Mandibulotomy	Middle, Inferior	Large
Trans-oral	Middle, inferior	Small
TO + Trans-cervical (TC)	Middle, anterior, inferior	
TC Inferior, anterior		

A recent paper[17] describes the relationship between the location of PPS tumour and the optimum surgical approach for their removal. It was possible after imaging CT and MRI to divide the PPS into 6-compartment classification scheme. Traditionally using axial CT or MRI, the PPS can be divided into 2 spaces – anterior and posterior by a line connecting the styloid process and the tensor veli palatine muscle. However using a coronal view, these two spaces could be further subdivided into three portions: superior, middle and inferior. The superior and middle portions at the level of the inferior border of the lateral pterygoid muscle, and the middle and inferior portion at the level of the line connecting both sides of the inferior edge of the lateral plate of the pterygoid process. Thus, by using both axial and coronal CT and/or MRI scans to identify key anatomic landmarks, it was possible to subdivide the PPS into six compartments. It was then possible to recommend a surgical approach for the excision of benign PPS tumours based on the tumour size and anatomic location. These surgical approaches can be influenced by other factors: extent of operative field, potential cosmetic and functional post-operative issues, and complications from injuries of the great vessels and/or cranial nerves **(Table 6)**.

Radiotherapy

Primary radiotherapy may be considered the appropriate treatment for paragangliomas of he head and neck in some clinical situations. Series have reported that the tumour growth is controlled in 90% of cases.

Complications and sequelae

The major morbidity of surgical approaches to PPS tumours are cranial nerve deficits, injury to major vessels and risk of recurrence[18,19] **(Table 7)**. The relative risk of complications increases when operating on recurrent or malignant lesions, paragangliomas or patients who have been previously been treated by radiotherapy[7].

Table 7: Postoperative complications associated with surgery on parapharyngeal tumours

Haematoma
Seroma
Airway obstruction
Infection
Tumour recurrence
First-bite syndrome[20-22]
Frey's syndrome
CSF leak
Meningitis
Nerve Injury
Greater auricular
Facial
Glossopharyngeal
Vagus
Hypoglossal
Spinal Accessory
Cervical sympathetic
Vessel injury
Stroke
Haemorrhage
Death
Mandibular osteotomy dysfunction.

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Principles of Radiotherapy in Cancer of the Head and Neck

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Abstract
Radiotherapy and surgery are the principal curative modalities for head and neck cancer. Treatment intensification using radiosensitising effect of chemotherapy improves survival in the concomitant setting. Organ preservation with radical chemo-radiation is increasingly becoming the standard of care as first line treatment for advanced head and neck cancer patients. Technological innovations have transformed the way radiotherapy is delivered over the last decade. This includes intensity modulated radiotherapy (IMRT) and image guided radiotherapy for normal tissue sparing and for better tumour coverage. Targeted biological agents (cetuximab and lapatinib) have showed benefit in combination with radiotherapy and offer a potential for treatment intensification. This article reviews the principles of radiotherapy and future advances in the treatment of head and neck cancer.

Key words
head and neck cancer, radiotherapy principles of, chemo-radiation

Introduction
Most cancers of the head and neck are squamous cell carcinomas (SCCHN) and these are generally considered to be radiosensitive lesions. Radiotherapy (RT) is an extremely effective treatment for head and neck cancer, both as a primary modality and as an adjuvant treatment following surgery. Radiation produces oxygen free radicals which cause single and double strand DNA breaks. The ability of the cells to repair this damage determines their radiation sensitivity. Cells unable to repair the damage undergo apoptosis.

There is a well-established relationship between the radiation dose delivered to the tumour and treatment outcome; beyond the threshold radiation dose, the higher the radiation dose delivered to the tumour the higher the chance of cure. However irradiation of normal tissues limits the dose that can be safely delivered to the tumour. In an attempt to circumvent this limitation on radiation dose delivery, novel radiotherapy techniques and combination treatment strategies have been developed in an attempt to improve the therapeutic index[1].

Role of Radiotherapy in Head and Neck Cancers
RT or surgery alone is effective in early stage (AJCC Stage I and II) SCCHN. For stage III and IV SCCHN, definitive chemo-radiation[4] or surgery and post-operative (chemo)radiation[3] are effective. Radical chemo-radiotherapy followed by neck dissection for residual nodal disease and salvage surgery is used as the first line organ conserving approach for stage III-IV head and neck cancer. The only exception is when there is bone or cartilage involvement, which radiation cannot sterilise the disease and the treatment of choice is surgery followed by post-operative radiotherapy.

Preoperative Radiation Therapy: Preoperative RT is infrequently used and should not be considered to be a standard of care.

Postoperative Radiation Therapy: Postoperative RT is considered when the risk of recurrence above the clavicles exceeds 20%. The operative procedure should be one stage and should allow irradiation to start no later than 6 weeks after surgery [5].

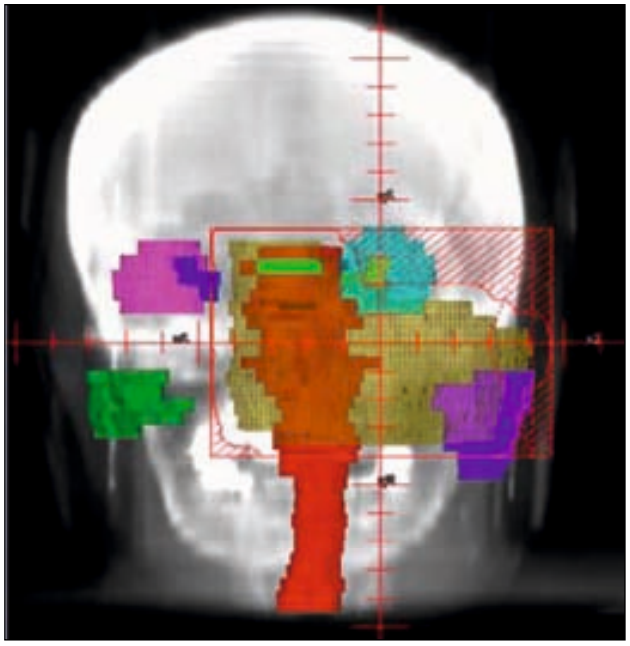

Figure 1. *3-D conformal radiotherapy. This figure demonstrates the planning target volume (PTV) and a number of organs at risk (OARs) superimposed on a digitally reconstructed radiograph. The green box represents a so-called beam's eye view of a lateral field for the treatment of a maxillary antral tumour. The PTV overlaps the parotid glands, which means that these structures can not be shielded. OARs such as the spinal cord and the eyeballs have been shielded from radiation using multi-leaf collimators (MLCs) where they lie outside the PTV.*

Absolute indications for postoperative irradiation include close (less than 5 mm) or involved (positive) margins at the primary tumour resection site, two or more involved cervical lymph nodes, extracapsular spread and invasion of the soft tissues of the neck[3]. The presence of lymphovascular space invasion and perineural invasion are relative indications. The advantages of postoperative, compared with preoperative, radiation therapy include less operative morbidity, more meaningful margin checks at the time of surgery, a knowledge of tumour spread for radiation treatment planning and no chance that RT-induced toxicity will prevent the patient from being able to undergo surgery. The potential disadvantages of postoperative RT include the delay in starting radiation therapy with the possibility of tumour growth (especially in contralateral neck nodes) and the higher radiation dose required to accomplish the same rates of loco-regional control because of disturbance in vascular supply in the operative bed.

Radiation Therapy Techniques

The central dogma that underlies radiation treatment technique is the absolute requirement to attempt to treat all areas at risk of harbouring disease while limiting the dose delivered to uninvolved normal tissues to the minimum that is practicable.

Conventional radiation therapy: Historically, so-called "conventional" RT involved treatment planning by fluoroscopic X-ray screening and treatment delivery by one to four regular square or rectangular fields. New techniques, such as 3-dimensional conformal RT (3-DCRT) and intensity-modulated radiotherapy (IMRT), have superseded this technique in most institutions.

Three Dimensional Conformal Treatment Planning: In this planning technique a CT scan is taken with the patient immobilised in the radiotherapy treatment position. As a result, on a slice-by-slice basis, the macroscopic tumour (gross tumour volume, GTV), the areas of probable subclinical spread (the clinical target volume, CTV) and the critical normal tissue structures (the organs at risk, OAR) can also be outlined on each slice of the CT scan **(Figure 1)**. Radiotherapy treatment planning computers are then used to design the optimal arrangement of radiation beams to cover the tumour and to spare the OARs.

Intensity Modulated Radiotherapy **(Figure 2)**: IMRT uses sophisticated computer software and hardware to vary the shape and intensity of radiation delivered to different parts of the treatment area. In the head and neck region IMRT has a number of potential advantages: (i) it allows for greater sparing of normal structures such as salivary glands, oesophagus, optic nerves, brain stem, and spinal cord[6,7]; (ii) it offers the possibility of simultaneously delivering higher radiation doses to regions of gross disease and lower doses to areas of microscopic disease (the so-called simultaneous integrated boost)[8].

Optimisation of Imaging for Radiotherapy Treatment Planning

A significant cause of failure of radiotherapy to control head and neck cancer is inadequate coverage of disease by the radiation fields, a so-called geographical miss. This may happen with suboptimal staging and delineation of the extent of disease prior to treatment planning. In an attempt to improve outcomes, new anatomical and functional imaging techniques are now being assessed for integration in the radiotherapy planning process.

Conventional Imaging: Radiotherapy treatment planning is conventionally carried out using contrast enhanced CT which provides not only anatomical information but also electron density data which facilitate calculation of radiation doses in tissues. Co-registration of MRI with planning CT scans has increased the accuracy of target volume definition. This co-registration of anatomical imaging modalities provides superior definition of OARs.

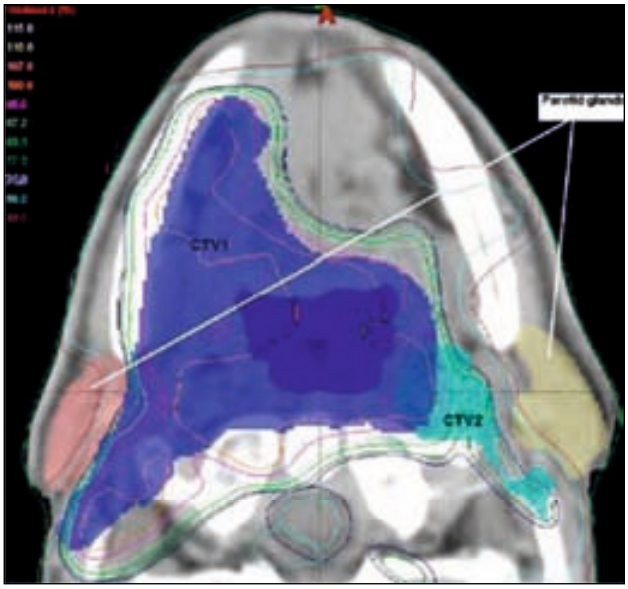

Figure 2. *Intensity-modulated radiotherapy. This treatment technique permits the generation of concavities in the isodoses within tissues such that normal structures can be spared from excessive radiation doses. In this example, CTV1 defines an area that contains the gross tumour volume and involved lymph node disease whereas CTV2 contains clinically uninvolved nodal areas to be treated electively. The coloured lines represent radiation isodoses (lines that join points of equal radiation dose) and clearly show that this technique permits a significant reduction in the dose delivered to the parotid tissue. This is in direct contrast to what would be achieveable with conventional or 3-D conformal radiotherapy where a full radiation dose would be delivered to the parotid glands.*

Functional Imaging: Functional imaging includes the following modalities; positron emission tomography (PET), single photon emission computed tomography (SPECT), magnetic resonance spectroscopy (MRS), and dynamic contrast-enhanced MRI and CT. Functional imaging may improve staging of disease by detecting subclinical (occult) carcinoma or by providing the radiation oncologist with increased information about the margins and extent of disease. Furthermore, it can provide information on tumour characteristics such as blood flow, vascular permeability, proliferation rate and oxygenation. Therefore, the introduction of functional imaging has a twofold benefit for radiotherapy planning in head and neck cancer. First, it may reduce the chance of a geographical miss and, second, it may delineate a biological target volume (BTV) i.e. a region defined by a biochemical pathway or physiology [11].

Radiation Doses and Treatment Delivery

A conventional course of RT for SCCHN is delivered over a 6-7 week course with small fractions of radiotherapy delivered 5 days a week (Monday to Friday). The standard schedule in the UK is 70 Gray (Gy) delivered in 35 fractions over 7 weeks. Radiotherapy is delivered in multiple small fractions to allow recovery of normal tissues between doses and thus facilitate the delivery of a larger total radiation dose to the tumour.

Chemo-radiation and Altered fractionation regimens: Recently a meta-analysis of hyperfractionated (more than one fraction/day) or accelerated RT (shorter overall treatment time) as radical treatment in SCCHN has been performed. The results showed that there was a significant survival benefit with the so-called altered fractionation which corresponded to an absolute benefit of 3.4% at 5 years. This benefit was particularly pronounced for hyperfractionated RT with an 8% benefit at 5 years[24]. The benefit gained by altered fractionation is of a similar magnitude to that gained by using chemotherapy in addition to radiotherapy. The overall benefit of combining chemotherapy with RT is 5% at 5 years with an absolute benefit of 8% at 5 years for the use of chemotherapy concomitant with radiotherapy[25]. Single agent cisplatin is the agent most commonly used.

Anti-Epidermal Growth Factor Receptor Targeted Therapy. Epidermal growth factor receptor (EGFR) is overexpressed in 90% of SCCHN and is known to promote tumour cell growth, invasion, evasion of apoptosis (programmed cell death) in response to radiotherapy and/or chemotherapy and the development of new blood vessels (angiogenesis). EGFR signalling also plays a role in repair of DNA damage. Anti-EGFR therapy has been shown to be a rational strategy for combination therapy with radiation in both preclinical and early stage clinical trials. More recently a large randomised phase III trial in patients with stage III/IV SCCHN confirmed the potential of this approach. Patients received primary radical RT with or without concomitant cetuximab (an inhibitory monoclonal antibody against EGFR). Patients in the cetuximab treatment arm had a statistically significant increase in median overall survival (49 vs 29.3 months, p= 0.03)[36]. These data are extremely encouraging but, unfortunately, at the time that the trial was set up concomitant chemo-radiotherapy was not the standard of care. A further follow-on phase III study is examining the role of cetuximab in combination with concomitant chemo-radiotherapy and these results are awaited with interest. Other EGFR-targeted agents are also being evaluated. These include the small molecule tyrosine kinase inhibitors gefitinib (Iressa) and lapatinib (Tykerb).

Hypoxia Modification as a Means of Targeting SCCHN

The rapid growth of tumours soon outstrips the blood supply leading to hypoxic areas within the tumours. The

response of tumours cells to radiation is highly dependent on the amount of oxygen they contain at the time of irradiation. This is due to the fact that the damage which occurs to DNA as a result of radiation becomes "fixed" by oxygen. This is borne out by clinical data which show good correlation between treatment outcome and pre-treatment pO2 measurements with less well-oxygenated tumours showing the worst results. It has also been shown that a low pre-treatment haemoglobin level is associated with poorer loco-regional control rates after radiotherapy.[26-29]. These observations have led to a number of different therapeutic interventions to optimize the oxygenation of tumours and, hence, increase radiosensitivity. These include increasing the haemoglobin concentration, hypoxic cell radiosensitisers, alteration of inspired oxygen content and use of bio-reductive (drugs that target hypoxic cells). A meta-analysis of hypoxia modification in head and neck cancers demonstrated a 7% benefit in terms of loco-regional control for patients who were treated with a regimen that involved hypoxia modification plus radiation compared with radiotherapy alone (46% vs 39)[35].

Conclusion

In this review we have discussed the specific issues of the technique of radiation delivery, the role of advanced imaging modalities in treatment planning and the selection of the optimal fractionation schedule. In addition, we have discussed ways in which agents other than cytotoxic chemotherapy drugs may interact with radiation and enhance (oxygen, hypoxic cell sensitisers, bio-reductive drugs, growth factor inhibitors) its effect in tumour tissues. This review should provide a useful background for understanding future developments in this rapidly advancing field of radiotherapy for head and neck cancer.

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The Aging Voice

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Abstract
As the elderly population increases, the medical community must address quality of life issues affecting the aged. Presbyphonia, or age related dysphonia, is a diagnosis of exclusion and other co-morbidities must be considered in a complete evaluation. The complexity of presbyphonia involves the changes in the diverse tissues of the true vocal folds, musculature, and cartilage. Patients benefit from treatment of voice therapy or surgical laryngeal augmentation procedures. In this review, we discuss the presentation, evaluation, and treatment of presbyphonia, as well as the molecular and cellular discoveries in laryngeal senescence and future directives.

Key words
Presbyphonia, aging, larynx, voice

The Aging of Society
By 2003, 35 million people in the United States of America will be over 65 years old and by 2030, 72 million[1]. In the UK, the population over 65 will increase from 16% in 2003 to 21% by 2031, and the population over 80 from 1.9% to nearly 4%[2]. With a growing, elderly population, the changes in quality of life associated with aging have become a focus in health care. The incidence of disordered vocal function in the elderly has been cited to be from 12% to 35 %[3-6]. These incidences have been misquoted for decades based on a 1986 reference in which of the 1,000 patients seen at a Canadian voice center, only 121 were older than 70[7]. In a recent community based cross-sectional study, 20% of patients over the age of 65, reported dysphonia of any kind[8].

Quality of Life in Aging
As one ages, the decline in tissue strength, be it skeletal muscle, integumentary, or nervous system, is accepted as a natural part of aging. Weakening of the voice is an overlooked issue in the elderly that can significantly disrupt ones quality of life. In patients 65 and older, 13% noted their quality of life to be moderately to profoundly reduced related to their dysphonia[8]. Altered acoustic properties of the voice, increased vocal roughness, increased patient-reported vocal instability, and avoidance of social events were all symptoms noted in 50 to 81 year olds over a 5-year span[9]. Voice-related effort and discomfort, combined with increased anxiety and frustration and the need to repeat oneself, are specific areas that adversely affected quality of life[10]. Vocal quality of life studies have found significant correlations between a patient's perception of life quality and vocal quality[11].

Epidemiology of Presbyphonia
Generally, presbyphonia or age related dysphonia, is regarded as a diagnosis of exclusion after completion of a full medical and vocal evaluation. Presbyphonia has been found to be the cause of dysphonia in less than 9% of patients, and 30% in another study[12-13]. The etiology of dysphonia may be multifactorial, and not due to aging alone. Roy and colleagues demonstrated a lifetime prevalence for a voice disorder in 47% of elderly 65 years of age and older[10]. Dysphonia was often chronic with 60% of the 29.1% with a current voice disorder having the problem for more than 4 weeks. Alternative causes of dyphonia in the elderly include those processes with infectious, phonotraumatic, reflux, neurological, and neoplastic etiologies[12]. Poor general health correlates to

negative objective vocal and laryngeal changes, showing that physiologic age may be a greater factor than chronologic age in some patients with dysphonia[14,15].

The Complexity of the Presbyphonia

Patients present with a complicated array of symptoms such as a weak, thin, or breathy voice, reduced projection, decreased range, unsteadiness, and pitch changes. Speaking fundamental frequency actually decreases in both men and women with age[16]. The etiology of presbyphonia is often multifaceted. Of the several organ systems that coordinate phonation, the actuator of voice is the lungs. In the elderly, pulmonary function declines on account of age, other co-morbidities, and intrinsic pathologies. This contributes to poor pulmonary reserve, which can affect subglottal pressure and vocal loudness. Coordination between the larynx and respiratory movements also declines[17].

Neurologically, aging effects are evident from the CNS to the motor end units of the laryngeal muscles. The central nervous system losses fine control and disease manifestations such as tremor, Parkinson's, ALS, and stroke may present. The peripheral nerves of the larynx undergo changes with age due to the disappearance of large axons, decrease in the diameter of axons, and decrease in Schwann cells and myelinated fibers[18]. The architecture of the neuromuscular junction of the thyroaryteoid muscles show changes in older rat specimens similar to that of denervated muscles with a reduction in axon terminal area and preponderance of unoccupied postsynaptic acetylcholine receptor areas[19]. Laryngeal muscle atrophy presents as vocal fold bowing. **Figure 1.** The thyroarytenoid muscles become weaker, thinner, and more fatigable with age[20]. Decreased muscle bulk occurs with decrease in myofibrils, replacement with collagen, and decreased blood flow[21,22]. Fatty degeneration and altered distribution of muscle fiber type has been shown along with change in myosin heavy chain composition[23].

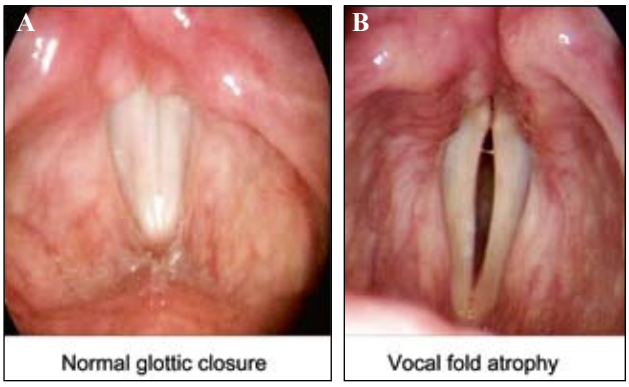

Figure 1. A. *Complete glottal closure.* **B.** *Vocal fold atrophy or "bowing", fullness of the vocal processes, and incomplete glottal closure of an aged larynx.*

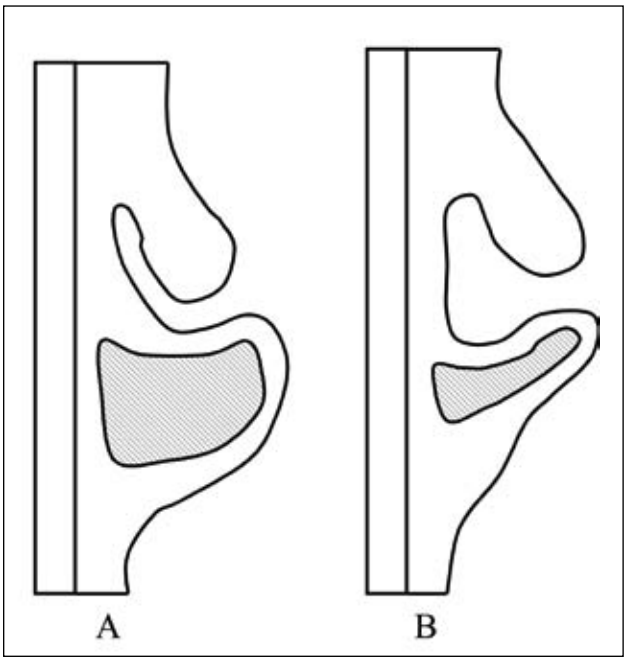

Figure 2. *Cartoon coronal hemilaryx.* **A.** *Normal glottis. Healthy true and false vocal folds, ventricle and thryoarytenoid muscle.* **B.** *Aged larynx. Thinning of the superficial lamina propria, muscle atrophy, and capacious ventricle.*

The vocal fold itself, a multi-layer structure of epithelium and collagen matrix, incurs many changes due to aging. Collagen fibers run in a basket weave configuration becoming denser near the vocalis muscle forming the vocal ligament. These fibers are more disorganized in an older population[24]. The collagen is interdigitated within a rich extracellular matrix (ECM). Hyaluronic acid is an important aspect of the ECM that allows for healing and much of the viscoelastic properties of the vibratory vocal fold. With age, the number of collagen fibers increase and the amount of hyaluronic acid decreases and elastic fibers become amorphous and depleted[25-27]. Fibroblasts and stellate cells are progenitors of ECM. Fibroblasts, along with their activation factors, and stellate cells undergo abnormal metabolism and degeneration in the aged vocal fold, therefore the amount of HA and other ECM components are decreased[28-30]. These changes all affect the viscoelasticity of the vibratory aspect of the vocal fold. Genetic mechanisms of vocal fold aging have shown that changes in genetic expression of proteins of the aging ECM are similar to that of skin and lung; however, telomere length in the true vocal fold does not significantly change with age[31,32]. The vocal fold becomes thinner with age; this is especially noted in men[33]. **Figure 2.** Thinning of the lamina propria and disorganization of collagen in the connective tissue of the vocal fold affect the vibratory and pliability characteristics. Along with muscle atrophy, this produces a bowed membranous vocal fold with possible glottal insufficiency during phonation[34, 35].

Many anatomical changes occur in laryngeal senescence. The larynx descends in the neck and the laryngeal cartilages ossify, altering the resonant properties of the larynx and pharynx[34,36]. This is likely due to the impairment of compression of the thyroid cartilage by the inferior constrictor, thereby impeding adduction. The joints undergo thinning of articular surfaces, breakdown of collagen fiber organization, and degenerative changes in the tendon attachements limiting range of motion of the cricoarytenoid joint[37-40]. The vocal tract changes with age due to increase in length and volume of the oral cavity[41]. Secretions, which provide important lubrication during vocal fold vibration, decrease and become thicker[42].

A Mature Evaluation and Diagnosis

Common etiologies of dysphonia must be excluded in the work up of presbyphonia. A complete history is a vital portion of the laryngological exam. The vocal demands of the aging patient can indicate the phonotrauma endured and the level to which they need their voice to perform daily activities. Dietary information, as well as a complete social history such a tobacco and alcohol use are also important questions. Ultimately, the highest-yield examination is laryngoscopy. Characteristic findings on stroboscopy are glottal gap, vocal fold bowing, prominence of vocal processes, edema, and atrophy[43,44]. Glottal gap is not found to be consistent with the degree of bowing, allowing for some compensatory mechanisms in the presbylarynx[45]. In evaluation of vocal fold motion, any asymmetry should lead to consideration of other diagnosis than presbyphonia. The aged vocal folds will exhibit an aperiodic or irregular vibration, increased amplitude, asymmetric mucosal wave, and a midline glottal gap[46]. As a diagnosis of exclusion, other systems must be considered as well in the cause of dysphonia. Patients must be neurologically intact with appropriate pulmonary function. As mentioned previously the vocal tract must also be thoroughly evaluated for causes of dsyphonia.

Rejuvenating the Aging Voice

Decision making framework

Dysphonia in the elderly requires an investigative approach to diagnosis and a multidisciplinary team for treatment. As discussed earlier, presbyphonia is a diagnosis of exclusion and other plausible etiologies or confounding symptoms must be incorporated into the decision-making framework. This multi-hit theory of aging will help guide the treatment plan of voice therapy and surgical intervention.

Voice Therapy

Current therapeutic tools for rehabilitation of presbyphonia include voice therapy, injection augmentation and laryngeal framework surgery. Voice therapy is the first line treatment. Strengthening exercises for respiratory and phonatory control likely increase neuromuscular coordination. This modality may result in subjective improvement in quality of life and perceived voice[47]. Therapy consists of vocal education regarding the physiology of the problem, practice producing a resonant tone for optimal vocal postures, and standard vocal function exercises to enhance the balance, strength, and tone of the vocal mechanism[48]. Voice therapy requires multiple clinic visits and may be less beneficial in severe cases.

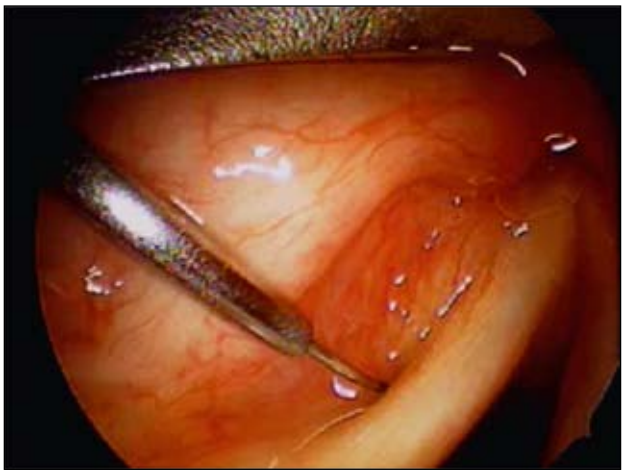

Figure 3. *Endoscopic image of left injection laryngoplasty.*

Injection Laryngoplasty

If a patient fails voice therapy, procedures to improve glottic closure may be employed. Often used for recurrent laryngeal nerve paralysis, augmentation of the paraglottic space provides medialization of the true vocal fold. This has been shown to be effective for bilateral vocal fold atrophy to improve glottal competence[49]. Injection augmentation may be performed for temporary means to plump the glottis and improve closure. **Figure 3.** Multiple substances may be used, most being a absorbable dermal or collagen matrix[50,51]. The augmenting material is injected lateral to the superficial lamina propria (SLP) in the paraglottic space medializing the vibratory vocal fold. **Figure 4.** Injection laryngoplasty is performed in the operating room or as an in-office procedure. In the OR, direct laryngoscopy provides the most control. This procedure, however, requires general anesthesia and does not allow one to titrate the injection with vocal improvement.

Awake procedures are becoming more commonplace with the use of local and topical anesthetic. Per oral or percutaneous injections also allow for vocal titration but are often technically difficult. Patients may require multiple injections to achieve the desired affect, but this obviates the need for general anesthesia. The pitfalls of

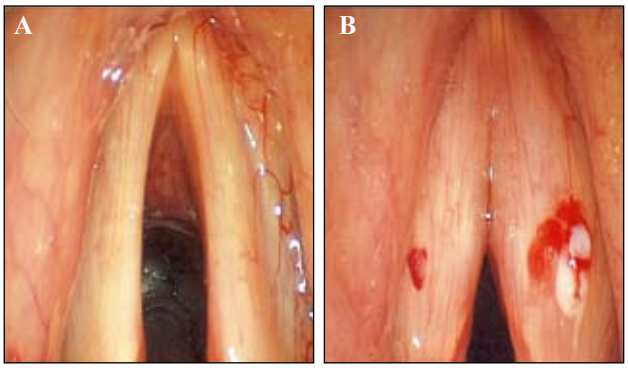

Figure 4. A. *Aged true vocal folds with bowing and atrophy prior to bilateral injection laryngoplasty.* **B.** *Aged true vocal folds after bilateral injection augmentation. Note improved medialization of vibratory SLP and better glottic closure.*

injection laryngoplasty include superficial injection or excessive overinjection[52]. Awake injections, therefore, have a higher morbidity than using direct laryngoscopy in the operating room[53].

Laryngeal framework surgery

Thyroplasty augmentation provides static medialization of the vocal folds. The aging larynx with muscle atrophy that benefits from injection laryngoplasty is a candidate for framework surgery as a permanent solution. Multiple synthetic materials are utilized, such as silastic and Gore-Tex. Bilateral medialization laryngoplasty is an effective option for the presbylaryngis[54]. With the administration of local anesthetic and light sedation, the neck is opened and the thyroid cartilage window is fashioned to expose the paraglottic space. The implant is strategically advanced in the paraglottic space while the patient phonates to locate the optimal placement of the implants, while cautiously avoiding glottal obstruction. Limitations of this procedure, as with injection laryngoplasty, are an adynamic glottal closure and failure to correct vocal fold vibratory or mucosal bulk, and due to its permanence, there is a risk of foreign body reaction, extrusion, or inflammation[55,56].

Advancing the Possibilities

As we learn more of the histomorphology of vocal fold aging, techniques for tissue rejuvenation revealed. The changes in the complex matrix of collagen, elastin, and hyaluronic acid have been described. Hirano, et al, showed that basic Fibroblast Growth Factor (bFGF) and Hepatocyte Growth Factor (HGF) stimulates cultured fibroblasts and increases the production of HA and decreases collagen[57]. They then went on to decrease the atrophy in aged rat larynges by injecting bFGF intracordally[58]. Likewise, Ohno administered HGF by injection into rat vocal folds. This increased MMP and HAS and decreased procollagen, thus augmenting the production of HA and reducing the collagen in aged rat vocal folds[59]. Improved glottal gap and decreased atrophy in human vocal folds was recently reported with injections of HGF[60]. Thibeault et al, describes injection of a modified synthetic derivative of HA into SLP to restore viscoelasticity with minimal inflammation[61]. Tissue engineering, with the use of cell cultures or stem cells is underway at some institutions. Work with fibroblast cell lines, different biomaterials such as collagen, acellular human-derived dermal preparations, and HA hydrogels as scaffolds are recent projects[62].

Other surgical technologies have been utilized to augment or revitalize the aged larynx. One author proposes the use of balloon thyroplasty for adjustable vocal fold augmentation[63]. For some time, electrodes have been used to reanimate paralyzed vocal folds for abduction in respiration[64]. In unilateral vocal fold paralysis, laryngeal adduction for airway protection and phonation has been described using electrodes to pace off the intact vocal fold[65]. These theories may have utility in the future to amplify the neuromuscular signal to atrophic larynges in the elderly.

Conclusions

While much has been discovered in regards to the histological changes in the aged vocal fold and musculature, much still remains to be learned of viable treatments that can translate into improved vocal quality. Our current treatment modalities and multidisciplinary approach offer significant improvements in vocal quality of life. With the elderly population increasing, as a medical community we will address the issue of presbyphonia and other age-related disorders more frequently. A patient's vocal health must not be overlooked along with its impact on overall general health.

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Early stage glottic squamous cell carcinoma: radiotherapy or endoscopic surgery current practice and controversies

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Abstract
There is perceived overall clinical equipoise between radiotherapy and endoscopic surgery for the treatment of early stage (T1-2) glottic squamous cell carcinoma. This review examines the evidence base for each modality, and the controversies that exist in treatment selection.

Key Words
Laryngeal Cancer; Radiotherapy; Surgery

Introduction
There are just under 2000 new diagnoses per annum of laryngeal squamous cell carcinoma in the UK[1]. Early stage (T1-T2 N0 M0) SCC of the glottic larynx is characterised by low tumour volume and low rate of regional metastasis, partly because of the poor lymphatic drainage from this area. For these reasons, early glottic SCC has a relatively high chance of cure, and low chance of metastatic spread.

The aim of treatment is to achieve local control with preservation of the larynx. The main modalities of treatment are with either external beam radiotherapy (RT) or transoral laser microsurgery (TOLS). Historically, early glottic SCC has been treated by external beam radiotherapy (RT). The fractionation schedule varies. Worldwide, 30 fractions are often given but 20 fractions is more common in the UK, with some centres using 16[2]. The choice of radiotherapy was based on good oncologic results in the absence of a low morbidity surgical option. Open (or external) conservation laryngeal surgery is associated with equivalent local control but at the expense of a major operation, temporary tracheostomy, temporary aspiration and significant dysphonia. However, the popularisation of transoral laser surgery in the 1990's has offered a low-morbidity operation, often performed as a daycase or one-night stay procedure, that has emerged as an equal option to RT for the curative treatment of glottic SCC.

A systematic review by Dey et al [3] of the management of early (T1, T2) squamous cell cancer (SCC) of the glottis (vocal cords) showed that there is insufficient evidence to guide management decisions on the most effective treatment. Only one trial comparing radiotherapy and surgery was eligible for inclusion, this dating back to patients treated in 1978 comparing radiotherapy and open surgery only. Endoscopic treatment is now established in the UK also, but it is one of the few countries still in clear clinical equipoise on this question. In most countries, radiotherapy still remains the predominant treatment.

This review will discuss issues and controversies when considering RT and TOLS for the treatment of new glottic cancers, T1-2. The arguably limited role of open conservation surgery is not discussed, nor is the treatment of recurrent disease.

Radiotherapy (RT) or transoral laser surgery (TOLS)?

(a) Oncologic results: local control
In early glottic SCC, local cure generally constitutes disease specific cure. With the obvious importance in avoiding total laryngectomy (TL), the important parameter is local control (LC) without laryngectomy. For most patients treated with RT, this is initial LC (as most patients with disease recurrence are salvage by TL). For TOLS, one perceived advantage is that LC without TL is more attainable because TOLS can be repeated for suspected residual or recurrent disease (and the option of RT for

salvage remains also)(4). For example, in one series from Steiner et al, the initial LC for T2a is 75% (the same as RT generally) but ultimate LC without laryngectomy is 95%(5). Similarly, the initial LC in a group of 51 patients with T1a tumours treated by endoscopic surgery was only 71% in a series from Groningen. However, 4/4 recurrences were successfully salvage with further endoscopic surgery and 7/9 by salvage radiotherapy, giving an ultimate laryngeal preservation rate of 95%(4).

The issue of avoiding eventual TL is mostly relevant to T2 tumours, although Schrijvers et al showed lower rates in T1a tumours with surgery compared to RT. However, it should be noted that initial local control with both RT and surgery were poor compared to other series (4).

A summary of oncologic results from reported series of RT- and TOLS-treated patients are presented in Tables 1 and 2. Initial LC is generally similar for T1 tumours, at just over 90% typically. LC for T1b tumours is generally worse than T1a with surgery; but the same (as T1a) with RT. For T2 tumours, the initial LC in RT series is generally around 70-80%. There is much less data with TOLS for T2 with good numbers, but the mean for T2 in **Table 2** is around 75%.

Many larger series reporting on one modality (RT or TOLS) reflect the treatment philosophy of the institution involved. However, reports from institutions in which the treatment modality is more balanced demonstrate the problem with comparisons between RT and TOLS. This arises, for example in T1a lesions, from the selection bias towards surgery whereby more favourable tumours (well defined, low volume, fitter patients) may be "cherry picked" for TOLS, leaving more unfavourable tumours for RT. This is demonstrated in a report of T1a tumours from an institution in which the RT/RTOLS split was around 50/50% in which the RT results were worse than from those unselected RT series(6).

In summary, there are no meaningful comparative studies between the two modalities. From the evidence available (and acknowledging its limitations), if can be reasonably assumed that: (1) for T1a cancers, the initial LC appears to be similar between RT and TOLS; (2) for T1b tumours, the LC is the same as for T1a with RT but poorer than T1a with TOLS; (3) for T2 tumours, the initial LC is similar but eventual TL rates are lower with TOLS.

Table 1: Radiotherapy for T1-2 glottic laryngeal SCC

Author/reference	n	stage	Initial LC	comment
Fanchin(16)	267	T1a	91	20/410 TL overall
	56	T1b	91	
	70	T2a	79	
	17	T2b	88	
Howell-Burke (17)	114	T2	68	
Kelly (18)	95	T1	94	3 year 148/187 T1-2 pts
	53	T2	76	
Johansen(19)	398	T1a	85	11%TL
	83	T1b	83	14%TL
	226	T2	61	26% TL
Pelliterri(20)	113	T1	93	
	48	T2	78	
	194	T1	91	
Terhaard 1991(21)	194	T1	91	
Mendenhall 2001(22)	230	T1a	94	
	61	T1b	93	
	146	T2a	80	
	82	T2b	72	
Raitola(23)	60	T1	85	13%TL
	16	T2	48	44%TL
Warde(12)	403	T1a	91	
	46	T1b	82	
	286	T2	69	
Nomiya(24)	115	T1a	85	10 year
	48	T1b	76	10 year
Lesnicar(25)	159	T1		
	60	T2		
Christie (unpublished)	213	T1a	91	Hypofractionated, accelerated
	38	T1b	91	
	79	T2a	89	
	41	T2b	70	
Gowda(2)	168	T1a	93	
	89	T1b	89	
Jorgensen(26)	315	T1	88	
	234	T2	67	
Garden(15)	114	T2a	74	36% had bd RT(79% vs 67% LC, p=0.06)
	116	T2b	70	
Schrijvers(4)	51	T1a	73	23%TL

(b) Other factors

The perceived advantages and disadvantages of each modality are complex and depend to a large extent on the exact location and size of tumour and patients' individual circumstances. Issues other than LC, notably voice outcome, are very important. Most of these perceptions are not substantially evidence based. These issues, together with oncologic issues, are summarised in **Table 3**.

Table 2: Transoral laser microsurgery for T1-2 glottic laryngeal SCC

Author/ reference	n	Stage	Initial LC	Ultimate LC with laryngeal preservation	Comments
Myers[27]	50	T1	92	100	
Steiner[5]	158	T1a	93	98	p-stage
	30	T1b	83	93	
	75	T2a	80	95	
Manola[28]	31	T1	95	100	24-48 mo FU
Gallo[29]	117	T1a	94	100	3 yr FU
	22	T1b	91	100	
Peretti[30]	96	T1	81	96	
	23	T2	74		
Goor[31]	54	T1a	94		2 year FU
Maurizi[32]	118	T1a	89	92	
	14	T2	79		
Sigson[33]	30	T1a	93		
	6	T1b	83		
Ledda[34]	68	T1a	99		
	14	T1b	86		
	7	T2	100		
Motta[35]	432	T1a (263) T1b (169)	85		
	236	T2	66		
Moreau[36]	62	T1a	100		
	24	T1b	100		
	11	T2	100		
Chone[37]	25	T1a	80		
	6	T1b	83		
	17	T2	100		
Eckel[38]	161	T1	87	94	
	93	T2	82	93	
Schrijvers[4]	49	T1a	71	95	

In summary, surgery is thought to be usually more convenient for patients. Voice outcome is probably similar for small volume T1a tumours but worse with TOLS for T1b and T2 tumours.

A small but significant proportion of patients are not suitable for surgery, because of inadequate endoscopic access, a poorly defined tumour or reluctance for another general anaesthetic because of co-morbidity. Tumours may be poorly defined de novo (e.g. in a field change) or because of the diagnostic biopsy (this often takes the form of a well-intentioned but oncologically ineffective "debulk").

The practice of determination of clear margins after TOLS is controversial and variable[7]. The rates of 2nd look TOLS to determine clear margins, when indicated, are not known.

A well-rehearsed argument in favour of TOLS is the option to use RT for "salvage". This may be for bone fide recurrent disease or for positive margins after TOLS. There is not a great deal of evidence to support this argument with the exception of the previously noted paper from Schrijvers et al[4] (in which 7/9 recurrent T1a tumours were successfully salvaged by RT). The author belives a great deal of caution should be applied before using RT for recurrent disease after TOLS or indeed to "sterilise" positive or suspicious margins. Unpublished data from Leeds shows a very poor outcome with positive or close margins after TOLS (for multiple tumour sites), despite post-operative RT[8]. This may relate to residual tumour cells being in a granulating bed (i.e. very favourable for cancer cell survival and growth).

Future developments

It can be seen that there is very little evidence base for much of the advantages and disadvantages of each approach. A UK trial, EaStER (Early Stage glottic cancer: Endoscopic excision versus Radiotherapy; Chief Investigator Prof M Birchall) was approved for funding by CRUK in 2004, dependent on the results of a feasibility study. This was a randomised trial with patients undergoing 1:1 randomisation to either TOLS or RT. Comparatively low numbers of patients were successfully randomised in the feasibility study and the trial was withdrawn in 2009. The main problem with recruitment for randomisation were the fact that the two arms of the trial were so completely different, posing problems for patients and clinicians (i.e. either patient or clinician strongly preferred one modality). Furthermore, a significant proportion of patients were not suitable for surgery.

Therefore, there are no forthcoming comparative studies to answer some of the questions raised. Another approach would be for a prospective audit/registration study. However, these studies are very difficult to successfully fund, and are still prone to the types of selection bias alluded to earlier.

For many clinicians and multi-disciplinary teams, most patients with T1a cancers are straightforward to manage, with surgery generally preferred in those patients suitable

Table 3 Summary of perceived advantages of RT and endoscopic surgery

Parameter	Radiotherapy	Endoscopic Surgery (TOLS)	Summary
Local Control	See Tables 1 and 2. Generally similar initial LC for T1 tumours, just over 90% typically. T1b tumours generally worse than T1a with surgery; but the same in RT. For T2 tumours, RT series generally around 70-80%. Much less data with TOLS for T2 with good numbers, but mean for T2 in Table 2 is 75%.		Overall equipoise, but no meaningful comparative studies. Proponents of surgery argue that LC for T2 tumours treated with RT significantly decreases and surgery may have particular advantage in this group- although this is in ultimate LC without laryngectomy rather than better initial LC (e.g. Steiner et al; initial LC for T2a is only 75% (same as RT generally) but ultimate LC without laryngectomy 95%[5].
Voice	No morphological sacrifice of vocal cords but RT affects whole glottis/larynx (including normal tissue)	Voice outcome dependent on depth of cordectomy required and anterior commissure involvement in resection	General consensus is worse outcomes with surgery, especially with anterior commissure involvement and larger tumours[39] [40]. [28]Little difference in voice outcome for small T1a tumours[41] [28] [31] [42]
Other risks and side effects	Transient oedema and potential airway compromise Mucositis	General anaesthetic-related complications. Haemorrhage Tooth damage	Both RT and surgery-related complications unusual
Duration of treatment	Usually 20 fractions in most UK centres + planning visits	Single visit (daycase or 1 night stay) + pre-op assessment visit if initial biopsy performed elsewhere Second surgery may be required for inadequate margins	Surgery more convenient for most patients
Patient candidacy	Virtually all patients	Not suitable if: - Unfit for (further) G/A - Poor endoscopic access - Poorly defined tumour (either de novo or due to effects of biopsy)	Small but significant proportion of patients not suitable for surgery
Options for residual or recurrent local disease	1. Endoscopic surgery 2. Open conservation surgery 3. Total laryngectomy	1. Further endoscopic surgery 2. Open conservation surgery 3. Radiotherapy 4. Total laryngectomy	Main difference is the option to use RT when surgery is carried out originally. Salvage conservation surgery only suitable for minority of recurrent disease after RT.
Measurement of success of treatment	Endoscopic outpatient examination after initial treatment effects settled	Same, although proof of clear histological margins should give strong indication	Surgery has benefit of histological analysis of margins, although there are problems with how to assess these with small margins, effects of laser on tissue and small specimens[7]
Chance of eventual total laryngectomy	Lower with TOLS on the basis of option of salvage by further TOLS or RT. Some patients require TL because of organ damage through RT. Laryngectomy rates generally lower in TOLS series than RT series (Tables 1 and 2).		
Cost	TOLS less expensive than RT[31]		

(e.g. well-defined T1a tumours). However, because of poor access or of lack of tumour definition, a proportion of patients are not suitable for TOLS.

For patients with T1b tumours, the key issue is that the voice outcome is significantly worse after surgery and oncologic results are worse compared to T1a (but not with RT). Therefore, most patients tend to be managed with RT, although audit information would be required to substantiate this.

The situation with T2 tumours is less clear however. Whilst initial local control appears similar between RT and TOLS, the eventual TL rate appears lower for TOLS patients. It is this group in particular, therefore, in which there is an apparent trade off between voice outcome and chance of eventual total laryngectomy.

Hence there remains a genuine need to perform further prospective comparative studies to answer these questions. Not only do we not understand the voice/laryngectomy equation with T2 tumours in particular, but do not know basic audit information, such as what proportion of patient do have TOLS in the UK overall? (it may be much less than we, as surgeons, believe); how many TOLS patients need further surgery?; what proportion go on to have post-operative RT?; in what proportion selected for TOLS is the surgery abandoned because of inadequate access?

Predictive biomarkers for response to RT in early glottic SCC

One of the major goals of oncological translational research is to individualise treatment according to biomarkers, and in HNSCC, this has focused on the prediction of response to RT. Most early progress in such biomarkers has centered around measures of tumour hypoxia and tumour adoption to hypoxia, using immunohistochemistry[9] or RNA expression[10]. Candidate biomarkers include pre-treatment haemogobin[11] [12] [13] and intrinsic markers of tumour hypoxia[14].

By determining predictive biomarkers for radiation response in early glottic SCC, this may provide the answer in selecting patients for RT and TOLS, especially for the T2 group of patients. Such predictive classifiers could also be used to select for treatment escalation with RT in patients not suitable for TOLS. RT escalation could be in the form of concurrent platinum or of accelerated hypofractionation regimes[2, 15].

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Granulomatous Disease in the Nose

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Abstract
Although uncommon, granulomatous conditions affecting the nose and sinuses may easily be misdiagnosed as simple allergic or infectious rhinosinusitis. They frequently involve multiple organs or systems and require a multidisciplinary management approach with other medical specialities. We present an overview of sinonasal granulomatous disease, paying particular attention to Wegener Granulomatosis, Churg-Strauss Syndrome and Sarcoidosis.

Key Words
Nose diseases; Granuloma; Wegener Granulomatosis; Churg-Strauss Syndrome; Sarcoidosis

Introduction
A granuloma is an organised collection of activated macrophages. Activation causes the macrophage nuclei to elongate and they may resemble epithelial cells, hence they are often referred to as *epithelioid*. They may fuse to form giant cells; occasionally contain other cells, such as eosinophils or neutrophils, which may give clues to the cause; and are usually surrounded by a cuff of lymphocytes **(Figure 1[1]).**

There are many granulomatous conditions that affect the head and neck, and those that involve the nose and paranasal sinuses are expanded on below. Most of these disorders present with similar sinonasal symptoms and signs (**Table 1)**. There are a number of other sinonasal conditions associated with systemic disease, which are not histologically granulomatous. These are listed in **Table 2**, and are not discussed further.

Inflammatory (Non-infectious)

Wegener Granulomatosis (WG) (ANCA-associated Granulomatous Vasculitis)
This is a multisystem disease characterised by necrotising granulomas of the respiratory tract, widespread vasculitis and glomerulonephritis. The annual incidence is approximately 5 in 100,000 in Europe, with the highest rates seen in Northern Europeans and the lowest in Afrocaribbeans. Males and females are affected equally

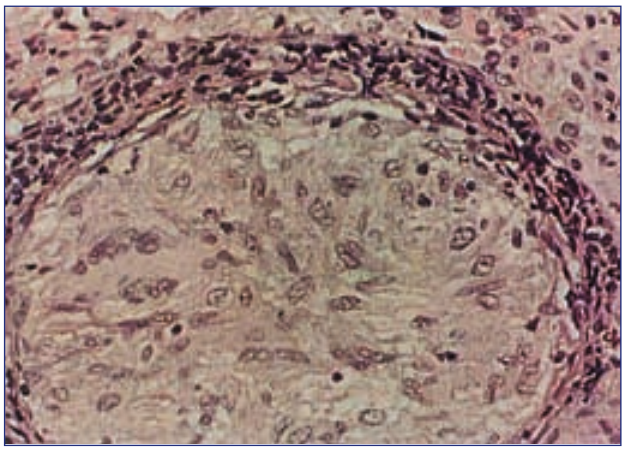

Figure 1. *Granuloma from the lung of a patient with Sarcoidosis (Hematoxylin and eosin, x40). Reproduced with permission from the Massachusetts Medical Society. Copyright © 1997, Massachusetts Medical Society. All rights reserved.*

and mean age at diagnosis is 40 years, but it may also present in childhood.[2]

Although the aetiology is unknown, there is mounting evidence that WG is an autoimmune disease in which Anti Neutrophil Cytoplasmic Antibody (ANCA) plays a role, causing tissue damage by stimulating degranulation of toxic oxygen radicals from leucocytes. Other theories about the pathophysiology of tissue damage seen in WG are that ANCA may activate neutrophils, leading to inflammation; or that circulating complexes of ANCA and neutophil degranulation products provoke a Type 3 hypersensitivity reaction.

Table 1. Common symptoms and signs in granulomatous conditions of the nose and sinuses.

Symptoms	Signs
• Congestion • Rhinorrhoea • Epistaxis • Crusting • Nasal/facial pain • Systemic upset	• Crusting • Mucosal oedema/ ulceration/ granulations • Septal perforation • Saddle deformity • Dorsal tenderness

Table 2. Non-granulomatous sinonasal conditions associated with systemic disease

Non-granulomatous sinonasal conditions associated with systemic disease
• Systemic Lupus Erythematosus
• Behcet's disease
• Relapsing polychondritis
• NK-cell lymphoma (Lethal midline granuloma)

Both c-ANCA and p-ANCA exist. The former has a granular cytoplasmic staining pattern; it targets protease-3 (PR3), an enzyme stored in azurophilic granules of neutrophils and monocytes; and is seen in 80-95% of WG patients **(Table 3)** The latter has a perinuclear staining pattern; is seen in only 25% of WG patients; and targets another azurophilic granule enzyme, myeloperoxidase (MPO). The evidence for an autoimmune aetiology is as follows:

- ANCA levels may be used to monitor disease activity and predict relapse.

Table 3: Diagnostic comparison of Wegener's Granulomatosis, Churg Strauss Syndrome, and Sarcoidosis. ANCA=Antineutrophil Cytoplasmic Antibodies; IgE=Immunoglobulin E; ESR=Erythrocyte Sedimentation rate; CRP= C-Reactive Protein; RhF=Rheumatoid factor; CXR=Chrest X-Ray; HRCT=High-resolution Computed Tomography; RBC=Red Blood Cell

Condition	Bloods	Imaging	Biopsy	Other
Wegener Granulomatosis[2]	c-ANCA (+ve in 80-89%) p-ANCA (+ve in 25%) Mild anaemia, leukocytosis, mild eosinophilia ↑ESR, CRP ↑Creatinine with renal involvement	CXR: nodules, fixed infiltrates, cavities CT paranasal sinuses	Small vessel vasculitis Focal necrosis Granulomas NB high false negative rate. Negative predictive value ~75%	Urinalysis: haematuria, casts, proteinuria if renal involvement
Churg Strauss Syndrome[10]	p-ANCA (+ve in 70%) ↑IgE, hypergammaglobulinaemia Mildly ≠RhF Anaemia, marked eosinophilia ↑ESR, CRP ↑Creatinine with renal involvement	CXR: Pulmonary opacities in 25-75% (patchy, peripheral & bilateral)	Small & medium- sized vessel necrotising vasculitis Necrotising granulomas	Urinalysis: haematuria, RBC casts, proteinuria ifrenal involvement Bronchoalveolar lavage: eosinophils in 33%
Sarcoidosis[11, 12, 22]	ACE (+ve in 60%; sensitivity 60%, specificity 70%) ANCA –ve Leukopenia, thrombocytopenia, eosinophilia (24%), anaemia (5%) ↑$Ca2^{+}$ (13%) ↑Creatinine with renal involvement	CXR and HRCT Chest: bilateral hilar lymphadenopathy, infiltrates or fibrosis CT paranasal sinuses: midline lytic lesions	Non-caseating granulomas, stains for fungi and mycobacteria -ve	Urinalysis: Hypercalciuria (50%)

- WG responds to immunosuppression
- 97% of affected individuals are ANCA positive
- There is an association with the Human Leucocyte Antigen system:
  - HLA-B8: Graves Disease, coeliac disease, dermatitis herpetiformis, sarcoidosis, autoimmune hepatitis, systemic sclerosis, primary biliary cirrhosis, primary sclerosing cholangitis, Type I diabetes mellitus, myasthenia gravis
  - HLA-DR2: systemic lupus erythematosus, narcolepsy, Goodpasture syndrome, multiple sclerosis, Behçet disease.
- WG patients have elevated levels of IgA and E

WG may also have an infectious aetiology, supported by the fact that many affected individuals have chronic nasal colonisation with *Staphylococcus aureus*. Proponents of this theory suggest that *S. aureus* may secrete a leucocyte-stimulating factor that activates neutrophils, causing fibrinoid necrosis [3, 4].

WG can involve almost any organ system, but most commonly affects the head & neck (73% at presentation), lower respiratory tract (48%), and kidneys (20%). In the head & neck, up to 80% have sinonasal and around 50% have tracheal involvement. 40-50% of patients have chronic sinusitis, and acute bacterial or fungal sinusitis is not uncommon. The nasal symptoms in patients with WG have a significant impact on their quality of life, particularly crusting and epistaxis.[5]

The mainstay of treatment is a combination of steroids and cyclophosphamide, with which up to 90% of patients show marked improvement. However, the relapse rate with this regime is high (50%), particularly in females and in the presence of severe renal dysfunction, and toxic side effects are common (40%). Other adjunctive treatments include methotrexate, cotrimoxazole, azathioprine, infliximab (anti-TNF monoclonal antibody), intravenous immunoglobulin and plasmaphereis. There is no place for surgery in the treatment of sinonasal WG. Mortality from untreated WG is high, with a mean survival of 5 months, but treatment improves this significantly to give symptomatic benefit in 90%, complete remission in 75%, and reduces mortality to 20%[2].

Churg-Strauss syndrome (CSS) (Allergic granulomatous angiitis)

Patients with CSS have a triad of asthma, systemic vasculitis affecting small-to-medium-sized blood vessels, and eosinophilia (peripherally and in mucosal lesions). The aetiology is unknown, although autoimmunity may play a role, since patients have hypergammaglobulinaemia, and raised titres of Rheumatoid Factor, IgE and p-ANCA **(see table 3)**. Annual incidence is 2-3 per 100,000, with a mean age at diagnosis of 50 years. In a recent study of 25 patients with CSS, 80% had nasal symptoms at presentation, most commonly congestion (95%), or rhinorrhoea (95%), followed by anosmia (90%), sneezing (80%), crusting (75%), purulent nasal discharge (65%) or epistaxis (60%).[6] Destructive lesions may be seen on examination, but these are not as common as in WG[7, 8]. Another recent paper suggests that nearly 60% of patients with CSS also have a degree of nasal polyposis at presentation.[9] Diagnosis is made by observing the presence of four or more of:

- Asthma
- Eosinophilia of more than 10% in peripheral blood
- Paranasal sinusitis
- Pulmonary infiltrates
- Histological proof of vasculitis
- Mononeuritis multiplex or polyneuropathy

Histological examination of mucosal lesions shows necrotising granulomas, eosinophilia and vasculitis. Treatment is with systemic steroids and immune suppression and in one series was successful in over 80% of patients[9]. One year survival with treatment is 90%, dropping to approximately 60% at 5 years[10].

Sarcoidosis

This is another multisystem disease of unknown aetiology, in which up to 9% of patients experience sinonasal disease[11]. The annual incidence is 10-15 per 100,000, but this figure is significantly higher in Afrocaribbeans and Scandinavians. Women are affected more commonly than men, and there is a bimodal age distribution, with one peak at ages 25-35 and another at 45-65[12].

Sarcoidosis may be a result of immune dysregulation, since over half of all patients demonstrate raised B-cells, hypergammaglobulinaemia, circulating immune complexes and a reduced Type 4 hypersensitivity reaction. One theory is that the persistent presence of a poorly immunogenic antigen leads to chronic T-cell activation and granuloma formation. Possible candidates for this antigen are infectious agents (e.g. mycobacteria, mycoplasma spp, herpes viruses, fungi), and environmental particles (e.g. aluminium, pollen, soil, talc).

As with other granulomatous conditions, sinonasal involvement is difficult to distinguish from chronic sinusitis, since the symptoms are similar. However, other signs such as mucosal changes (granulations, yellow submucosal nodules) and lytic lesions of the septum, turbinates or palate, should help to differentiate clinically. The lupus pernio skin lesion is a raised, red-purple,

indurated plaque or nodule, and is characteristic of sarcoidosis, often seen on the nose (50% of patients), cheeks or ears. Patients with sinonasal involvement tend to have more severe systemic disease, a longer history of disease, and require systemic treatment in higher doses than controls with sarcoidosis but without sinonasal involvement[13].

The diagnosis of sarcoidosis rests on the identification of non-caseating granulomas (NCGs) on biopsy.[11] Macrophages in NCGs secrete 1,25-dihydrocholecalciferol, causing hypercalcaemia (13%) and hypercalciuria (49%); they also secrete Angiotensin Converting Enzyme (ACE), which possibly acts as a cytokine and may be helpful in making the diagnosis (Table 3).

Table 4. Infectious organisms causing granulomatous reactions in the nose and paranasal sinuses[15].

Bacterial	Fungal	Protozoal
Mycobacteria (Mycobacterium tuberculosis, leprae, atypicals) Rhinoscleroma (Klebsiella rhinoscleromatis) Syphilis (Treponema pallidum) Actinomycosis (Actinomyces israelii) Catscratch disease (Bartonella henselae)	Aspergillus fumigatus, flavus, niger Zygomycosis (Conidibolus coronatus, Rhizopus oryae) Dermatacietes (Curvularia, Alternaria, Bipolaris) Rhinosporidiosis (Rhinosporidiosis seeberi) Blastomycosis (Blastomyces dermatitidis, Cryptococcus neoformans) Histoplasmosis (Histoplasma capsulatum) Sporotrichosis (Sporotrichum schenkii) Coccidioidimycosis (Coccidiodes immitis)	Leishmaniasis (Leishmania spp.)

Krespi[11] developed a staging system for sinonasal sarcoidosis based on a study of 28 patients, and suggested treatment for each stage:

- **Stage I:** Mild, reversible nasal disease, no sinus involvement
- High-dose intranasal steroids, emollients & saline douching
- **Stage II**: Moderate, potentially reversible nasal disease with sinus disease
- As above, plus intranasal intralesional steroid injection
- **Stage III:** Severe, irreversible disease
- As above, plus systemic steroids

Corticosteroids are the mainstay of therapy for systemic disease, although other agents such as methotrexate, chlorambucil and anti-TNF drugs may be used in conjunction with or instead of steroids in resistant disease. Surgery (e.g. rhinoplasty) should be avoided if possible, but may be considered if the patient has been in remission for several years, or for complications (e.g. CO2 or Nd:YAG laser to adhesions, nasal stenosis or lupus pernio)[11, 14].

Cholesterol granuloma

This is presumed to be a foreign body reaction to cholesterol crystals produced during the breakdown of haemoglobin following trauma. It typically affects the frontal or maxillary sinuses and causes bony expansion, which may lead to facial swelling or proptosis. Treatment is by excision[15].

Inflammatory (Infectious)

A variety of organisms **(Table 4)** incite a granulomatous reaction in the nose and sinuses, but all are rare in the UK.

Neoplastic

Fibrous histiocytoma

Sinonasal benign fibrous histiocytoma is very rare, possibly originating from undifferentiated mesenchymal stem cells. Presentation is with rhinorrhoea and nasal obstruction due to a polypoid mass and treatment is by excision.

Malignant fibrous histiocytoma is the most common soft-tissue sarcoma seen in adults, but nasal manifestations are rare. Patients present with nasal, obstruction, facial pain, cheek swelling or epistaxis. Treatment is by wide local excision, and although distant metastasis is rare, local recurrence is common[16-18].

Giant-cell granuloma

This benign condition is most frequently seen in the maxilla and mandible. Giant cell aggregates cause bony

expansion and patients complain of painful facial swelling. Bilateral facial involvement is seen in the rare inherited disorder, cherubism. Treatment is by excision[15].

Other

Langerhans Cell Histiocytosis (Histiocytosis X)

Langerhans Cell Histiocytosis (LCH) is a spectrum of diseases of unknown pathophysiology characterised by proliferation of dendritic cells and eosinophils:

- Unifocal LCH (Eosinophilic Granuloma): chronic, solitary bony lesions, characteristically affecting the skull in 50% of cases.
- Multifocal LCH (Hand-Schuller-Christian disease): a triad of Diabetes Insipidus and proptosis (due to lesions of the sella turcica and orbits), with lytic bone lesions. May also have mucocutaneous ulceration, nodules or crusting, occasionally affecting the nose.
- Acute disseminated LCH (Letterer-Siwe disease). Crusting, petechial cutaneous lesions affecting scalp, face & trunk, with fever, anaemia & thrombocytopenia, lymphadenopathy and hepatosplenomegaly.

Treatment is by curettage (unifocal bone lesions), systemic or intralesional steroids, or indomethacin, (multifocal or painful bone lesions), radiotherapy (large or inaccessible bone lesions), or chemotherapy (acute disseminated disease); other treatments under development include bone marrow transplantation, monoclonal antibody targeting and cytokine inhibitors[15, 19, 20].

Table 5. Suggested diagnostic investigations for granulomatous sinonasal disease.

Diagnostic workup for suspected granulomatous sinonasal disease
• Haematology: Full blood count, ESR
• Biochemistry: Urea and electrolytes, Calcium, CRP, ACE, Serum Protein Electrophoresis
• Immunology: ANCA, Rheumatoid factor
• Urinalysis
• Imaging: Chest X-Ray, CT nose and paranasal sinuses
• Biopsy, sent for histological and microbiological investigation (including fungal stains), if above investigations are inconclusive

Myospherulosis

Foreign body granulomas have been reported to form in the presence of lipid-based substances, notably petrolatum used on nasal packing following sinonasal surgery, and may be associated with adhesion formation [21].

Diagnostic Workup

The majority of patients with chronic rhinosinusitis will respond to treatment aimed at controlling inflammation, infection and allergy, with some requiring surgery to relieve ostial obstruction. However, in those with persistent symptoms, or with suspicious signs at presentation, granulomatous disease should be considered, and a more in-depth line of investigation pursued **(Table 5)**.

Conclusion

Although uncommon, granulomatous disease affecting the nose and sinuses may easily be misdiagnosed as simple allergic or infectious rhinosinusitis. It is important to recognise these patients, since granulomatous diseases frequently involve other organ systems and need specialist treatment in conjunction with other specialities (e.g. rheumatologists, respiratory physicians or dermatologists), so a working knowledge of these conditions is essential for otorhinolaryngologists.

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Endoscopic Lacrimal surgery – how and does it work?

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Abstract
Dacryocystorhinostomy (DCR) is a procedure performed for nasolacrimal duct obstruction. Historically performed via an external approach by Ophthalmologists, recent advances in endonasal equipment coupled with an increased understanding of the surgical anatomy have popularised the endonasal approach in the management of this condition. In this article we review the relevant anatomy, aetiopathogenesis and management, discussing the preoperative assessment and surgical techniques available for performing DCR

Key Words
Mechanical Endonasal Dacryocystorhinostomy. External Dacryocystorhinostomy. Epiphora.

Introduction
Dacryocystorhinostomy (DCR) is a procedure performed for nasolacrimal duct obstruction. Historically performed via an external approach by Ophthalmologists, recent advances in endonasal equipment coupled with an increased understanding of the surgical anatomy have popularised the endonasal approach in the management of this condition. In this article we review the relevant anatomy, aetiopathogenesis and management, discussing the preoperative assessment and surgical techniques available for performing DCR.

Anatomy
The nasolacrimal drainage system comprises of an upper a lower puncta situated at the medial aspect of the eyelids. These drain into two canaliculi, each having a 2mm vertical portion followed by an 8mm horizontal segment with an angle of 90O at their junction. The two canaliculi converge into the common canaliculus which pierces the lacrimal sac in its upper portion. The sac lies within the lacrimal fossa, bound anteriorly by the frontal process of maxilla and posteriorly by the lacrimal bone, and the fundus is positioned 8.8mm superior to the axilla of the middle turbinate (MT)[1]. The sac drains into the inferior meatus via nasolacrimal duct which has a 12mm intraosseus and a 5mm membranous portion.

Aetiopathogenesis
Lacrimal pathway obstruction can occur at any of the levels and is thus divided into pre-saccal (punctual or canalicular), saccal and post-saccal (nasolacrimal duct). The causes may be idiopathic or acquired. It is well known that females have a narrower intraossesus nasolacrimal duct[2] and further stenosis may cause a direct impediment to the free flow of tears. Stasis of content in the lacrimal sac may cause recurrent dacryocystitis which can lead to further inflammatory scarring or mucocele formation. Less common causes include trauma or neoplasia. DCR is indicated in cases of saccal or post-saccal obstruction.

Management

Preoperative assessment
Patients should ideally be reviewed in a joint lacrimal clinic with Otolaryngologsts and Ophthalmologists allowing for a team based approach to the preoperative assessment of patients. Slit lamp examination may identify, lid laxity, tear film abnormality, meibomian gland disease or for puntal stenosis and ectropion It is essential to identify patients that may have causes other than nasolacrimal obstruction pror to DCR. Endonasal

examination is mandatory and serves to identify any sinonasal pathology that may be a cause, or may need to be addressed if the patient requires DCR. These may include conditions such as septal deviation or nasal polyposis. A useful clinical test is the fluorescein dye test. A drop of 2% fluorescein is placed in the eye. In the presence of a patent and functioning lacrimal pathway the dye should make its way into the inferior meatus and is visible on nasal endoscopy (Jones 1 test). A simple assessment of function can be made by comparing fluorescein clearance between the two eyes by observing the degree of staining of the tear film.

Radiological imaging of patients is not mandatory but can include dacryocystography with a radio-opaque dye injected into the lacrimal system. This may show anatomical narrowing of the intraosseus duct. This is not a physiological test as dye is injected into the system under pressure (pressure testing of patency is also termed a Jones 2 test). In order to assess functional status of the tear drainage, dacryoscintillography can be performed. Concomitant sinonasal pathology that would require operative intervention is assessed with CT scanning.

Surgical Procedure

The technique for MENDCR is as described by Wormald[3] and points of note in the surgical technique are described in **Table 1** and **Figures 1-11**. A degree of septal deviation is extremely common in the region adjacent to the axilla of the middle turbinate and in our experience we have needed to perform access septal surgery in over 50% of cases. An important point that must be highlighted in order to produce good outcomes is the anatomic basis of this technique. Previous techniques only involved exposure of lower portion of the sac. Part of this reasoning may lie with the description of the modern endonasal DCR by McDonogh and Meiring[4], who advised that bony removal was only necessary from the axilla of the middle turbinate down to the inferior turbinate. An anatomical study using a series of CT dacryocystographs[1] showed this to be incorrect and that the fundus of the lacrimal sac actually lay 8.8mm above and 4.1mm below the axilla of the MT. Thus, previous techniques were effectively producing an

Table 1: Key Points in Surgical Technique

Septoplasty required in up to 50% of cases
Mucosal incision on lateral nasal wall and creation of posterior based flap
Thin lacrimal bone elevated and inferior portion of frontal process of maxilla removed with Hajek-Kofler punch
Powered drill equipment (diamond tipped DCR burr) required to drill out superior portion of maxilla
Full exposure of the lacrimal sac including fundus of sac
Routine exposure of agger nasi cell (if present)
Sharp dissection to open lacrimal sac with DCR spear and sickle knife
Apposition of lacrimal sac mucosa with nasal mucosa
Healing by primary intention
Superior and inferior flap replaced
Insertion of O'Donoghue tubes

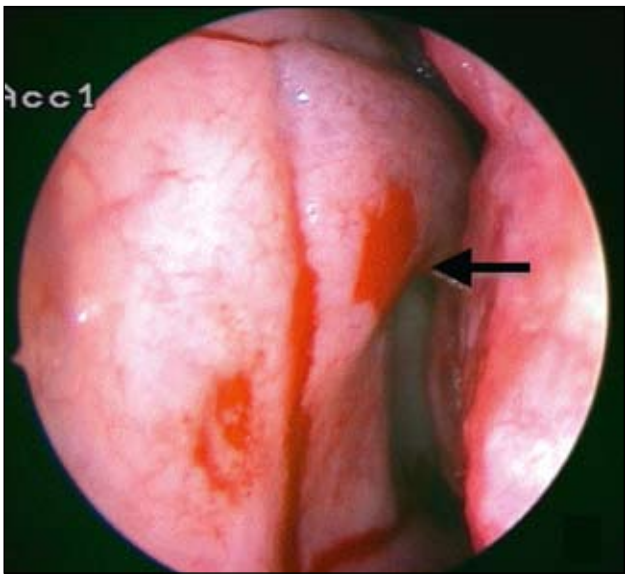

Figure 1 Mucosal Incisions: *Incisions are made 8-10mm above and anterior to the axilla of the Middle turbinate (arrow)*

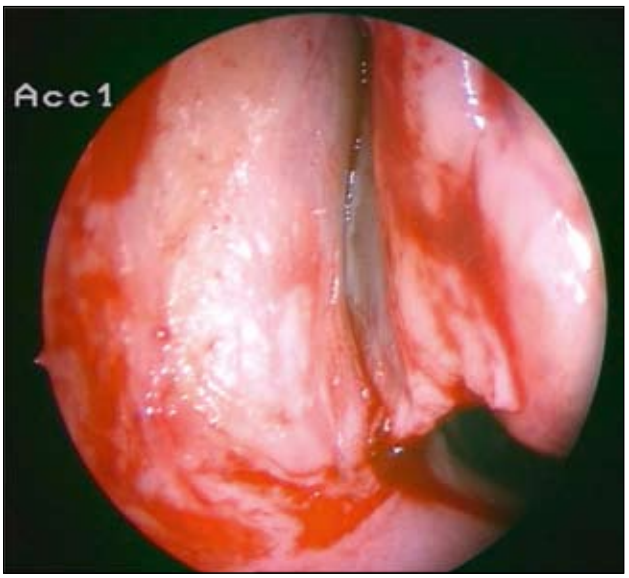

Figure 2: *Flap elevation*

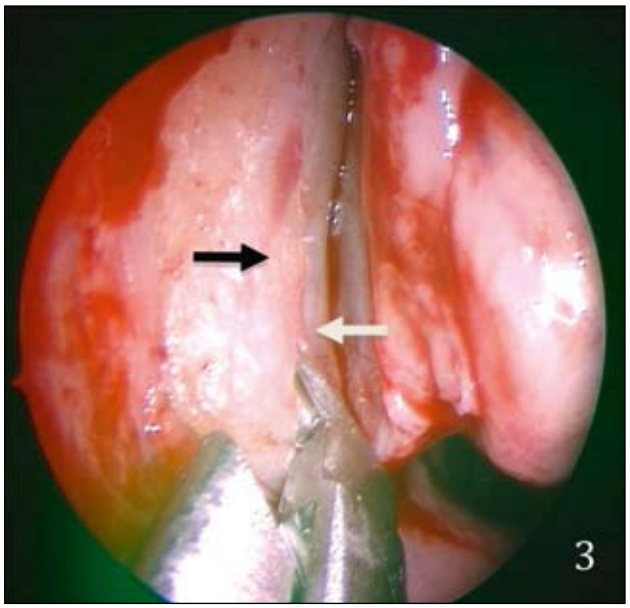

Figure 3: *Removal of frontal process of maxilla (Black arrow) using rongeur. Lacrimal bone is seen posteriorly (White arrow)*

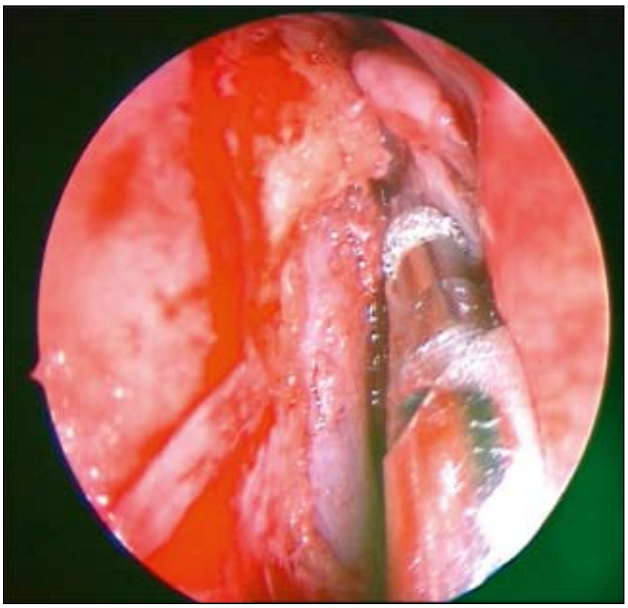

Figure 4: *Diamond burr used to remove the thick bone superiorly which allows exposure of the fundus of the lacrimal sac*

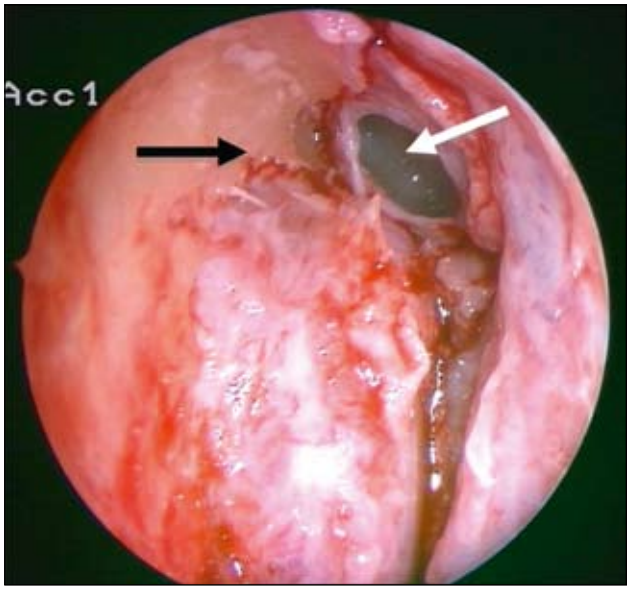

Figure 5: *Exposure of the fundus of the sac (black arrow) with opening of the agger nasi cell posteriorly (white arrow)*

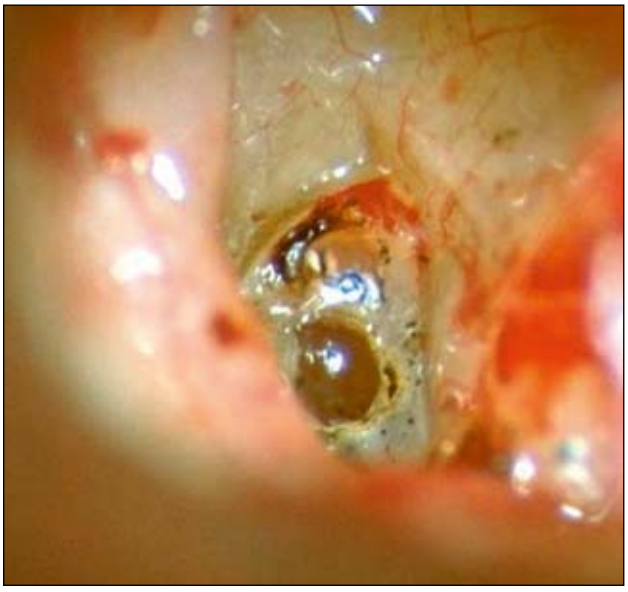

Figure 6: *The sac is incised posteriorly (white dotted line) to allow a larger flap to be rolled anteriorly (arrows)*

dacryocystorhinostomy sited in the inferior part of the sac. MENDCR allows for complete exposure of the lacrimal sac such that the entire sac is marsupialised and opened like the pages of a book.

Other Techniques

A number of other techniques have been described in the modern literature. These can be separated into Cold Steel Endonasal DCR (En-DCR), Laser Endonasal DCR (EnL-DCR) and Modified Cold Steel Endonasal DCR.

Cold Steel Endonasal DCR

Initial outcomes using EnDCR were very variable. This is thought to be due to, in part, the inadequate opening of the lacrimal sac as previously discussed. Hartikainen et al[5] (performed an early randomised trial demonstrating success rates of 91% and 75% between external and endonasal groups respectively. Although there was no statistical significance between the groups there is a clear trend noted. Cokkeser et al.[6] described a comparative study of 79 external and 51 endonasal DCR's with success rates of 89.8% and 88.2% respectively. Prior to

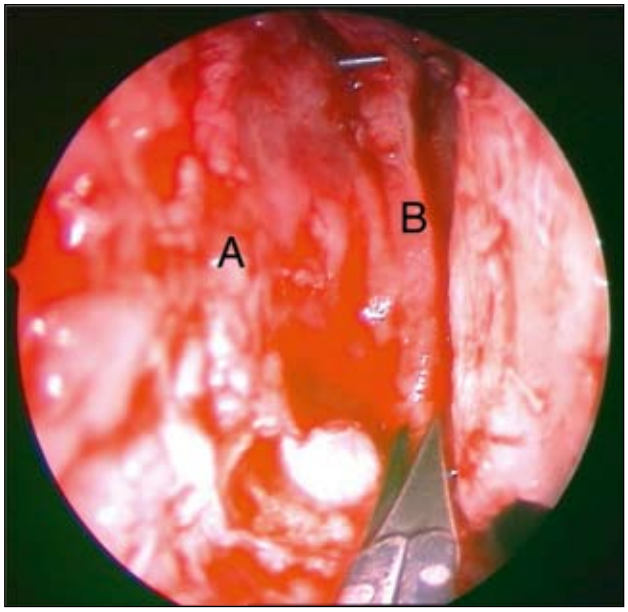

Figure 7: *Lacrimal sac opened – posterior flaps are created using micro-scissors. A lacrimal probe can be seen at the top of the image. Anterior flap (A), Posterior flap (B).*

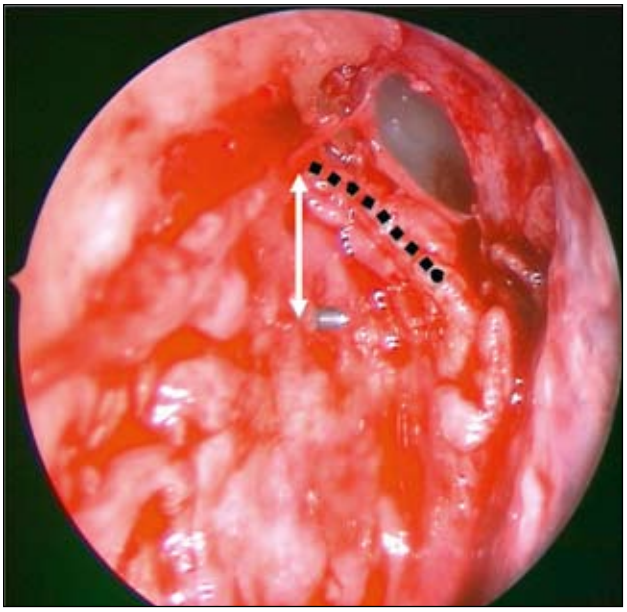

Figure 8: *The common canaliculus opening lies a few millimeters below the fundus of the sac (white arrow). The mucosa from the opened agger nasi cell is juxtaposed to the posterior sac flap allowing good mucosal apposition (dotted line)*

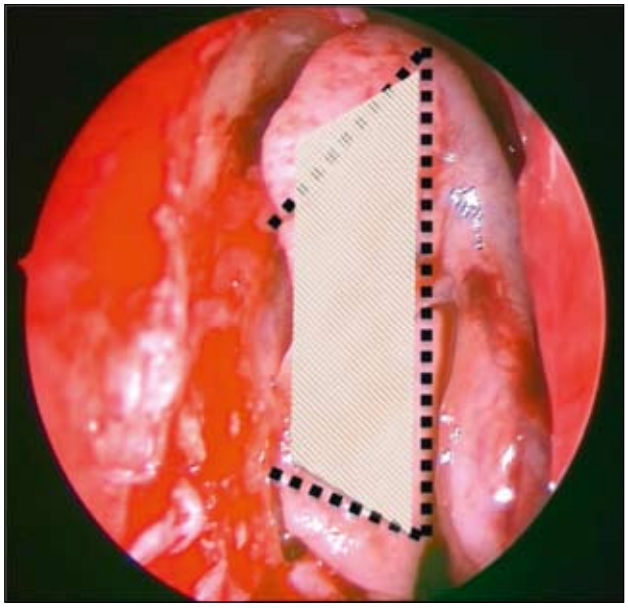

Figure 9: *The elevated mucosal flaps are trimmed to size (dotted lines) to allow coverage of as much exposed bone as possible.*

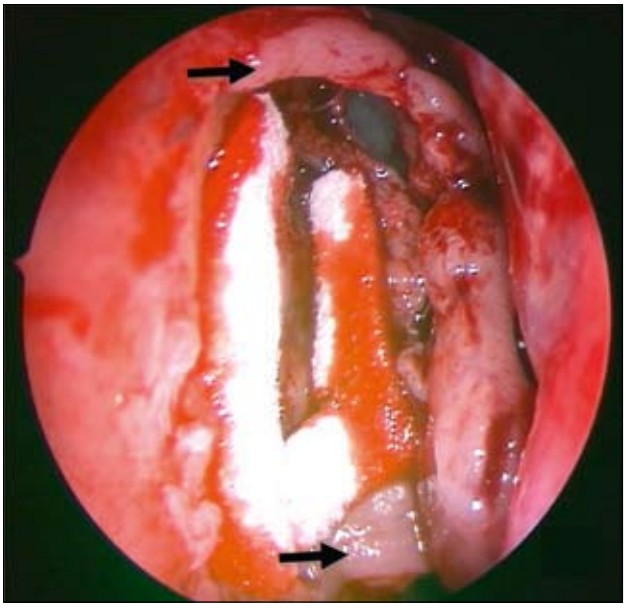

Figure 10: *Trimmed mucosal flaps are repositioned (black arrows). A 'U' shaped piece of absorbable dressing is placed over the rolled out lacrimal sac flaps. No tubes have been placed.*

this a study by Weidenbecher[7] including 56 patients of which 86% reported being symptom-free at postoperative follow-up. An interesting study by Onerci[8] compared DCR performed by experienced versus inexperienced surgeons. They found success rates between the two groups to be 94.4% and 58% respectively, indicating an appreciable learning curve to the procedure. Other reports of case series' have had variable outcomes ranging from 83% to 93% and are summarised in **Table 2**.

Endonasal Laser DCR

Endonasal laser DCR has been demonstrated to have poorer outcomes than other methods. Initially reported in 1993 by Woog[14], a holmium:YAG laser was used via an endonasal approach with a success rate of 82%. However,

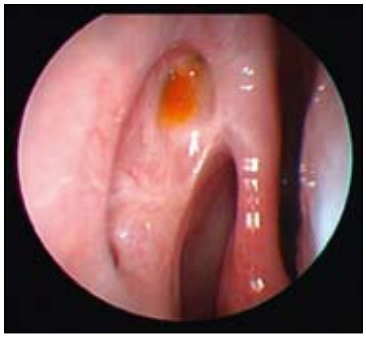

Figure 11: *Postoperative appearance. Fluorescein can be seen draining via a patent rhinostomy.*

further studies have shown that long term outcomes are poor, primarily thought to be due to the significant heat generated during vaporisation of the thick bone of the frontal process of maxilla. This leads to increased fibroblast proliferation and therefore early stenosis of the neo-ostium. A randomised controlled trial comparing external and endonasal laser DCR gave success rates of 91% and 63% respectively with a statistically significant difference in outcome noted[15]. Other studies confirm this with results ranging from 56% - 71%[16-18]. The EnL-DCR has fallen out of favour as a routine method for the treatment of epiphoria.

Modified Cold Steel DCR

A number of further techniques have been described to deal with the removal of bone from the frontal process of maxilla. Massegur[19] performed a trial comparing two techniques of bony removal. In the first group this was performed with a 4mm curved Cottle chisel and in the second this was done purely with Smith-Kerrison forceps. The success rates were 92.7% and 87.5% respectively, however they reported complications of orbital fat exposure and periorbital haematoma in 5% and 17.5% within the groups. We feel that use of a diamond burr allows for accurate bone removal with minimal trauma to surrounding tissues.

Stenting of the Neo-Ostium

Traditionally stents made of silicone or other material has been inserted through the neo-ostium via the upper and lower canaliculi and left in situ for 4-12 weeks. This was thought to reduce ostium shrinkage in the early postoperative period. Recently its use has been questioned and a number of randomised trials have been reported indicating that stents do not offer any outcome benefit, and that results between stented and non-stented groups

Table 2: Results of External, Endonasal DCR (En-DCR), Endolaser DCR (EnL-DCR) and Mechanical Endonasal DCR (MENDCR)

Study	No. of Patients	Technique	Success (%)
Hartikainen et al 5	32	External	91
Cokkeser et al 16	79	External	89.8
Hartikainen et al 5	32	En-DCR	75
Cokkeser et al 6	36	En-DCR	88.2
Weidenbecher et al 7	56	En-DCR	95
Onerci 8	108	En-DCR (experienced)	94
Onerci 8	50	En-DCR (inexperienced)	58
Sprekelson et al 9	152	En-DCR	85.5
Eloy et al 10	28	En-DCR	89
Moore 11	36	En-DCR	83
Yung and Hardman-Lea 12	191	En-DCR	89
Fayet 13	100	En-DCR	86
Woog 14	40	EnL-DCR	82
Hartikainen et al 15	32	EnL-DCR	63
Umpathy 16	65	EnL-DCR	56
Moore 17	31	EnL-DCR	71
Mirza et al 18	76	EnL-DCR	64
Massegur et al 19	96	En-DCR (Chisel)	92
Massegur et al 19	40	En-DCR (Kerrison)	87
Wormald 3	105	MENDCR	95

are similar or even better in the non-stented group[20-23]. After external DCR, where stents were traditionally used, recent evidence in the form of a prospective randomised trial found no difference in outcomes between groups of stented and non-stented patients[24].

Ostium Size

One of the significant differences between historical modern EnDCR is the size of the neo-ostium created between the lacrimal sac and nasal cavity. Failure of DCR is well attributed to closure or early stenosis of the neo-ostium. A study using CT dacryocystographs[25] compared ostium size between successful and failed DCR's. They found that in 94% of failures the ostium size was smaller than 15mm as opposed to 60% of successful ones. This statistically significant difference gives evidence that ostium size directly affects success rate. Another study demonstrated that there is a statistically significant decrease in ostium size in the first postoperative month, but thereafter remains stable[26]. This means that any anatomical failures should occur early in the postoperative course.

Conclusion

Accurate assessment of patients with epiphora is important. A multidisciplinary Lacrimal clinic is an ideal setting which helps to reduce unnecessary patient appointments. In the treatment of adult epiphoria, Mechanical Endonasal DCR is a well accepted procedure that has an excellent success rate rivalling that of external DCR. Although a number of surgical techniques have been described to deal with bony removal of the frontal process of maxilla, the diamond tipped DCR burr allows for accurate drilling with the minimum risk of damage to the underlying lacrimal sac.

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Olfactory dysfunction – Assessment and management

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Abstract
The diagnosis and management of olfactory disorders has been described as a neglected topic in otolaryngology. Olfactory disorders can have a significant impact on quality of life and may be the only manifestation of potentially life-threatening disease. This article reviews the physiology of olfaction and aetiology of olfactory disease. The investigation and management of patients presenting with disorders of smell is discussed, with reference to current literature.

Key words
Olfaction disorders, Smell, Diagnosis, Therapy

Introduction
Olfaction is the sensation arising from the nasal cavity, following stimulation of the olfactory epithelium by volatile compounds. A normal sense of smell is undervalued, playing a vital role in the enjoyment of food and detection of environmental hazards. Some occupations depend heavily on an intact sense of smell i.e. cooks, wine tasters. Olfactory perception is heavily associated with memory and emotion, due to projections to the limbic system1. Olfactory symptoms may be the primary manifestation of serious intracranial pathology. The incidence of olfactory disorders in the United Kingdom is poorly documented but 2 million people per annum in the USA are thought to be affected. The Skövde study describes a 19.1% prevalence of olfactory dysfunction, composed of 13.3% with hyposmia and 5.8% with anosmia[2]. Men perform less well in olfactory testing and olfactory sensitivity deteriorates with age[3].

Physiology of olfaction
Olfaction is mediated via cranial nerves I and V. The olfactory nerve is responsible for the identification of odorants via specialized olfactory epithelium, and the trigeminal nerve is responsible for common chemical sensation and detection of pungency. The olfactory mucosa is a 1mm area of specialized neuroepithelium overlying the cribriform plate. Olfactory mucosa extends below the anterior middle turbinate and onto the nasal septum, more anteriorly and inferiorly than originally thought[4]. This should be considered when performing nasal surgery.

When odorant molecules reach the olfactory epithelium, they interact with olfactory mucus before binding with the olfactory receptor cells. The olfactory receptor neurones are bipolar, with a cilia-bearing, club-shaped peripheral receptor. Their thin, unmyelinated axons travel several centimetres, when bundles of the fibres become ensheathed by Schwann cells and pass through the 15-20 foramina of the cribriform plate before synapsing in the olfactory bulb[5]. Each neurone expresses a single receptor and can combine with a range of odorant molecules before its associated axon projects to glomeruli in the olfactory bulb[6,7]. It is suggested that an odorant provides an 'olfactory code' by activating a set pattern of receptors and glomeruli, which is recognised by the olfactory cortex and identified as a specific odour[8].

The primary olfactory cortex consists of the prepyriform and periamygdaloid areas of the temporal lobe, while the entorhinal area of the pyriform lobe is known as the secondary olfactory cortex. Projections from the olfactory pathways to the thalamus, forebrain and limbic system are

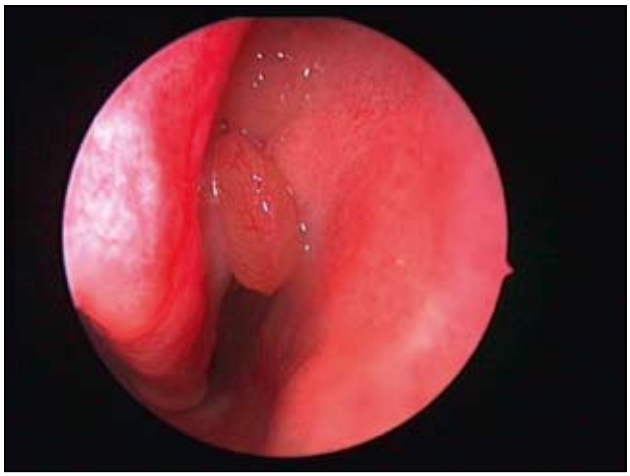

Figure1. *Nasal polyp – a 'conductive' cause of hyposmia*

thought to relate to the associations between odour perception, memory and emotional stimuli. Cyclic AMP (cAMP) is the common mediator of the olfactory pathway[9].

Pathophysiology of olfactory disorders

Olfactory disorders may manifest as hyposmia or anosmia (reduced or absent sense of smell) or as distorted smell (parosmia/troposmia – distorted quality of a perceived odorant, phantosmia – perceived smell in the absence of an olfactory stimulant, or cacosmia – perception of an unpleasant smell in the absence of olfactory stimulation[10].

Analogies are drawn between causes of olfactory disturbance and causes of hearing loss[11]. 'Conductive' disorders result from odorant molecules failing to access the olfactory mucosa e.g. nasal polyps, rhinosinusitis **(Figure 1)**. 'Sensory' losses are caused by olfactory mucosal damage e.g. chemical exposure, viruses, neoplasms, whilst neural causes result from defects in the peripheral or central neural pathways e.g. head injury. Up to 22% of cases are idiopathic and iatrogenic causes of hyposmia should always be considered[12]. The causes of olfactory disturbances are summarised in Table 1[13].

Olfactory dysfunction following head injury

Head injuries account for 18% of olfactory disturbances[12]. Olfactory insult results from damage to nasal mucosa, shearing of olfactory fibres due to cribriform plate fracture and oedema of the olfactory tracts and bulbs. Damage to peripheral olfactory apparatus results in anosmia, whereas central olfactory damage manifests as an inability to discriminate odours[14,15]. The anterior temporal lobes and orbitofrontal poles are most vulnerable[16,17]. Post-traumatic olfactory impairment is more pronounced with less chance of recovery than post-infection or chronic rhinosinusitis.

Table 1. Causes of olfactory loss (Seiden 1997 13)

Aetiology	% patients
Head injury	19
Post URTi	17
Nasal / sinus disease	16
Idiopathic - nasal	17
Toxic exposure – nasal	5
Multiple	5
Congenital	2
Age	1
Idiopathic –oral	9
Miscellaneous -	6
Toxic-exposure – oral	1

Predictive factors may allow identification of likelihood of recovery. Factors noted to negatively influence recovery include a Glasgow Coma Scale (GCS) score of <13 at presentation, loss of consciousness > 1 hour, post-traumatic amnesia and radiological abnormalities with occipital, frontal and skull base fractures[18,19]. 40% of such patients suffer an olfactory deficit, although this may only manifest on formal testing[20]. Recovery of normal smell following head injury is unlikely, although improvement can take place over a longer time period than previously realised. Recovery has been noted up to 5 years post-injury, although such patients are unlikely to return to normosmia[21,22].

Olfactory dysfunction following upper respiratory tract infection (URTi)

Temporary anosmia can occur with URTi, when oedema prevents odorant molecules reaching the olfactory cleft. Viral URTi accounts for 20-30% of identified olfactory losses, typically parainfluenza 3 virus[23,24]. In a small percentage, olfaction remains permanently distorted, particularly in women (70-80%) and in those aged 40-60[25]. This is partly due to cumulative degeneration of the olfactory apparatus with age, however, viral infections cause reduction in olfactory receptors with replacement by respiratory epithelium[23,26]. Stem cells may persist with the potential for regeneration[27]. The prognosis for recovery from URTi – induced hyposmia varies in the literature from 6 months to 3 years, although other studies describe minimal recovery[27-29].

Olfactory dysfunction post rhinosinusitis

It seems logical that treating mucosal oedema and polyposis to improve access of odorant molecules to the olfactory apparatus would result in a symptomatic improvement. However, the effectiveness of surgical intervention for

hyposmia secondary to chronic rhinosinusitis is open to debate. A correlation between nasal airflow and odour identification in patients with chronic rhinosinusitis has been demonstrated, suggesting surgery to improve nasal airflow and eliminate mucosal disease would be helpful 30. Rowe-Jones collected prospective data on 115 patients, evaluating subjective symptoms and olfactory detection thresholds, prior to and 6 weeks following endoscopic sinus surgery (ESS)[31]. All parameters significantly improved, including nasal volume on acoustic rhinometry. Improvement in olfactory scores was proportional to the increase in nasal volume. A recent study found that anosmic patients with chronic rhinosinusitis improved significantly following ESS and the improvement was maintained at 1 year follow-up[32].

The relationship between airway patency and olfactory function has been questioned 29. In an extensive literature review, Doty comments that neither surgical nor medical interventions result in a return to normosmia. This could be due to reduction in olfactory epithelium and replacement with normal respiratory mucosa in patients with chronic rhinosinusitis[33]. Inflammatory changes within the olfactory mucosa may account for hyposmia, independent of airflow alteration[34]. Recovery of smell in patients with chronic rhinosinusitis/polyposis seems to be time-dependent, with prolonged disease resulting in degeneration of olfactory mucosa and persistent olfactory dysfunction.

Management of olfactory disorders

Clinical assessment

A thorough clinical history should be taken, including presence of associated nasal symptoms, taste disturbance and allergy. The duration, speed of onset and pattern of olfactory disturbance should be determined. The patient should be asked about taste disturbance as this often has an underlying olfactory component. Details of any head injury should be elicited, particularly regarding loss of consciousness, direction of impact and radiological findings[18-20]. Preceding URTis should be documented. **Tables 2** and **3** summarise details of medical conditions and prescribed medications that should be explored[35]. Occupational history may reveal exposure to noxious chemicals e.g. cadmium, benzene, and a smoking history is important[36]. Iatrogenic causes must be considered, including medication, neurosurgical intervention, radiotherapy and previous nasal surgery. Family history should be elicited.

Congenital disorders of smell, including isolated absence/hypoplasia of the olfactory bulbs are associated with Kallmann syndrome, Turner syndrome and premature baldness and may be diagnosed on assessment of the patient's habitus **(Figure 2)**[37]. Nasendoscopy may show evidence of rhinosinusitis and polyposis, or reveal no abnormality. Cranial nerve examination should always be included.

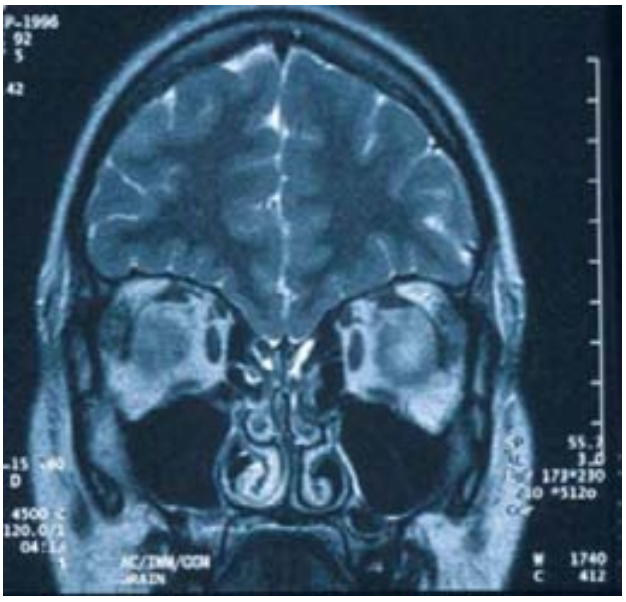

Figure 2. *MRI image demonstrating absent olfactory apparatus*

It is important for the evaluating clinician to advise patients of the potential risks associated with reduced smell, with particular regard to detection of environmental hazards e.g. smoke and gas detection.

Olfactory testing

Cain describes 3 criteria necessary to maximise odour recognition in olfactory testing[38]. Odours must be familiar to the patient, with a longstanding association between the odour and its name, and help should be given to recall the name. Reliability is improved using both threshold testing and odour discrimination assessment. 'Forced-choice' procedures reduce response bias. Patients scoring less than chance are likely to be malingering, as are those who fail to identify trigeminal nerve stimulants, such as ammonia or 4% butanol. Formal olfactory testing allows monitoring of progression/resolution of dysosmia, particularly following surgical or other therapeutic intervention.

The UPSIT (University of Pennsylvania Smell Identification Test) system appears to be the most commonly used test amongst UK clinicians[39]. This is a forced-choice supra-threshold test with 40 micro-encapsulated odours, acting as a 'scratch and sniff' test. This test indicates a level of smell function i.e. mild to total anosmia and has score ranking for age and gender[40]. However, the system has not been validated on a UK

Table 2 - Categories of medical disease and olfactory dysfunction (Jones 1998 63 – adapted from Schiffman 1993 64)

Group of conditions	Examples
Neurological	Alzheimer's disease Down Syndrome Epilepsy Multiple Sclerosis Parkinson's Disease
Congenital	Kallman Syndrome Choanal atresia
Nutritional and metabolic	Chronic renal failure Liver disease Vitamin B12 deficiency
Endocrine	Diabetes Adrenal cortex insufficiency Hypothyroidism Cushing's disease
Trauma	Head injury Laryngectomy
Inflammatory	Rhinosinusitis/ nasal polyposis Sarcoid Wegener's disease
Neoplasms	Olfactory neuroblastomas Anterior skull base tumours
Degenerative	Age
Infective	Acute viral hepatitis HIV Influenza-like
Others	Adenoid hypertrophy Familial Psychiatric

population. The Cross-Cultural Smell Identification Test (CCSIT) is a self-administered 12-item test based on UPSIT, which can be carried out in 5 minutes[41]. 'Sniffin' Sticks' are a test of olfactory function based on felt-tip pens and assesses odour threshold, discrimination and identification[42]. Currently, the only test validated in a UK population is the Combined Olfactory Score, assessing odour discrimination and threshold testing[43].

There is considerable variation in the reliability of olfactory tests, related to length of testing. Results from different testing methods should not be compared, as variations may result from differing reliabilities rather than reflecting clinical findings [44].

Table 3 – Classes of medication that can affect olfaction (Jones 1998 (63)– Adapted from Schiffman 1993 (64))

Drug class	Example
Local anaesthetics	Cocaine hydrochloride
Antihypertensives	Nifedipine
Antimicrobials	Streptomycin Amphotericin B
Antithyroids	Carbimazole Thiouracil
Opiate	Codeine Morphine
Antidepressants	Amitryptilline
Radiation therapy	To head
Sympathomimetics	Amphetamines
Vasodilators	Diltiazem
Ameobicides	Metronidazole Nidazole
Immunosuppressants	Methotrexate Azathioprine
Antirheumatics	Gold Colchicine Allopurinol

Radiological evaluation of olfactory dysfunction

Imaging may be required in the evaluation of olfactory disorders. There are no current guidelines regarding the indications for imaging in olfactory disorders. Computerised tomography (CT) is more appropriate for patients with sinonasal disease, regarding surgical planning. However, magnetic resonance imaging (MRI) is more useful for diagnosis of olfactory apparatus abnormalities and parenchymal disease, particularly in congenital disease. Phantosmias and olfactory hallucinations may have peripheral or central origins and should be imaged 10. Decreased volume of the olfactory bulbs is noted with increasing age. Absent olfactory bulbs, hypoplastic olfactory sulci and loss of temporal and/or frontal lobe volume are described in Kallmann's syndrome[45,46].

Olfactory groove or frontal lobe tumours may reach a significant size (>4cm) before presentation, due to a gradual deterioration in olfactory function and preservation of unilateral olfactory function[47]. It has been suggested all patients with lateralised dysosmia should have a radiological evaluation, after noting 50% of patients with olfactory meningiomas had unilateral dysosmia on formal

testing. Accurate diagnosis of site of skull fracture and associated parenchymal injuries may allow prediction of the likelihood of recovery of smell[7]. A positive correlation has been shown between number of plaques and olfactory function in patients with multiple sclerosis. Functional assessment of hyposmia with SPECT imaging demonstrates reduced frontal blood flow in patients with schizophrenia[47].

One study suggests that patients with negative endoscopy findings do not require routine imaging, as no significant pathology was demonstrated[48]. However, this is a retrospective, unblinded study of 20 patients and should be interpreted with caution.

Pharmacological therapy of olfactory disorders

The evidence suggests that a trial of oral corticosteroids may be useful, although there is little information on the required dose or length of treatment. Improvements in subjective and objective olfactory measurements are described, particularly in patients with allergic rhinitis or nasal polyposis and anosmia[49-51]. The improvement is likely to be due to a reduction in mucosal oedema, even when a conductive olfactory loss may not be apparent[52]. However, while hyposmic patients appear to improve, they are unlikely to return to normosmia. No improvement in olfactory scores was demonstrated in anosmic patients. Corticosteroid nasal sprays seem to be less effective in improving olfactory scores and symptoms. There are studies showing an improvement to the mid-hyposmic range with topical steroid application, contrasting with others which either fail to show an improvement or fail to maintain the improvement resulting from oral corticosteroid use or ESS[51-56].

A small number of studies assess therapies other than steroids, including zinc replacement, alpha-lipoeic acid and caroverine[57-59]. However, the evidence is unconvincing and, at present, no medical therapy other than oral corticosteroids appears to be successful in the treatment of hyposmia.

Antidepressants and anti-convulsants have been used in the treatment of olfactory distortions although no published trials are available[60]. Topical cocaine hydrochloride can temporarily disrupt olfactory neurones, but the patient should be fully informed of potential complications, including permanent anosmia or phantosmia.

Surgical intervention for olfactory disorders

The outcomes of ESS on olfaction have previously been highlighted in this discussion. Other surgical techniques have been described in the management of patients with olfactory distortions. These include bifrontal craniotomy and removal of the olfactory bulbs, and excision of the olfactory mucosa via an endonasal approach[61,62]. Both approaches result in permanent anosmia, but with a lower complication rate in the endonasal approach.

Conclusions

Patients with olfactory disorders should undergo a comprehensive clinical assessment. CT imaging is most appropriate for planning surgery for sinonasal disease, while MRI evaluates the olfactory apparatus more accurately. Olfaction may remain permanently distorted following head injury, viral infection and chronic rhinosinusitis. However, recovery has been documented over longer periods than previously thought. Oral corticosteroids appear to be the only effective pharmacological treatment for hyposmia.

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Facial pain in a Rhinology Clinic

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Abstract
Most patients who present to a Rhinology clinic with facial pain and headaches believe they have 'sinusitis,' although in reality very few of these patients have true sinogenic pain. Headaches that are due to sinusitis are very uncommon and confined to a minority of patients who have acute frontal sinusitis or sphenoiditis. In a study of 973 consecutive patients collected prospectively presenting to a rhinology clinic who filled the criteria of facial pain, headache and/ or symptoms of rhinosinusitis, 409 (42%) had symptoms of facial pain and or head pain or pressure. The majority of these had pain due to a neurological condition with only 76 (19%) having pain that was attributed to sinus disease. The common causes of facial pain are reviewed and their management discussed.

Keywords
Facial pain, Rhinology clinic, Sinusitis

INTRODUCTION
Facial pain has special emotional significance as it is often influenced by cognitive, affective and motivational factors. For a few patients, facial pain may be the channel through which they express emotional distress, anxiety or the psychological harm associated with coexisting or previous disease, trauma or surgery. It may be the means by which the patient demands attention or obtains some secondary gain.

Facial pain affects a large proportion of patients referred to a rhinology clinic. Most patients arrive with an initial diagnosis of "sinusitis," from their General Practitioner, although in reality very few of these patients have true sinogenic pain. Headaches that are due to sinusitis are very uncommon and confined to a minority of patients who have acute frontal sinusitis or sphenoiditis. The International Headache Society classification is robust in qualifying the term sinus headache and states "chronic sinusitis is not validated as a cause of headache and facial pain unless relapsing into an acute stage.[1]"

In a study of 973 consecutive patients collected prospectively presenting to a rhinology clinic who filled the criteria of facial pain, headache and/ or symptoms of rhinosinusitis, 409 (42%) had symptoms of facial pain and or head pain or pressure. The majority of these had pain due to a neurological condition with only 76 (19%) having pain that was attributed to sinus disease (mean follow up 2 years 2 months)[2]. **See Figure 1**.

Arriving at the correct diagnosis is crucial and requires a detailed rhinological history and knowledge of the common diagnostic categories.

Midfacial segment pain
This is a distinct group of patients who have a form of facial neuralgia that has all the characteristics of tension-type headache with the exception that it affects the midface and up to 60% have coexisting tension type headache. It is not related to sinusitis[3, 4]. The definition of midfacial segment pain is:

- A symmetrical sensation of pressure or tightness. Some patients may say that their nose feels blocked even though they have no nasal airway obstruction.
- Involves the areas of the nasion, under the bridge of the nose, either side of the nose, the peri- or retro-orbital regions, or across the cheeks. The symptoms of tension type headache often coexist.

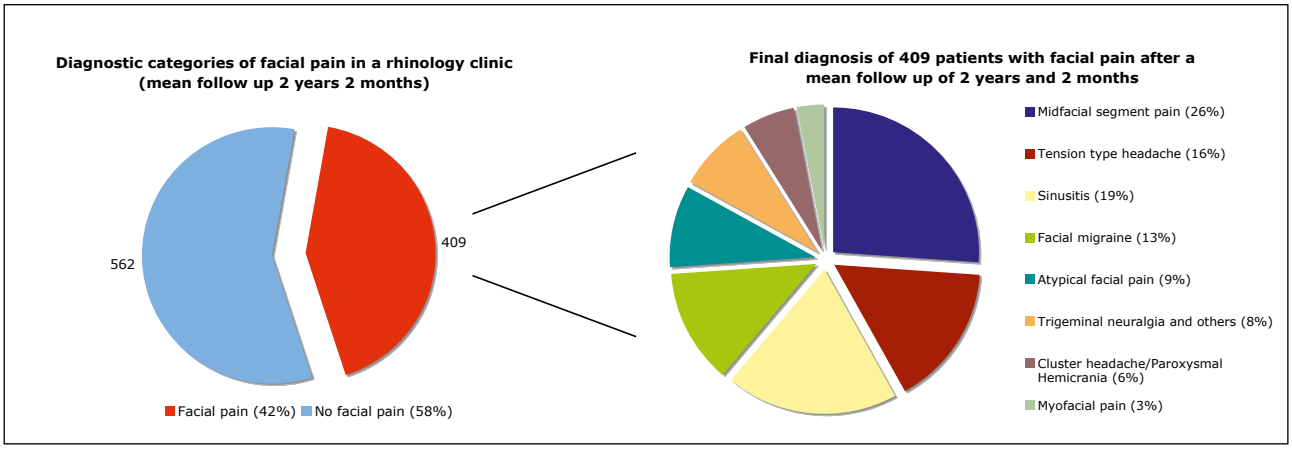

Figure 1. *Diagnostic categories of facial pain in a rhinology clinic (mean follow up 2 years 2 months).* *Adapted from 2*

- There may be hyperaesthesia of the skin and soft tissues over the affected area.
- Nasal endoscopy is normal.
- Computerised tomography of the paranasal sinuses is normal (note a third of asymptomatic patients have incidental mucosal changes on CT).
- The symptoms may be intermittent (<15 days/month) or chronic (>15 days/month).
- There are no consistent exacerbating or relieving factors.
- There are no nasal symptoms (note that approximately 20% of most populations have intermittent or persistent allergic rhinitis, which may occur incidentally in this condition).

The majority of patients (80%) with this condition respond to low dose amitriptyline, but usually require up to 6 weeks of 10 mg (occasionally 20 mg) at night before it works[2]. Amitriptyline should then be continued for 6 months, and the 20% whose symptoms return when they stop it need to restart it if the pain returns. It is our practice to inform patients that amitriptyline is also used in higher doses for other conditions such as nocturnal enuresis and depression, but its effectiveness in midfacial segment pain is unrelated to its analgesic properties, which would take effect much more quickly and normally require 75mgs. It is often reassuring for patients to know the dose used for depression is some 7 or more times the dose used in tension-type headache or midfacial segment pain. If amitriptyline fails, then relief may be obtained from gabapentin or pregabalin.

Sinogenic pain

Acute sinusitis usually follows an upper respiratory tract infection and is typically unilateral, severe, associated with pyrexia and unilateral nasal obstruction with nasal discharge. This differs from chronic sinusitis which is typically painless with pain only occurring during acute exacerbations, often precipitated by an upper respiratory tract infection or when there is obstruction of the sinus ostia by polyps[5]. Key points in the history of sinogenic pain are an exacerbation of pain during an upper respiratory tract infection, an association with rhinological symptoms, worse when flying or skiing and a response to medical treatment. A normal sinonasal examination with no evidence of middle meatal mucopus or inflammatory changes makes the diagnosis of sinogenic pain very unlikely, especially if the patient is currently in pain or has had pain in the past few days. If the patient is asymptomatic it is often useful to review them when they have pain in order to clarify the diagnosis.

Tension type headache

Almost all patients who present with a symmetrical frontal or temporal headache have a tension type headache. It is described as dull, a feeling of pressure, or a tight feeling. It can be chronic or episodic. It most often responds to low dose amitriptyline, but propranolol, sodium valproate, or a change in lifestyle may all result in the successful relief of symptoms[2].

Facial migraine

This can be either classic or common. Classic is easier to recognise because there is not only nausea, but also an aura and photopsia. The patient has sharp severe pulsatile pain. Classic migraine responds to aspirin, if given early, or one of the triptans. If episodes are frequent, pizotifen, propranolol, amitriptyline, nifedipine or sodium valproate can be given for prophylaxis. The common variant of migraine is also described as sharp, severe, and pulsatile in nature and is often accompanied by nausea, but there is no aura or photopsia. Medical treatment is the same.

Atypical facial pain

This is a deep, ill-defined pain. No organic cause for the pain can be found, and it often crosses recognized

neurological dermatomes. It is usually unilateral, more common in women over the age of 40 and may alter its location. Psychological factors play a major role. It responds to either higher doses of amitriptyline, or gabapentin, and it may take up to 6 weeks for there to be any effect.

Paroxysmal hemicrania

Paroxysmal hemicrania is an excruciating unilateral pain in women, which is usually ocular, and frontotemporal with short-lasting (2-45 minutes), frequent attacks (usually more than 5 a day); with marked autonomic features (rhinorrhoea, nasal congestion, conjuctival injection, lacrimation, facial flushing) that are ipsilateral to the pain. A response to indomethacin is essential in the current criteria for diagnosis[6].

Cluster headache

Cluster headaches are defined as a primary neurovascular headache that is very severe and is characterised by recurrent, strictly unilateral attacks of headache, that are usually retro-orbital, of great intensity and last up to one hour. They usually occur in men aged 30-50 years. The pain is also accompanied by ipsilateral signs of autonomic dysfunction such as the ipsilateral parasympathetic signs of rhinorrhoea, lacrimation, impaired sweating and sympathetic signs of miosis and ptosis.6 This usually has a nocturnal predominance with longer duration and lower frequency of attacks with pain-free intervals lasting months. The most salient feature is its periodicity, in terms of active or inactive bouts, separated by clinical remission. Patients with cluster headache typically respond to triptans and pizotifen[6].

Myofacial pain

This condition is five times more common in postmenopausal women and has a strong association with stress. It has many features in common with temporomandibular joint dysfunction. There is widespread, poorly defined aching in the neck, jaw and ear with tender points in the sternomastoid and trapezoid muscles. The treatment is controversial but tricyclic antidepressants can play a role.

Trigeminal neuralgia

Trigeminal neuralgia is an agonising, lancinating pain. There is often a trigger point and it is more common in the maxillary and mandibular divisions of the trigeminal nerve. It occurs more commonly in women over 40 and responds to either carbamazepine or gabapentin[2].

Investigations

Sinonasal endoscopy is the cornerstone of the examination with a sensitivity of 84% and specificity of 92% in patients with any nasal symptom[11].

Plain sinus x-rays, even in acute bacterial sinusitis, are so insensitive and non-specific that they are very poor in the diagnosis of sinusitis[7]. Interpretation of the appearance of the sinuses on computerised tomography (CT) scans must also be treated with caution as approximately 30% of asymptomatic patients will demonstrate mucosal thickening in one or more sinuses on CT scanning. The presence of this finding is certainly not an indication that pain is sinogenic in origin[7,8]. CT scanning is therefore generally reserved as a preoperative roadmap for patients undergoing endoscopic sinus surgery and is not used routinely in the diagnostic workup of patients with facial pain. However, if a CT scan shows no evidence of mucosal thickening it is very unlikely that any facial pain is secondary to paranasal sinus disease.

Patients who have two or more bacterial sinus infections within 1 year should be investigated for an immune deficiency[9,10].

Conclusions

The majority of patients presenting to a rhinology clinic with facial pain do not have a sinogenic cause. A detailed rhinological history and endoscopic examination leads to the correct diagnosis and the majority of these patients respond well to neurological treatment. Surgical intervention is unnecessary in the majority and can be counterproductive.

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Outcome in Functional Endoscopic Sinus Surgery (FESS) for Rhinosinusitis

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Keywords
sinusitis, rhinosinusitis, nasal polyps, endoscopic sinus surgery, outcome

Introduction
Rhinosinusitis is defined as an inflammatory process involving the mucosa of the nose and one or more of the paranasal sinuses[1]. Previous lack of uniform criteria has led to a shortage of epidemiological data in rhinosinusitis. However, it is a common health condition and is estimated to affect more than 30 million Americans[2] resulting in more than 200 000 surgical procedures annually in the United States[3]. The epidemiological data of chronic rhinosinusitis (CRS) with or without nasal polyps (NP) are more difficult to grasp. In different surveys and studies the prevalence of doctors-defined CRS without NP appears to be 1,1-9,6%[4-8], while the prevalence of CRS with NP in reported studies range from 0.5% to 4.3%[9-13] and increase with age[12,14,15].

In 2005 the first European Position Paper on Rhinosinusitis and Nasal Polyps (EP3OS) was published, which offered evidence based knowledge on rhinosinusitis[1]. A revision followed in 2007 with criteria of acute and chronic rhinosinusitis (see **Table 1**). When EP3OS2007 was published there were 104 randomized controlled trials on CRS. Recently further 17 trials have been published. In this paper we focus on the effect of FESS on CRS with and without NP.

Table 1. Defintion of rhinosinusitis according to EP3OS1.

Rhinosinusitis (including nasal polyposis) is defined as:
presence of two or more symptoms one of which should be nasal congestion/obstruction/blockage or nasal discharge (anterior/posterior nasal drip):
+/- facial pain/pressure;
+/- reduction or loss of smell;

and either

- Endoscopic signs:
  - mucopurulent discharge from middle meatus
  - oedema/mucosal obstruction primarily in middle meatus

and/or

- CT changes
  - mucosal changes within ostiomeatal complex and/or sinuses

In acute rhinosinusitis (ARS) the symptoms last <12 weeks and there is complete resolution of the symptoms, whereas in chronic rhinosinusitis (CRS) the symptoms is lasting >12 weeks without complete resolutions of the symptoms.

The FESS technique
In 1966 Messerklinger published his technique to perform endoscopic sinus surgery along the natural sinus ostia, which allows recovery of an untouched diseased mucosa[16]. This concept, to restore sinus ventilation and normal

mucociliary clearance system called FESS, was spread world-wide by Stammberger and Kennedy. The basic idea of FESS has evolved over the time and the extent of the procedure vary from mere uncinectomy to radical nasalization, where one can question whether the surgery still is "functional". New instruments as microdebriders have refined the FESS technique and the endonasal surgery has now even reached beyond the paranasal sinuses into the brain and orbit.

Confounding factors

The aetiology and pathogenesis of CRS seem multifactorial with major impact of genetics and environment including allergy, bacterial, viral and fungal infection as well as varying immunological response. Consequently there is no single but rather individual solution for the problem. FESS has proven to be effective following medical therapy in both CRS and chronic recurrent rhinosinusitis (recurrent acute rhinosinusitis)[17]. It is known that the presence of NP in CRS has an impact on the outcome of sinus surgery. Moreover, the surgical outcome is influenced by patient dependent factors as gender, extent and duration of disease, previous surgery, concomitant diseases such as ASA-intolerance, asthma, or cystic fibrosis, and particular aetiologies including dental, autoimmune, immune and fungal disease[18-21]. Since 2004 the existence of biofilms i.e. organized, complex community of bacteria anchored to biotic and abiotic surfaces, has been documented in a subgroup of CRS, contributing to the progression of CRS[22] and subsequently may affect the outcome of FESS. Mode and duration of pre- and post-operative drug therapy may also alter the outcome of the surgery.

Outcome measures

As recently written by Fokkens in an editorial there has been an immense change in rhinology in the last two decades[23]. Previous lack of strict criteria of rhinosinusitis has obstructed well conducted outcome studies. From reporting subjectively experienced results in sinus surgery in the 1990´s, there are now numerous published assessments resulting in evidence-based knowledge in FESS.

In published materials FESS has proven to be significantly effective in treating CRS with success rates ranging from 73% to 98%[24]. However, there are numerous different kinds of outcome measures in FESS. As surgery should be performed merely on patients with sinonasal symptoms, the symptom scores and the effect on quality of life (QOL) should be the indicators we as surgeons focus on. According to the World Health Organization QOL includes psychological and social functioning as well as physical functioning and incorporates positive aspects of well-being as well as negative aspects of disease or infirmity. It is stated in the EP3OS document that CT and endoscopic scores correlate well[21] but the correlation between CT findings and symptom scores has generally been shown to be poor and subsequently CT is not a good indicator of outcome[25-27].

In summary CT-staging of the paranasal sinuses and endoscopic scoring have been found to be bad predictors on how satisfied the patient with CRS is after FESS, whereas preoperatively QOL scoring has proved to be predictive for ultimate patient outcome[28].

QOL questionnaires

There are generic (or general) QOL questionnaires, such as SF-36 which is the most widely used in published materials on CRS both pre- and postoperatively. Since sinonasal conditions have significant adverse impact on QOL, questionnaires focused on the symptoms specific to rhinosinusitis and rhinitis have been developed. One of the most used disease specific questionnaires is the 20-item Sino-nasal outcome test (SNOT-20), which is a modification of the 31-Item Rhinosinusitis Outcome Measure (RSOM-31)[29]. It contains 20 nose, sinus, and general items. In SNOT-22 the previous lack of the important questions related to EP3OS on nasal obstruction and lack of smell and taste have been added. SNOT-22 was used in the largest outcome study made up to now for surgery of patients CRS with and without NP30. Chester and Sandwini reviewed symptom outcome in FESS and reported that that up to then the most frequent used survey instruments were: Chronic Sinusitis Survey (CSS), SNOT-20 and SF-36 of which the two latter are considered as QOL instruments[31].

In 2007 Oene et al published a review article on what disease-specific QOL questionnaire to use in rhinitis and rhinosinusits[32] (Oene 2007). All available QOL questionnaires up to 2007 were graded and the best scoring were the rhinosinusitis questionnaire RSOM-31 and RhinoQOL (a rhinosinusitis specific test that measures symptom frequency, bothersomeness and impact). A validation study on SNOT-22 by Hopkins and colleagues is in press33 (oral correspondence).

Results

Only a minority of the published studies on the effect of FESS are prospective and randomized trials. In addition many studies merge patients with and without NP with varying pre- and postoperative medical treatment, which might result in inconclusive outcome after surgery.
In the EPOS document it is concluded that surgery should be preserved for those patients with CRS±NP who do not

satisfactory respond to medical treatment. In opposition to this Khalil stated in his review report that "FESS as practiced in the included trials has not been demonstrated to confer additional benefit to that obtained by medical treatment".

Below we merely present a small selection of reported outcome studies (additional references can be retrieved from the authors) and we focus on the effect of FESS on CRS with and without NP.

I. CRS without NP

Hopkins et al used SNOT-22, endoscopic grading and Lund-Mackay CT staging as outcome measure in "National Comparative Audit of the Surgery for Nasal Polyps and CRS" including the work of 287 surgeons working in 87 hospitals in England and Wales30 representing the most comprehensive prospective outcome study till now. One third of the 3128 included patients had CRS without nasal polyps. These patients had lower mean CT scores and their mean SNOT-22 scores were slightly higher than the patients with NP. It should be stated that all sorts of sinus surgery were analyzed, but the majority was performed endoscopically.

Giger et al followed 77 patients with CRS without NP with symptom and endoscopy scores during three to nine years after FESS. More than 90% reported symptom improvement of 80% or more[34].

In 2004 there was a retrospective evaluation of 123 patients with CRS without NP who were followed during at least one year[35]. SNOT-20, CT scores and the need of revision surgery were the outcome parameters in this study. There was a 85% improvement of SNOT-20 scores postoperatively after 12 months.

II. CRS with NP

The impact of NP on FESS symptom outcome is unclear[36]. Bhattacharyya in a prospective study concluded that there is no substantial effect of the presence of NP on the degree of symptom improvement postoperatively[37], whereas in the National Comparative Audit it was reported that patients with CRS with NP benefited more from surgery than CRS patients without NP26. In the latter study revision surgery was indicated in 11.8% of the patients at 36 months, however, all putative sinus surgery procedures were considered i.e. not only FESS.

The clinical effectiveness of FESS for CRS with NP was reviewed by Dalziel and colleagues in 2003 reporting three randomized controlled studies comparing FESS with conventional endonasal surgery or Caldwell Luc procedure, three non-randomized studies comparing different surgical techniques and 27 case studies[38]. In summary, patients reported their symptoms to be "improved" or greatly improved" in 75-95%.

Noteworthy is that the extent of polyps could be of importance to the result. In a case series study with 118 CRS pat with particularly extensive NP[39] there was a recurrence of 60% in spite of pre- and postoperative nasal and oral steroids in the majority of the patients. The impact of aspirin-intolerance, asthma, smoking on FESS outcome seem contradicting.

III. Recurrent acute rhinosinusitis

Poetker and colleagues have prospectively compared the effect of FESS in patients with recurrent ARS (RARS) matched with patients with CRS without NP[40]. There were no differences between the two groups when comparing Lund-MacKay CT soring, Lund-Kennedy endoscopy scores or QOL (as measured with CSS and RSDI). Both groups achieved improved QOL postoperatively, but no statistically significant improvement in CT-scores.

IV. Extent of surgery

Extended surgery does not yield better results than limited procedures. Surgical conservatism is recommended. In the National Comparative Audit simple polypectomi had the same effect in terms of HRQOL as polypectomi with additional surgery[26]. No randomized trials comparing different FESS techniques like the use of classic instruments vs. powered instrumentation or FESS with or without navigation device have been published.

Computer Assisted Surgery (CAS) has been developed to help the surgeon to navigate in complicated areas. It is still investigated whether this technical aid leads to better outcome in FESS. American Association of Otolaryngology (AAO) recommends that CAS is used in revision and tumour cases.

V. Revisions surgery

Revision surgery is indicated only if medical treatment is not satisfying after primary surgery. It is known that approximately 10% of primary cases respond insufficiently to FESS with attendant adequate medical therapy41 (prospective study). In both CRS with and without NP the effect of revision surgery is significant but one should be aware of that the risk of complications are higher in revision surgery[1].

Litvack et al stated in an article from 2007 that previous surgery can offer the same success rate on QOL scoring as

primary surgery in patients both with and without NP[42] (prospective study). It should be noted that the criteria of CRS was according to the American Academy of Otorhinolaryngology-Head and Neck Surgery Rhinosinusitis Task Force (RSTF) which is not the same as the EPOS criteria as is it based upon the presence of one major or two minor factors[43] (for definitions see reference).

VI. Postoperative care

Nasal postoperative packing is placed to control or prevent bleeding, but also may be used to prevent adhesions to form. In a review from 2008 Weitzel and Wormald concluded that resorbable packing has no advantage over either no or non-resorbable packing, when the purpose is preventing adhesions. The most effective resorbable packing up to then was Flo-Seal, however this product caused an increase in adhesion formation[44].

FESS in children

We only briefly comment on FESS in children as CRS in children differs from that in adults. Cystic fibrosis (CF) causes frequent and recurrent infections of the airways as well as CRS. There might possibly be time to revaluate the surgically conservative standing point, as it has been shown that there is a poor development of the sinuses in paediatric patients with CF[45]. An interesting question is whether chronic inflammation affects the development of the sinuses, and if so FESS and drainage of the sinuses would affect a normal development of the sinuses.

Discussion

Patients obviously like their surgeons to be technically skilled, up to date and experienced. Assessment of our outcome data is a natural way to provide the patients with knowledge on how much FESS will improve their QOL – their function in life and at work. Further, each surgeon should have an interest in proving her/his skills.

What is relatively new is that society and patients want reassurance that they are offered treatment with the highest quality. Accordingly, we have to be able to present our outcome results, preferably in open national registers. Evidently we then cannot present selected surgical outcome, but the results should be based on consecutive materials.

It has been proved that measuring of QOL is a good indicator on outcome of FESS and subsequently we recommend that a validated QOL questionnaire to be used when performing outcome measure. When treating rhinosinusitis and performing outcome measure in FESS, defined and uniform criteria should be used to facilitate comparison and achieve evidence-based know-how. Together with the surgeon's experience and up-dated knowledge, we suggest that the criteria and recommendations in the EPOS document are used. Further, multi-centre trials with uniform criteria of rhinosinusitis and the indications of surgery are essential. A good example is National Comparative Audit and there is at present an ongoing Swedish multi centre-study, which is to be closed in December 2009. As it has been proved that measuring of QOL is a good indicator on outcome of FESS, we recommend that a validated QOL questionnaire is used when assessing outcome in FESS.

Conclusion

In summary it can be stated that FESS should be considered in CRS only when medical treatment has failed and only in case of clear surgical goals. In many review articles it is concluded that there is lack of good evidence in the literature that FESS is superior to medical treatment. It is our recommendation that validated QOL instruments are used when assessing outcome in FESS.

There is still a place and an urge for randomized controlled trials comparing the outcome of the different medical and surgical FESS techniques or combinations.

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Abstract
With the development and implementation of cochlear implantation it is now possible to restore hearing in the profoundly deaf population. The outcomes following the surgical insertion of a cochlear implant (CI) remain truly remarkable and with the advent of bilateral implantation we are approaching the near restitution of normal hearing abilities in this group. With the recent publication of guidance from the National Institute of Health and Clinical Excellence, there has been an expansion in the availability, within the UK, of the provision of bilateral CIs. This is in light of a growing body of evidence highlighting the improved outcomes, in particular, speech perception in noise and localisation ability gained from bilateral versus unilateral cochlear implantation. However, further work is needed to evaluate the longitudinal functional and quality of life outcomes of the early implanted paediatric population.

Keywords
Paediatric, cochlear implant, bilateral, review

Introduction
Cochlear implantation involves the surgical insertion of an internal receiver and a multi-channel electrode typically into the scala tympani of the cochlear. A CI device processes acoustic information into an electrical signal that is transferred directly to the auditory nerve **(Fig. 1)**. The CI thus facilitates the restoration of hearing in profoundly deafened individuals. As the CI devices have developed from the single channel electrode used in the early 1980's the outcomes have dramatically improved. While a recipient of a single electrode device was able to perceive only environmental sounds the multi-channel users can now perceive speech often in challenging acoustic environments.

Unilateral CI
The benefits of a unilateral CI are remarkable. Profoundly deafened individuals who derived no benefit from

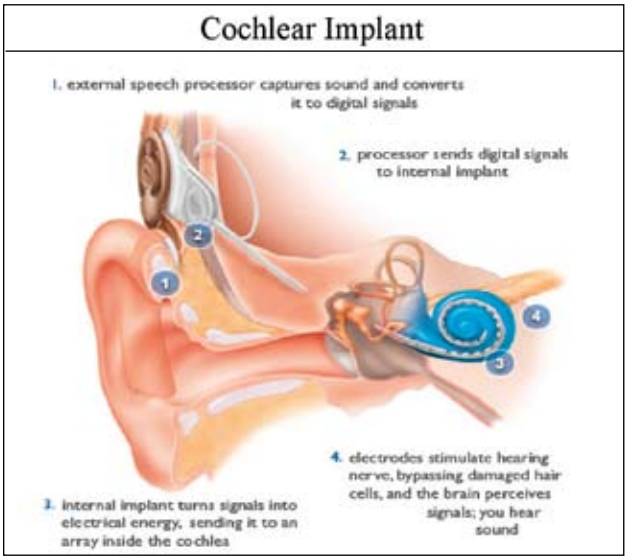

Figure 1: *A cochlear implant device at work.*

traditional acoustical hearing aids can perform effectively in mainstream society. A unilateral adult CI user can achieve open-set speech test scores, in quiet, on average approximately 75% correct, and these patients report significant improvement in their overall quality of life following cochlear implantation[1]. The speech recognition of CI children can reach that of normally hearing, age-matched controls[2] and they have an improved likelihood of developing near-normal or normal verbal and auditory abilities[3]. Although unilateral implantation is remarkable it does not fully restore an individuals hearing ability, in particular, a spatial hearing deficit will remain.

Independent reviews and analysis from the leading cochlear implant manufacturers[4] have illustrated that unilateral CIs are a cost-effective use of NHS resources in the UK[5]. However, up until recently the cost of the second devices has prohibited the provision of bilateral CIs in many healthcare systems including the UK. Profoundly deaf individuals were thus routinely provided with a single CI and were unable to benefit from binaural hearing.

Binaural hearing

Binaural or spatial hearing refers to the abilities gained from listening with two ears. These abilities facilitate the improved perception of speech in background noise and localisation acuity. The auditory performance of a listener in a noisy environment is improved by having an ear with a favourable signal-to-noise ratio (SNR). When a target sound and an interferer are spatially separate the head acts as an acoustic barrier and the perception of the sound can thus be improved by listening with the ear that has the favourable SNR. This is known as the "head shadow" effect. In addition the auditory cortex can centrally process the acoustic information it receives from the two ears. Binaural summation refers to the additive effect of receiving the same stimulus at both ears and binaural squelch or unmasking is the ability to suppress the auditory signal received from the ear with the poorer SNR. Normally hearing listeners use binaural hearing to facilitate improved listening in complex acoustic environments.

Localisation ability allows attention to be directed towards a target noise which is important in accessing additional cues, such as speech reading and can alert a listener to the direction of a potentially harmful source (e.g. traffic). The major cues used for localisation are the relative differences in the time of a sound reaching the ears and the difference in the sound intensity levels. These are known as the interaural time difference (ITD) and interaural level difference (ILD). The dominant cues for normally hearing listeners are the ITDs[6] whereas for bilateral CI users the principal cue is the ILDs[7]. The relative influences of these two cues are dependant on the frequency of the sound. At low frequencies (long wavelengths), the head acting as an acoustic barrier, has less affect on the time the signals reach both ears and ITDs dominate whereas at high frequencies (short wavelengths) the head has more affect in the attenuation of the intensity thus ILDs dominate **(Fig. 2)**.

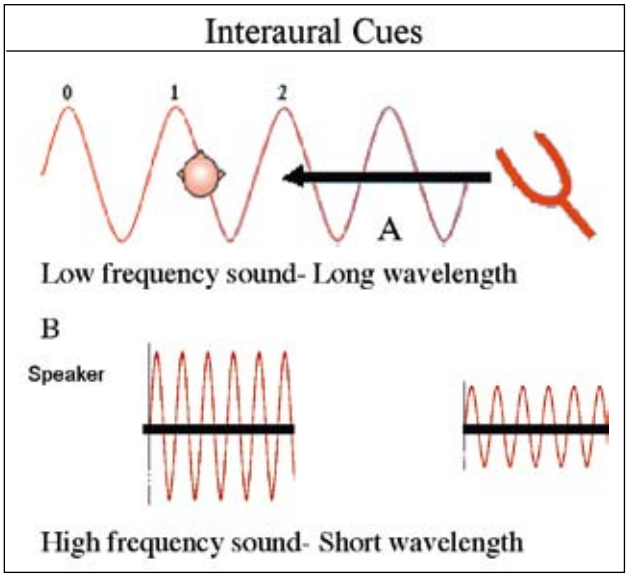

Figure 2: *(A) The dominant role of ITDs at low frequency (B) The dominant role of ILDs at high frequency.*

Bilateral implantation

In the early 1990s bilateral cochlear implantation started to emerge in the adult domain and it appeared that bilateral CI subjects were able to benefit from an improved performance. Ramsden et al[8] presented data from a non-randomised case-controlled study. They examined 30 adult CI users and looked at their speech perception in noise. They used both word (Consonant-Nucleus-Consonant: C-N-C) and sentence tests (City University of New York: CUNY) as the outcome measures and tested the users in their unilateral CI condition prior to receiving their second implant. The same outcome measures where used in the bilateral condition and they found a 21% improvement with the addition of a second implant. Verschuur et al[9] looked at the same population and examined their localisation ability. They found localisation acuity of 24° with the addition of the second device, compared to unilateral performance that was around chance (67°).

Within the paediatric domain there were real concerns about operating on the second ear of these deaf children which may prohibit the use of future technologies or

regenerative options. Although bilateral implantation has lagged behind the adult population, as the advantages are being clearly demonstrated, bilateral devices are now being used with much greater frequency in children. Recent paediatric studies have highlighted the bilateral advantage in both speech perception in noise and localisation ability[10-17]. It appears that the age at implantation in children has a reciprocal relationship to performance on outcome measures[12]. However, the ideal age at which to implant a congenitally deafened child has not yet been determined. With the advent of universal neonatal hearing screening in the UK it has become feasible and preferable, with the early identification of congenitally deafened children, to implant within the first year of life. Implantation on infants before one year of age does have implications particularly with respect to anesthetic risk and the associated morbidity. These risks have to be balanced against the potential advantages e.g. the development of oral language can progress at a greater rate in those children implanted before the age of 4yrs[18]. This evidence is supported and reinforced by electrophysiological studies indicating that a "critical period" exists until 3.5yrs, beyond which cortical maturation fails to achieve normally hearing levels[19].

Bilateral CIs can be simultaneously (during the same operative procedure) or sequentially (during two different procedures) inserted. Many of the studies undertaken on bilateral users include both groups of CI recipients which may have influenced the results obtained. Data recently published has demonstrated the outcomes from an inter-implant delay of >2ys is associated with poorer outcomes although still greater than unilateral implantation alone[20]. The long-term development of auditory performance, particularly in the paediatric population, must also be taken into account as binaural integration has been shown to continue several years after activation[21]. It is therefore conceivable that as bilateral implantation proliferates, the improved outcomes may be more readily seen.

There are additional advantages to bilateral implantation which have yet to be fully demonstrated. The implantation of the better hearing ear, which is difficult to predict preoperatively[22], is ensured; a bilateral implant user has a back-up device should one fail and incidental learning with a greater ease of listening appears to occur. Despite the exclusion of these potential benefits the cost-utility seems to be emerging as favourable in some healthcare systems[23]. However, there remain disadvantages to bilateral implantation and not all patients with a profound hearing loss are suitable candidates. CI recipients occasionally are unable to benefit from using the device either from lack of comprehension or unpleasant sensory innervation. With the decrease in cortical plasticity of the auditory cortex, adults can experience difficulties with the integration of the sensory information from a second device and may fail to realise the potential benefit. In addition the overall length of simultaneous surgery inevitably requires a certain level of cardiovascular performance prohibiting certain individuals and if stem cell regeneration proves effective bilateral CI recipients may be unable to benefit from intervention in a non-implanted ear.

NICE Guidelines

Within the UK healthcare system the National Institute for Clinical Excellence (NICE) have recently published guidance on bilateral cochlear implantation for individuals with profound sensorineural hearing loss (<90dBHL @ 2kHz & 4kHz)[4]. Bilateral simultaneous implantation should be offered to all children and adults with additional sensory deprivation. This is in line with similar position papers published internationally[24]. These guidelines mean that although large numbers of profoundly deafened individuals will benefit from the restitution of binaural hearing, there will remain a sizable cohort who will not, primarily due to financial constraints. At present within the UK, a network of CI programmes is undertaking an audit of bilateral cochlear implantation to evaluate its safety and effectiveness. This will need to be combined with the provision and development of appropriate testing facilities that will elucidate the benefits in real terms. The cochlear implant companies presently offer discounts on the provision of a second aid and market forces may facilitate further cost reductions. These factors may promote a wider encompassing set of guidelines when they are revisited in 2011.

Conclusions

On review of the world literature to date there seems to be compelling evidence demonstrating the advantages of bilateral cochlear implantation over the provision of a single device. The major advantages appear to be an improvement in localisation ability and understanding of speech in noise. Further work is needed to evaluate the ideal age for paediatric bilateral implantation and the longitudinal functional and quality of life outcomes of these early implanted children.

Acknowledgements

We thank the Cochlear™ corporation for the reproduction of "How Nucleus Freedom™ works" **(Figure 1)**.

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Current Concepts in Juvenile Nasopharyngeal Angiofibroma

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ABSTRACT

Juvenile nasopharyngeal angiofibroma (JNA) is a rare vascular tumor occurring almost exclusively in adolescent males. This article reviews the recent relevant literature on the subject, and its impact on the current practice and management of this tumor. A recent interesting hypothesis states that it is a vascular malformation resulting from incomplete regression of the first branchial arch artery. Surgery remains the recommended modality of therapy. Recently there has been a shifting trend towards a less invasive endonasal endoscopic approach. Though associated with a frustratingly high recurrence rate, reducing the tumor volume with an antiandrogen like flutamide, preoperative embolization, careful selection of surgical approaches, meticulous surgical extirpation of the tumor and drilling of the vidian canal helps reduce the incidence of recurrences. Radiotherapy as an alternative modality of treatment is often reserved for advanced unresectable tumor or multiple recurrences.

KEY WORDS

Juvenile Nasopharyngeal Angiofibroma, preoperative preparation, surgery

Introduction

JNA (Juvenile Nasopharyngeal Angiofibroma) has evinced interest from generations of Otolaryngologists and Head-Neck Surgeons, if only for the clinical and intellectual challenges posed by this peculiar tumor. It is rare in the developed world, but is not unusual in our practice at a tertiary care referral centre with a referral base from all of north India and possibly beyond. In the author's practice, in a 2 year period (Jan 2007-December 2008), a total of 26 cases (23 primary and 3 recurrent tumors) have had surgical excision for JNA.

The tumor is histologically benign but may simulate malignancy by its seemingly relentless growth and destructiveness. Its intense vascularity may lead to life threatening epistaxis. The tumor is almost exclusive to adolescent males, though cases have been reported in men over 25 years and in females[1,2,3,4,5]. It accounts for less than 0.05% of all head and neck neoplasms[1,6,7,8]. Though no population prevalence rates are available, the reported incidence ranges from 1 in 9000 to 1 in 50,000 new outpatient clinic visits[9,10].

This review seeks to encapsulate the recent relevant literature on the subject, and its impact on the current practice and management of this tumor.

Pathology and Etiopathogenesis

JNA, though generally found to be well demarcated at surgical excision, is noted on histology to be devoid of a histological capsule. It is composed of a proliferating and irregular vascular component within a collagen rich stroma consisting predominantly of fibroblasts[11,12]. The

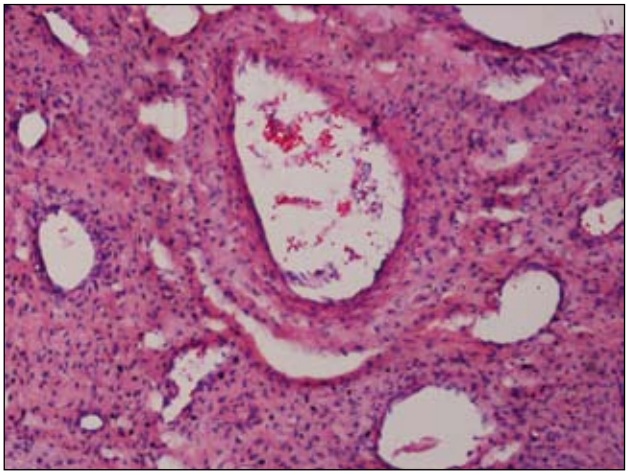


Fig 1- *Microphotograph (H&E, X100) demonstrating the vascular and fibrous components of the tumor and the lack of smooth muscle and elastic fibres in the vascular channels.*

actively proliferating vascular component is superficially located, while the central portion is more fibrous. The lack of smooth muscle and elastic fibres on the vascular channels is said to be the reason for the unremitting bleeding encountered in some patients. **(Fig 1)** As part of its natural evolution, the tumor is believed to progress from an initial predominance of the vascular component, to a subsequent increasing proportion of the fibrous component[2,13].

Many theories have been proposed with regard to the tumor's exact site of origin – current opinion indicates it to originate from the postero-superior margin of the sphenopalatine foramen, or from the contents of the distal vidian canal14. The tumor has previously been proposed to originate from the periosteum of the skull base, the fascia basalis, the cranio-pharyngeal duct, from paraganglionic cell rests, or to be a vascular hamartoma[2,10,15]. A particularly attractive recent hypothesis by Schik[12] postulates JNA to be a vascular malformation resulting from incomplete regression of the first branchial arch artery which connects the internal and external carotid arteries during embryonic development. The internal maxillary and sphenopalatine artery take origin from the first branchial arch artery and this theory explains the tumor location close to the sphenopalatine foramen. This hypothesis is based on the regular detection of Laminin _2, a marker of early embryonal angiogenesis, in the perivascular wall of the tumor[16]; and is also lent credence to by the senior author's observations at surgical excision that the tumor often has a small additional blood supply from an arterial feeder at the mouth of the vidian canal.

The near exclusivity of the tumor to males and its predominance in the adolescent years has pointed towards an obvious hormonal influence. Increased tumor growth with testosterone and a regression with estrogens was noted by workers in the 1950s[17,18,19]. Diethylstilbesterol, an estrogen analogue, was previously used to bring about tumor regression[18,19], but it remains unclear as to whether the effect of estrogen was by a direct action on the tumor, or secondary to feedback inhibition on the pituitary and a consequent decrease in gonadotropin and testosterone levels.

Initial studies looking at hormonal receptors on the tumor may have suffered from technological limitations because of cross reactivity between the different sex-hormone receptors. Current investigations using monoclonal antibody based techniques have demonstrated to the predominant presence of androgen receptors on JNA. These receptors are thermostable and can bind both di-hydrotestosterone (DHT) and testosterone with a higher affinity towards DHT[20,21,22]. Recently, the ER-b Estrogen receptor has also been demonstrated in stromal pericytic and endothelial cells[23]. No alterations in the serum hormonal levels of any of the sex-hormones has however been noted.

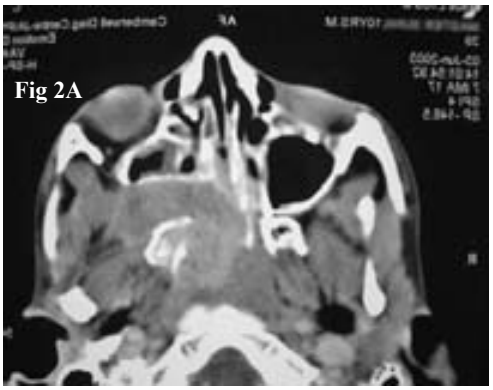
Basic science workers have also found evidence of a role for vascular endothelial growth factor (VEGF), transforming growth factor (TGF _1), basic fibroblast growth factor, platelet derived growth factor (PDGF) and insulin-like growth factors (IGFs) in the growth of these tumors, and it has been suggested that that inhibition of these factors may find a therapeutic role in the future[24].

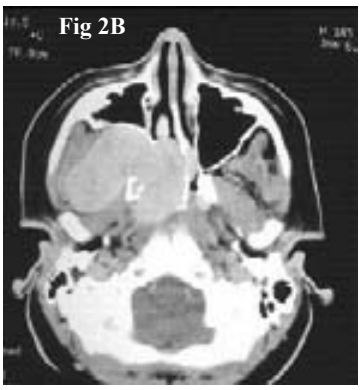
A genetic basis for this tumor is suggested by the association noted between JNA and familial adenomatous polyposis (FAP). It is proposed that alteration of the adenomatous polyposis coli/ _-catenin gene pathway may increase tumor androgen sensitivity[25].

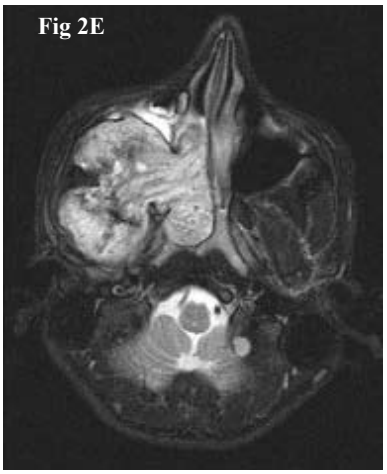
Tumor Extensions and Staging:

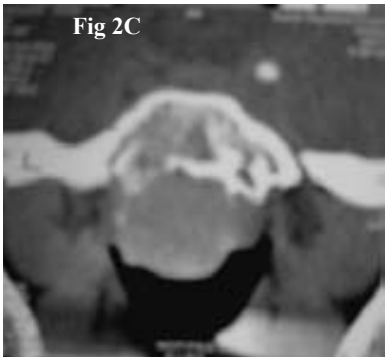
Extra-cranial extensions **(Fig 2a-e)** - The initial origin of this skull base tumor from the vidian canal/ spheno-palatine foramen provides it direct access to the pterygo-maxillary fissure (PMF). The pterygo-maxillary fissure (aka "the Piccadilly Circus of the face") houses a plexus of nerves and vessels and has direct preformed pathways for the traversal of these nerves/ vessels to various sites in the face and skull base. The tumor in the pterygo-maxillary fissure thus extends along the pathways of least resistance by way of these preformed pathways in all directions.

Medial extension is to the nose and sinuses (via the spheno-palatine foramen), superior extension to the orbit (via the inferior orbital fissure), and lateral extension to









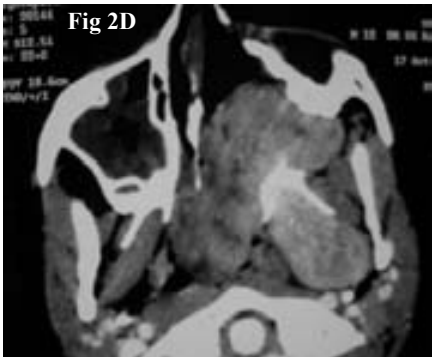


Fig 2: *Extracranial extension of Juvenile Nasopharyngeal Angiofibroma demonstrating anterior bowing of the posterior maxillary wall and erosion of the pterygoid base* **(fig 2a, 2b)**, *erosion of the floor of the sphenoid and extension to the cancellous bone of the clivus* **(fig 2c)**, *extension posterior to the pterygoid plates* **(fig 2d),** *and the typical salt and pepper appearance of the tumor on MR scanning* **(fig 2e).**

the infratemporal fossa[14,26,27] **(Fig 2a, b. Fig 3b)**. Posteriorly, the tumor may expand so as to cause either - a) a simple pressure erosion of the pterygoid base and the vaginal process of the sphenoid **(Fig 2a and b),** or b) extend deeply into the cancellous bone at the base of the pterygoid process via the vidian canal and lead to invasion and expansion of the diploe of the body and the greater wing of the sphenoid[28] **(Fig 3d)**.

The nasal and nasopharyngeal component of the tumor may further expand into the ethmoids and maxillary sinuses. Extension to the sphenoid sinus is either by erosion of its anterior wall or of its floor. The tumor in the nasopharynx is typically attached to its roof and is submucosal, and may extend deeply into the cancellous bone of the clivus **(Fig 2c)**. The nasopharyngeal tumor may also occasionally extend laterally to the pterygoid fossa behind the pterygoid plates **(Fig 2d)**. This particular extension, though unusual, is as per the authors' experience important to identify prior to surgical treatment, as it is one of the sites that is not directly accessible by the usual anterior surgical approaches (nasal endoscopic / midfacial degloving) and so remains a relatively common site for recurrent/ residual tumors.

Intracranial extension **(fig 3a-d)** - The continual improvements in sectional imaging have demonstrated that intracranial extensions are much more common than initially believed, and reported in as many as 10-30% of cases[29,30]. Such extension is always extradural, with the dura being typically in direct contact with the tumor but not being invaded[31,32,33]. Intradural extension has only been reported in isolated instances.

Extension intracranially is typically by one of the following 3 routes:

a) Expansion of the ethmo-sphenoidal tumor so as to erode the fovea ethmoidalis, cribriform plate, planum sphenoidale and the lateral wall of sphenoid. The latter erosion places the tumor medial to, and in direct contact with the cavernous sinus **(Fig 3a)**.

b) Expansion of the superior orbital fissure- Tumor from the pterygo-maxillary fissure accesses the posterior orbit and then passes posteriorly through the superior orbital fissure so as to reach lateral to the cavernous sinus and adjacent to the internal carotid artery. This is the commonest mode of intracranial extension **(Fig 3b and 3c)**.

c) Extension through the cancellous bone at the base of the pterygoid process surrounding the vidian canal leading to invasion and expansion of the diploe of the body and the greater wing of the sphenoid **(Fig 3d)**. Such extension reaches up to the foramen lacerum, the ICA, and the cavernous sinus (inferior invasion). Such tumors demonstrate no pseudocapsule at surgery, are infiltrative in character, and may lead to significant intra-operative blood loss.

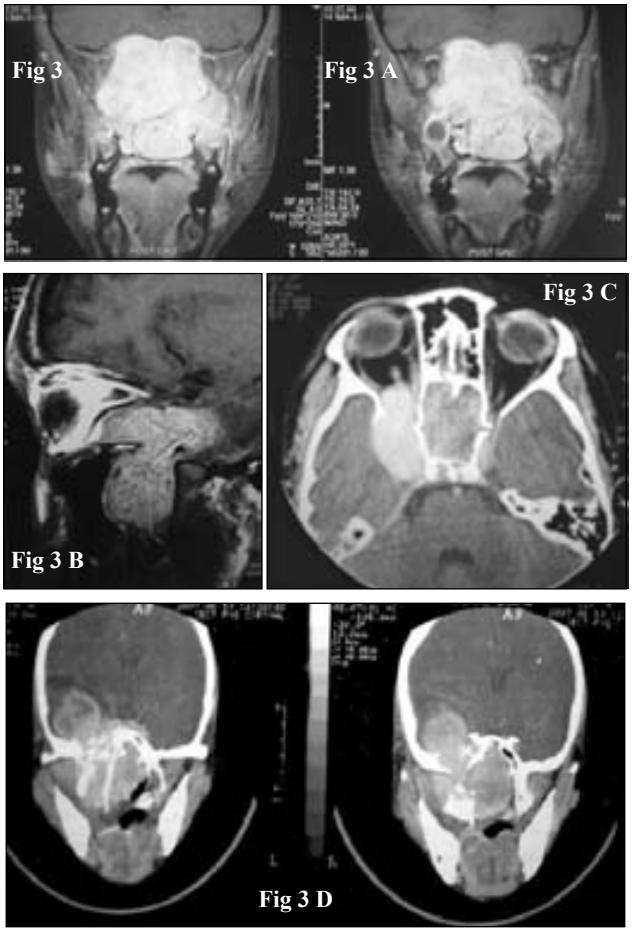


Fig 3 - *Intracranial extension of Juvenile Nasopharyngeal Angiofibroma demonstrating the three usual routes of intracranial extension.*
Fig 3a – *Tumor in the ethmosphenoid causing erosion of the skull base and tumor extension medial to the cavernous sinus.*
Fig 3b and 3c – *Illustrating tumor extension from the orbit to the Middle cranial fossa via an expanded superior orbital fissure.*
Fig 3d – *Tumor infiltration into the diploe of the sphenoid bone with erosion and extension to the middle cranial fossa.*

Staging

Many staging systems have been proposed, including the ones by Fisch et al.[34], Chandler et al.[9], Session et al.[35], Tandon et al.[10], and Andrew et al[36]. In current times, the Radkowski classification (1996, **Table 1**)[11] is the most widely used and accepted. This classification is reported to reflect the incremental rise in tumor recurrence observed at progressively higher levels of skull base/intracranial involvement[33].

All classifications (including the Radkowski classification) fail to take into account the current concept of the tumor's origin from the pterygo-maxillary fissure. Current radiologic techniques, and the improved visualization at surgery, have demonstrated to us the universal involvement of the medial pterygo-maxillary fissure in all cases. Stage I as described **(Table 1)** is never encountered, and it may be appropriate for the classification to be appropriately modified so as to include pterygo-maxillary fossa involvement in all stages.

Clinical features and Diagnostic assessment

The diagnosis of JNA is to be strongly suspected in any adolescent male with epistaxis, nasal obstruction and the presence of a pink non-ulcerated mass in the nose or nasopharynx with or without facial deformity. Proptosis secondary to orbital extension is not unusual, and visual loss caused by optic nerve compression is occasionally noted. Intracranial extension is usually silent.

Pre-treatment histological confirmation by a biopsy runs the risk of precipitating severe hemorrhage and is not routinely undertaken. Initial diagnosis is based on radiology, which demonstrates the characteristic radiological features of an expansile and enhancing mass occupying the posterior nose and nasopharynx with extension to the pterygo-maxillary fissure. Further extensions as described in the previous section on tumor extension corroborate the diagnosis.

Table 1: Staging System for JNA as proposed by Radkowski, 1996.

Stage I	IA: Tumor limited to posterior nares and/or nasopharyngeal vault IB: Tumor involving the posterior nares and/or nasopharyngeal vault with involvement of at least 1 paranasal sinus
Stage II	IIA: Minimal lateral extension into the pterygo-maxillary fossa IIB: Full occupation of the pterygo-maxillary fossa with or without superior erosion of the orbital bones IIC: Extension into the infratemporal fossa or extension posterior to the pterygoid plates
Stage III	IIIA: Erosion of the base of skull (middle cranial fossa/base of pterygoids)-minimal intracranial extension IIIB: Extensive intracranial extension with or without extension into the cavernous sinus

CT and MR scanning provide complimentary information. CT scanning is initially preferred as it depicts the bony anatomy and is less prone to motion artifact[10]. Characteristic CT signs which are considered confirmatory of the diagnosis include:

a) Anterior bowing of the posterior maxillary wall (Holman-Miller sign[37]) **(Fig 2a,b)**
b) Erosion of the floor of the sphenoid sinus, and contiguous tumor extending from the nasopharynx to the sphenoid sinus **(fig 2c)**.
c) Erosion of the base of the pterygoid plate **(Fig 2a,b)**.
d) Characteristic tumor distribution with a lobulated, enhancing, and well demarcated tumor involving the infra temporal fossa and expanding through the inferior orbital fissure, posterior orbit, and superior orbital fissure **(Fig 2b,3b,3c)**.

MR scanning displays the characteristic "salt and pepper" appearance of the tumor, and intense enhancement with gadolinium **(Fig 2e and 3b).** The "salt and pepper" appearance is consequent to the multiple flow voids caused by vascular channels in the tumor. MR is considered essential in cases with intracranial extension as it better defines the soft tissue interfaces, elucidating the question of whether the tumor is intradural or extradural, and offer better insight into the relationship with major vessels[38,39]. Preoperative angiography is helpful in evaluating the arterial supply to the tumor. Prior to the advent of sectional imaging it was the essential and diagnostic test to confirm the diagnosis, but is no longer considered necessary for this purpose. It is however frequently undertaken in the immediate pre-operative period as a precursor to pre-operative embolization. The predominant vascular supply is from the internal maxillary artery as seen in 95-100% cases[40,41]. This is typically from the ipsilateral vessel, but as many as 69% may receive supply from bilateral internal maxillary arteries[42]. Other contributions may be from the ascending pharyngeal artery, accessory meningeal artery and facial artery (6.6%). The internal carotid artery may also contribute in a significant proportion of cases.

Treatment

Though natural regression of the tumor has been documented[43,44,45], this is most unusual and very rarely complete, and cannot be relied on as a therapeutic option in any significant tumor with the potential to cause life threatening hemorrhage. The therapeutic options are therefore limited to surgical excision and radiation therapy. The application of radiation therapy for a benign tumor in young children raises natural concerns, and is therefore best reserved for cases considered inoperable or wherein surgery is considered to have unacceptable risks and morbidity. With the improvements in pre-surgical assessment as by imaging, and further improvements in surgical approaches and techniques, the proportion of patients wherein surgery is considered inadvisable is definitely shrinking.

Surgical excision therefore remains the prime and only treatment modality for all except the rare and exceptional case.

Surgical treatment

Irrespective of the extent of disease, certain principles are universally applicable to all cases wherein surgery is undertaken. These are divided into pre-surgical and surgical maneuvers and are listed in **Table 2**. These principles are part of the routine clinical practice of the authors.

Pre surgical preparation

a) Anti- androgen therapy

Laboratory experiments have demonstrated that the growth rate of JNA tumor fibroblasts increased when testosterone was added to the culture media, whereas the addition of the anti-androgens cyproterone acetate and flutamide led to a reduced growth rate[22]. Flutamide (2-Methyl-n-[4-nitro-3{trifluoromethyl}phenyl] propanamide), is an orally active non-steroidal androgen antagonist (NSAA). Unlike the previously used di-ethyl stilbesterol, flutamide is a pure anti-androgen compound, and therefore causes no suppression of gonadotropin or testosterone levels.46 The loss of libido and sexual potency noted with the previous therapies, and any temporary feminizing effects are therefore significantly mitigated[46].

Clinical literature regarding the use of Flutamide in JNA is sparse and limited to 2 studies and 11 cases. Conflicting results are reported with Gates et al[47] observing an average

Table 2: Therapeutic principles applicable to all cases undergoing surgical treatment of JNA

Pre-surgical
• Anti- androgen therapy / Flutamide
• Embolization
Surgical
• Adequate exposure
• Surgical control of vascular supply
• Lateral to medial dissection
• Measures to minimize residual tumor/ prevent recurrence

tumor reduction of 44% in 4 of 5 cases receiving a 6 week treatment course, and Labra et al[48] noting a maximum tumor reduction of only 11.1% in 6 cases receiving a 3 week treatment course. The authors own experience with a 6 week treatment course (10 mg/kg in 3 divided doses, oral) within an ongoing clinical trial has been most encouraging in the post-pubertal patients but disappointing in the pre-pubertal patients. On current evidence, the authors advocate a 6 week course of flutamide as adjuvant therapy in the post-pubertal patient, so as to bring about pre-surgical volume shrinkage and facilitate surgical excision.

b) Embolization

Embolization undertaken immediately prior to surgery (24-48hrs) decreases tumor vascularity and facilitates tumor excision. A concern has however been voiced that embolization may lead to increased recurrences[14,28,49] in situations wherein the cancellous bone is invaded, as it may lead to the shrinkage of tumor into the inaccessible bone and thus lead to greater residual disease[14]. The general consensus however would be that the benefit of a clearer surgical field consequent to embolization is far more likely to ensure a complete surgical excision[50], and the concern of embolization facilitating recurrent disease may prove insignificant.

Surgical principles for JNA

The essential steps in the execution of the surgical procedure for excision of JNA are as below:

a) Adequate surgical exposure / selection of the appropriate surgical approach

It remains paramount that adequate surgical exposure be achieved prior to any attempt at tumor removal. It is reiterated that the tumor though seemingly well demarcated at surgical exploration, has no histological capsule, and some of the previously prevalent surgical approaches entailing blind dissection may lead to residual disease.

The approaches as currently preferred by the authors include the endoscopic approach, the midfacial degloving approach, lateral rhinotomy with lip split, maxillary swing and the preauricular subtemporal- infratemporal approach (Fisch type D approach). **Table 3** lists the general selection criteria for these approaches. It needs to be noted however, that significant difference of opinion may exist between individual surgeons and the choice of procedures may vary in different centres.

The current literature indicates of an increasing shift towards the endoscopic endonasal procedures[32,38,40,41,49]. It has been expressed that open approaches with removal of bone from the midface may lead to interference with the growth of the facial skeleton[38], but such concerns may have been overemphasized[51] and the application of an open procedure is certainly justified if it facilitates a better and more complete excision of the tumor. Open approaches such as the midfacial degloving approach[52,53] and the lateral sub-temporal infratemporal approach[34,54] are especially attractive as they do not leave an obvious facial scar and further facilitate a two handed and safe dissection wherein the subsequent surgical steps as enumerated are easily undertaken.

Table 3: Suggested surgical approaches for variously staged JNA.

Radkowski Stage I, IIA, IIB	• Endonasal Endoscopic Approach. • Midfacial degloving approach- may be appropriate for cases with significant anterior nasal extension, or with invasion of the cancellous bone of the pterygoid base or clivus.
Radkowski Stage IIC- infratemporal fossa extension	• Midfacial degloving approach • lateral rhinotomy approach sometimes appropriate for cases with significant dural exposure or massive lateral extension
Radkowski Stage IIC- pterygoid fossa extension	• Midfacial degoving / lateral rhinotomy with removal of pterygoid plates • Lateral subtemporal-infratemporal approach without temporal craniotomy
Radkowski Stage IIIA, IIIB with tumor medial to cavernous sinus	• Facial translocation / Maxillary Swing approach (ipsilateral maxillary swing or contralateral naso-maxillary swing)
Radkowski Stage IIIB with tumor extension via superior orbital fissure or invasion of sphenoid bone, tumor lateral to cavernous sinus	• Lateral subtemporal-infratemporal approach with temporal craniotomy (Fisch Type D Approach) - May need to be supplemented with an anterior approach (usually endoscopic) for tumor in the nose and sphenoid.

b) Control of the vascular supply

The internal maxillary artery which is the main feeder to the tumor is routinely identified and ligated prior to any attempt at tumor excision. The artery can be easily identified lateral to the pterygomaxillary fissure but is

often posterior to the tumor in the infratemporal fossa. When using an anterior approach, this component of the tumor may therefore need to be mobilized prior to identification of the vessel.

c) Lateral to medial dissection

As opposed to the tumor attachments which are routinely identified to the base of the pterygoid process and the opening of the vidian canal, and also secondary adhesions which may form between the tumor and the nasal mucosa, the lateral tumor has few attachments in the infratemporal fossa and is easily mobilized. The only usual lateral attachment is the attachment to the internal maxillary artery and this is routinely ligated in the preceding step. Lateral to medial dissection allows for a controlled and improved exposure of the medial attachments of the tumor.

d) Attention to microscopic residual tumor / Prevention of recurrence

The principal cause of post surgical recurrence is incomplete tumor excision. The previous literature has documented a high rate of recurrence ranging from 20 to 50%[7,14,11]. The trans-palatal approach- possibly because of its inappropriate application to extensive tumors unidentified in the pre-CT scanning era - has been associated with a recurrent rate as high as 75%[11,49]. Appropriate and adequate surgical exposure is therefore the prime intervention to decrease recurrence rates.

The recent understanding of the tumor's site of origin from the vidian canal/ base of pterygoid plate has directed specific attention to this area. Lloyd et al[28] indicated that invasion of the sphenoid is the main predictor of recurrence. Meticulous removal of tumor infiltrating the pterygoid canal and basisphenoid, is achieved by drilling these areas[55,40] subsequent to a presumably complete tumor excision, may decrease recurrence rates. Such drilling may remove microscopic residual disease, and seems prudent for all cases.

Radiotherapy for JNA

Radiation therapy in a dose of 36-40 Gy aims to bring about local tumor control and not necessarily complete regression of the tumor. Reported local control rates after RT range from 43% to 100%[56-60]. The final impact of radiation may not be noted till 24-30 months after its administration.61 The largest series of patients with JNA treated with primary external beam radiation has been reported by Cummings et al[58] (55 cases) with an initial local control rate of 80%.

The long term complications reported include the development of malignant tumors (orbital squamous cell carcinoma, basal cell carcinoma, thyroid carcinoma, fibrosarcoma and other sarcomas), orbital complications (cataract, posterior capsular opacification, optic nerve atrophy), panhypopituitarism and growth retardation, temporal lobe necrosis, radiation osteoradionecrosis and osteomyelitis[57]. The advent of conformal radiation therapy and IMRT may limit these complications[59,60].

Considering the potential long-term risks of radiation therapy, most workers discourage its use even for cases with intracranial extension, and restrict it to advanced unresectable tumor or multiple recurrences.

CONCLUSION

Juvenile nasopharyngeal angiofibroma (JNA) poses a treatment challenge to surgeons, owing to its high vascularity, local invasiveness and high recurrence rates following surgery. Though "watchful waiting" and radiation therapy may be appropriate in a very small minority of cases, surgical excision is the prime therapeutic modality for almost all cases.

The principles of pre-surgical preparation and surgical execution as listed above have the potential to improve outcomes and decrease recurrence rates following surgical therapy.

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Pediatric Drooling

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Introduction

Drooling or sialorrhea, is defined as the dribbling or leakage of saliva out of the mouth. Although drooling may be a symptom of acute illnesses such as tonsillitis or peritonsillar abscess, the focus of this article will be the evaluation and management of chronic sialorrhea. There are many medical as well as social issues which arise from chronic drooling. This burdensome pathology can be immensely frustrating for parents, who may have to spend hours a day dealing with the sequelae. Furthermore, in those less common instances when it occurs in children without intellectual impairment, psychologic distress related to the awkwardness of social interaction and self confidence can ensue. The management of these patients is best achieved in a multidisciplinary setting based on complete clinical and social evaluation of these patients. Treatment needs to be tailored based on the age, severity, associated comorbidities,

Salivary Physiology

Daily average salivary flow is in the range of 1-1.5 L (or about 1 mL/min)[2]. 71% of total saliva for a 24 hour period is produced by the submandibular gland, with 25% and 3-4% produced by the parotid and sublingual glands respectively[3].

It is thought that because of this higher basal rate and the location of the Wharton's ducts anteriorly in the mouth that the submandibular glands may be the primary culprit in most chronic drooling patients. The parotid gland, however, is the driving force in stimulated saliva production and flow rates can reach as high as 7mL/min[3]. Salivary flow can be influenced by many factors, including circadian rhythm (decreased flow at night), psychologic factors such as pain or depression, hormones, exercise, stress, local or systemic diseases, or medications[4-7].

Salivary secretion is controlled by both the parasympathetic (PNS) and sympathetic (SNS) nervous systems. But parasympathetic innervation is the principal catalyst for the higher volume, lower protein secretions which predominate and contribute to the pathology of drooling. The primary neurotransmitter of the PNS is acetylcholine, and is the most common target of medical treatments of chronic sialorrhea.

Pathophysiology of Drooling

Pathologically, drooling occurs from either the overproduction of saliva or because of difficulty handling/clearing a normal quantity of saliva. Some degree of drooling is normal in younger children, and is often found when children are teething. Salivary overproduction is a relatively uncommon cause of sialorrhea. Common causes in children are medication and toxin induced. Other common causes of oversecretion include gastroesophageal reflux disease, liver disease, pancreatitis, and oral ulcers and infections.

Decreased clearance of normal saliva, not hypersecretion, is the most common cause of drooling in children. The overwhelming majority of these children have some underlying neuromuscular dysfunction. The most common neurologic disorder in the pediatric population is cerebral palsy. Cerebral palsy represents a spectrum of nonprogressive neuromuscular dysfunctions that most commonly occur during pregnancy or childbirth. Its incidence is approximately 2-2.5 per 1000 live births and as high as 30-35% of patients with cerebral palsy will manifest drooling as part of their disease[8,9].

Management

A multidisciplinary approach is generally recommended, with the otolaryngologist or pediatrician as the lead[10]. Obtaining a history from the parent or caregiver is perhaps the most critical step in the evaluation of the drooling patient. This is because the effect on quality of life of both the patient and parent will often dictate the aggressiveness of treatment. Specific questions regarding the amount of drooling, including number of bibs soiled, frequency of clothing changes, concomitant skin problems, and contamination of other instruments and devices allow the otolaryngologist to get an objective idea of the severity of

the problem. A detailed medical and medication history as well as questions regarding potential toxin exposure may identify easily reversible sources of the sialorrhea. As usual, a complete head and neck physical exam is performed, but special attention should be paid to head position and movement, the viscosity of the sialorrhea, dental occlusion and condition of the teeth and gums, as well as tongue size and mobility. Any tonsillar hypertrophy that may be physically obstructing normal swallowing should also be assessed.

Speech pathology assessment allows evaluation of oromotor function, as well as recommendation of motor control remediation exercises. Dental involvement allows further assessment of the teeth and gums and Craniofacial Plastic Surgery involvement can be considered if bony anatomic abnormalities are encountered. Pulmonology consultation allows assessment of lung function, particularly in those children with associated chronic aspiration. Neurology evaluation is also considered in those children with dynamic/progressive neuromuscular problems to better gauge the course and stability of disease.

Radiologic evaluation may be necessary when there is suspicion of aspiration. In a cooperative patient, a modified barium "cookie" swallow or functional endoscopic evaluation of swallowing (FEES) is the recommended test of choice to assess swallowing function, allowing different food consistencies to be evaluated and giving a good picture of overall oromotor and swallowing function. A large segment of these patients, however, will not be candidates for this exam as they are unable to cooperate. In these patients, a nuclear medicine salivagram can be performed. A radionuclide tracer is placed in the mouth of a supine patient and the patient is watched over a 2 hour period of time. Evidence of tracer within the lung fields confirms aspiration. One disadvantage is that tracheal penetration without frank pulmonary aspiration cannot be assessed with this study.

Once a complete evaluation has been performed, the decision to treat is discussed. First it must be decided if the patient requires treatment. Those patients with only mild to moderate symptoms, particularly younger, neurologically normal children may "outgrow" their drooling by early school age. Patients with more "acute" sialorrhea associated with trauma or tumor may improve clinically rapidly after treatment and not require intervention. Treatment options should be discussed at length with parents, particularly when pharmacologic or surgical options are considered.
All underlying reversible causes of sialorrhea should be addressed. A complete list of the patient's medications as well as toxin exposures should be obtained for possible causality. Severe reflux if present should be controlled. Treatment of dental caries, gingivitis and other disease is required. Adenoid hypertrophy can lead to mouth breathing and drooling; more rarely, tonsillar hypertrophy can impede swallowing. Unfortunately, addressing these entities collectively will only improve about 10% of patients[11]. When these factors are corrected and further intervention is still required, it will fall into one of four basic categories: oral motor training, biofeedback, pharmacotherapy, and surgery.

Treatment

Oral Motor Therapy

Oral motor therapy is considered the first line therapy for sialorrhea in patients who have had other situational factors controlled. A speech and language pathologist or physical therapist will usually perform these interventions, which focus on assisted movement, movement against resistance, and stretch reflexes of the lips, cheek, tongue and jaw. The focus is to increase the functional response to pressure, range, strength, and control of movement for tasks such as lip closure, tongue mobility, and jaw elevation. This will ideally increase swallowing as well. It is widely recommended that at least six months of oral motor therapy, including daily maintenance therapy performed by parents, should be performed before other therapies are considered[10]. In those patients with severe neuromuscular and cognitive dysfunction, however, oral motor therapy is much less successful because some level of compliance is usually necessary for full benefit. Knowing that most drooling pediatric patients will fall into this category makes this a much less practical option, and in one large pediatric study, it was a primary management recommendation in only 1-2% of patients[10]. A newer technology of transcutaneous electrical stimulation (VitalStim) to cervical muscles has shown some promise in sialorrhea/dysphagia in adult patients in limited studies, but data in the pediatric population has yet to be published[12].

Biofeedback

Biofeedback is another noninvasive treatment option that uses a repeated auditory stimulus in an attempt to condition the patient to swallow more frequently. In limited published work, it has been shown to significantly decrease drooling[13]. After completion of the training, the patient will wear a device with headphones that emits a sound about every 30 seconds, triggering the swallow mechanism. There are, however, many drawbacks to this therapy. First, it is very time consuming and labor intensive for patients and caregivers. Long term results are also suboptimal related to failure to wear the device and acclimation to the

sound. Finally and perhaps most importantly, is the very narrow patient population that qualifies for this treatment. Only those patients with normal intelligence and of sufficient age (usually eight years old) in conjunction with motivated parents meet the criteria.

Systemic Pharmacotherapy

Anticholinergic medications have been the most commonly used pharmacotherapy to control sialorrhea, this includes glycopyrrolate, scopolamine, benztropine, and benzhexol hydrochloride. Systemic side effects are very common, these include urinary retention, tachycardia, headache, blurred vision, constipation, and excitation. Glycopyrrolate has repeatedly been proven to significantly decrease drooling, but the rate of adverse effects ranges from 40-70% with 20-30% of subjects withdrawing secondary to these adverse effects[14,15]. Transdermal scopolamine has also been shown to be effective and has the advantage of only needing to be placed every 3 days[16], however, because it is another systemic anticholinergic, long term side effects are still significant[17]. Antireflux therapy has also been used in sialorrhea, but a randomized controlled trial with ranitidine showed no difference when compared with placebo[18]. More recently, modafinil, a psychostimulant used to treat spasticity in cerebral palsy patients, was shown to have beneficial effects on drooling found incidentally in two patients[19]. These two cases are the only published reports and further study in certainly needed before any conclusions can be drawn.

Botulinum Toxin

Several studies have shown a reduction in sialorrhea in children with cerebral palsy with injection into either the parotid glands, the submandibular glands, or both[24-26]. It appears that the peak effect occurs between about 2-6 weeks after injection, and then begin to wear off, although the length of benefit appears to be variable in each particular child[17]. There has been very little agreement or standardization regarding the dosage into each salivary gland, with different studies using between 10-30 U in each submandibular gland and 15-40 U in each parotid gland[17,25,26]. Injections generally are performed at 2 sites per gland. The side effects that have been reported in the literature include temporary difficulty swallowing, neck pain, diarrhea, and altered gait[17]. Reduction of adverse effects is thought to be possible by using ultrasound guidance of the needle in each gland[24,27]. In a controlled trial comparing botulinum with an oral anticholinergic agent, there was a similar reduction in drooling (49-53%), but nearly _ of patients on the anticholinergic developed systemic side effects, compared with only temporary local side effects in 5% of the botulinum group[17]. Furthermore, there may be atrophy of the salivary glands with repeated injections which theoretically could lead to much longer injection intervals. This will need to be proven with better long term controlled data.

Surgical Treatment

Surgical therapy is generally deferred until at least 5-6 years of age. In cases of recurrent and chronic pneumonitis from chronic aspiration, however, surgery is considered at much younger ages. Most surgical candidates will have profuse drooling and neurologic impairment to a degree that precludes compliance with nonsurgical therapy. Pharmacologic failure is not a prerequisite, but many patients who present to an otolaryngologist for drooling will have failed oral anticholinergic therapy in the past, most commonly secondary to the side effects.

When classifying surgeries aimed at controlling sialorrhea, there are two broad categories: those that decrease the overall amount of saliva produced (tympanic neurectomy, submandibular gland excision, submandibular and parotid duct ligation) and those that redirect salivary flow more posteriorly so it is more readily swallowed (submandibular duct relocation, parotid duct relocation)[29].

Tympanic Neurectomy

This procedure has largely been abandoned in the treatment of drooling, as within 6 months most patients will have sialorrhea return to preoperative levels.

Submandibular Gland Excision and Submandibular/Parotid Duct Ligation

Bilateral external submandibular gland excision with or without parotid duct ligation is the most common flow reducing procedure for sialorrhea. A review of nearly one hundred children showed significant improvement in 65% of patients at an average follow up of over 4 years[29]. The complication rate was 13%, most of which were related to xerostomia and dental caries. Other potential complications include marginal mandibular, hypoglossal, and lingual nerve injury, as well as hematoma. It also requires a hospital stay and leaves external neck scars. Some authors argue that parotid duct ligation is unnecessary in most cases as basal saliva is produced primarily by the submandibular gland: the Drooling Control Clinic in Toronto reported that only 5% of patients needed parotid duct ligation secondary to persistent drooling after submandibular duct relocation[10].

Submandibular duct ligation, instead of gland excision, has recently been described[31]. This technique eliminates many of the complications and morbidity of open excision of the submandibular glands, in addition to decreasing operative time. Functional atrophy of the gland is thought to be the physiologic basis for the success of this

procedure. In the aforementioned review of 5 patients, there was substantial improvement with a median follow up of 13 months, with only temporary postoperative neck swelling described[31]. No cases of xerostomia were observed. Ranula formation, although not described in this study, is a possible risk and larger long term data will be needed to address this.

Intraoral submandibular gland excision has also recently been published as an alternative to open excision[32]. A review of 77 patients, mainly adults with sialadenitis, who underwent this technique showed good long term results without external neck scar or risk of marginal mandibular nerve injury. There was a high incidence of decreased tongue mobility (70%) and lingual nerve paresis (74%) but these complications were temporary in all cases, resolving by 6 weeks without intervention. One disadvantage to this technique is the more difficult surgical dissection when compared to an external approach.

Parotid Duct Relocation

This procedure has been largely abandoned, particularly given the lower morbidity and decreased operative time of ductal ligation.

Submandibular Duct Relocation/Sublingual Gland Excision

Submandibular duct relocation was first described in 1969 and has been the workhorse in saliva-diverting procedures for the past 30 years. This procedure involves creating a mucosal island with an oval incision around both ductal papillae. The ducts are then identified and dissected back to the level of the submandibular gland. The mucosal islands are then separated and each duct with its own papilla is brought posteriorly submucosally and sutured in place in the ipsilateral tonsillar fossa. This is often performed in conjunction with tonsillectomy, particularly in cases of tonsillar hypertrophy or those with deep debris-filled crypts. This procedure was reported with excellent results and little morbidity from two large drooling centers, but ranula formation necessitating sublingual gland excision occurred in 8-13% of cases[34,35]. In an effort to eliminate ranula formation, sublingual gland excision was added to ductal relocation in the late 1980's[34]. Long term data showed control of drooling in 2/3 of patients at 5 years with no postoperative ranulae noted[28]. A complication rate of about 10% has been reported, including airway obstruction secondary to tongue swelling, lingual nerve injury, abscess, and aspiration pneumonia.

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Auditory brainstem implantation: indications and outcomes

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Introduction

The last two decades have witnessed a transformation in the management of hearing loss through the utilisation of auditory prostheses. Cochlear implantation is an established healthcare intervention in selected children and adults with severe to profound sensory deafness and middle ear implants are being increasingly utilised in individuals with sensory, mixed and conductive hearing loss. Both types of device rely upon a functioning auditory nerve. In a small group of individuals however the auditory nerve function is compromised or the cochlear anatomy or architecture precludes cochlear implantation. In such patients, the auditory brainstem implant may be indicated and this article describes the utility of this particular intervention.

The auditory brainstem implant

The auditory brainstem implant (ABI) is essentially the same as a cochlear implant in that there are two components: the implanted hardware and the external components **(figure 1)**. The difference lies in the implanted active electrode array which is designed to be inserted into the brainstem via the lateral recess of the fourth ventricle (foramen of Luschka) in order to stimulate the dorsal and ventral cochlear nuclei. To this end, unlike the linear electrode array of a cochlear implant, the stimulating contacts of the ABI are housed on a flattened paddle. The remaining internal components of the (receiver-stimulator package and reference electrode) as well as the external components (microphone and speech processor) are similar to a cochlear implant.

Indications

Broadly speaking, individuals receiving an ABI fall into 2 groups: Those with neurofibromatosis type 2 (NF2) and the non- NF2 group. The former are predominantly older children and adults whilst the latter represent an emergent group of children with congenital deafness or children and adults with acquired disorders that preclude cochlear implantation. Both groups are considered in more detail.

The neurofibromatosis type 2 group

This familial disorder is characterised by autosomal dominant inheritance, high penetrance and variable expression. The hallmark of NF2 is bilateral vestibular schwannomas **(figure 2)** but the additional tumour load may include other cranial nerve schwannomas, meningiomas and spinal tumours. The non-tumour manifestations include ocular lens opacities, skin lesions

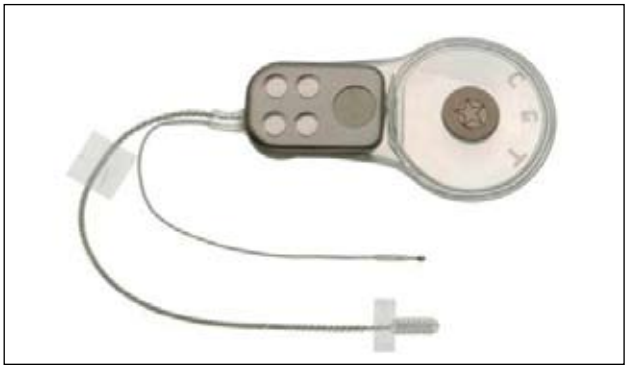

Figure 1: *Implanted component of the auditory brainstem implant.*

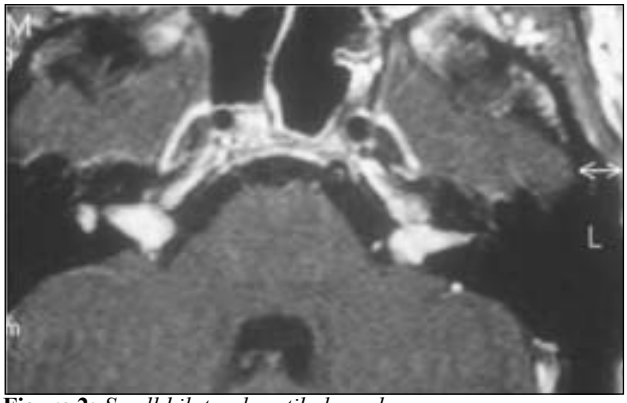

Figure 2: *Small bilateral vestibular schwannomas.*

and mono/polyneuropathies. Whilst the phenotype may therefore differ significantly from patient to patient, the spectre of total deafness hangs over affected individuals, either as a consequence of the vestibular schwannomas themselves or surgery to remove them **(figure 3)**. The management of the individual with NF2 may be complex and require considered input from the multidisciplinary team that should be looking after such patients. The over-riding principle however is to avoid producing additional neurological deficit. Factors such as disease phenotype, previous surgery or radiotherapy, the tumour and hearing status of the opposite ear and the demands of auditory rehabilitation need to be carefully considered. The conservative approach, adopted by many NF2 teams, particularly in the UK and mainland Europe means that the vestibular schwannomas tend to be removed if there is sustained growth of the tumour and concern around impending neurological effects. It is generally accepted that the most appropriate time to insert an ABI is at the time of tumour removal, particularly if the tumour resection is going to render the patient bilaterally profoundly deaf. In addition, even if there is good or aidable hearing in the opposite ear, the ABI can be inserted as a "sleeper" whereby the device serves to maintain electrical input to the deafened side in readiness for the eventuality that the patient becomes deaf on the opposite side as a consequence of the natural history of the disease or subsequent contralateral tumour removal. Clearly the decision to offer the patient an ABI, the counselling process, the surgery and post-operative care and the rehabilitation requires the skills of a team that is well versed not only in lateral skullbase surgery but also implantation otology.

The non-NF2 group

As the global experience of the ABI in NF2 has increased and the outcomes disseminated, in recent years consideration has been given to the utilisation of this device in individuals with bilateral severe or profound hearing loss in whom a cochlear implant cannot be used. Such individuals can be

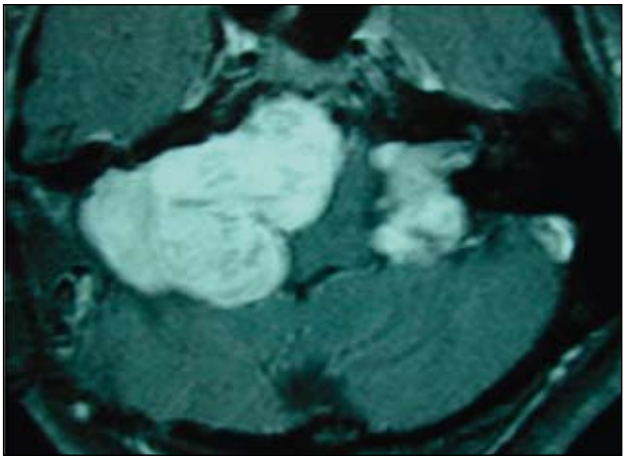

Figure 3: *Large bilateral vestibular schwannomas with gross distortion of the brainstem.*

stratified as those with congenital abnormalities of the cochlea, auditory nerve, internal meatus or combinations thereof and those with an acquired disorder of the cochlea precluding insertion of a cochlear implant.

Congenital cochlear abnormalities

In a review of 298 children undergoing cochlear implantation over a 10 year period, a radiological abnormality of the inner ear was found in 103 individuals (35%) (Papsin 2005). The majority of these abnormalities such as isolated enlargement of the vestibular aqueduct or incomplete cochlear partition type II **(figure 4)** do not preclude conventional cochlear implantation and are associated with auditory outcomes that are comparable to those individuals with a normal cochlear anatomy. However the presence of a more severe cochlear dysplasia and certainly cochlear aplasia has prompted implant teams to consider utilising the ABI as an alternative. In isolated complete aplasia of the inner ear **(figure 5)** or in cochlear

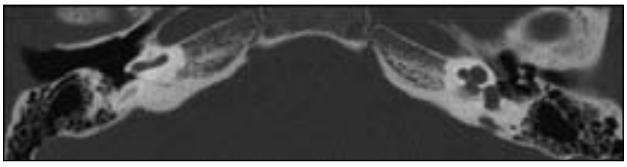

Figure 4: *Incomplete partition of the cochlea, type II as seen in the Mondini abnormality.*

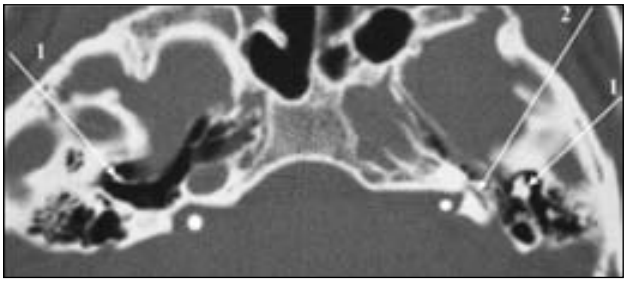

Figure 5: *Cochlear aplasia.*

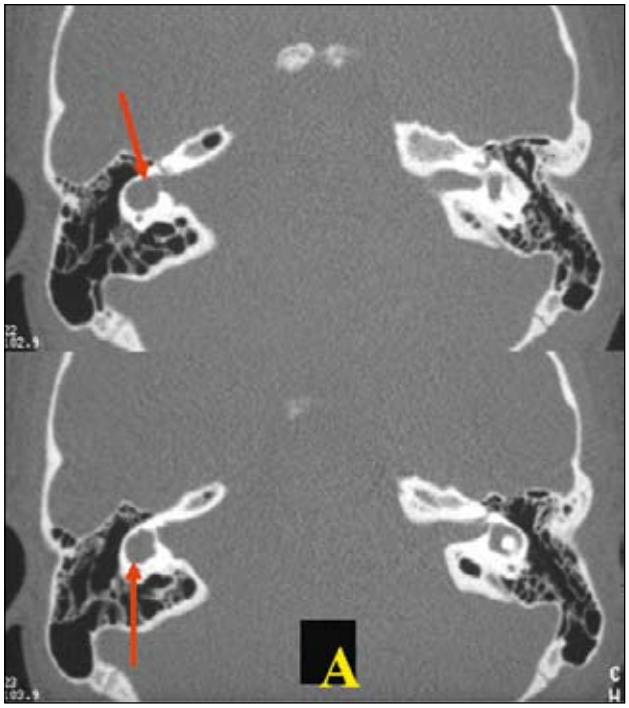

Figure 6: *Common inner ear cavity.*

aplasia there is a growing body of opinion that such children should be considered for an ABI as clearly cochlear implantation is not a viable option. In the presence of a common inner ear cavity **(figure 6)**, a radiological distinction needs to be made between a dilated vestibular cavity (ie cochlear aplasia) which again is potentially an indication for an ABI and a cochlear common cavity in which a modified cochlear implant electrode array may be utilised (Sennaroglu, 2009).

However the reported outcomes from cochlear implantation in the latter are variable and potentially such individuals might also be considered for an ABI from the outset as there is some debate as to precisely where the auditory neuroepithelium resides in the cochlear common cavity and how effectively it can be stimulated with a cochlear implant.

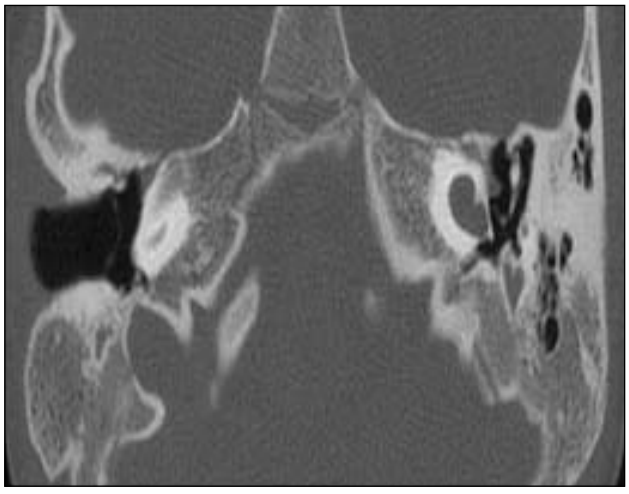

Figure 7: *Incomplete cochlear partition type 1.*

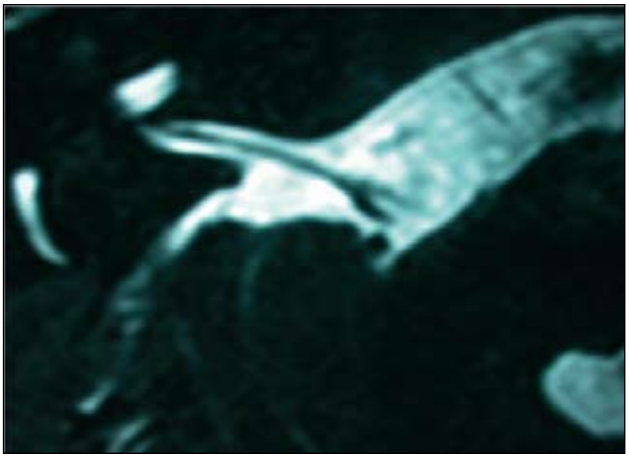

Figure 8: *Audiovestibular nerve aplasia. The internal meatus contains the solitary facial nerve.*

With regards to incomplete cochlear partition (types I and III) **(figure 7)** the current evidence favours cochlear implantation rather than ABI but such inner ears pose challenging surgical issues such as the control of florid CSF efflux during surgery as the fundus of the internal meatus opens directly into the abnormal cochlea. Finally, in the hypoplastic cochlea type I, the cochlea is essentially a small bud anterolateral to the internal meatus and again this situation represents a potential indication for an ABI rather than a CI.

Congenital audiovestibular nerve abnormalities

Abnormalities of the auditory nerve may take one of two forms: either it is absent or hypoplastic. In both instances however the inner ear may be normally formed or be dysplastic or aplastic as described above. Irrespective of the inner ear anatomy, there is a consensus emerging that in eighth nerve aplasia **(figure 8),** consideration should be given to the insertion of an ABI (There have been anecdotal reports of some auditory perception in such infants implying an alternative pathway between the cochlea and the brainstem but these are limited). The area of current debate lies in the management of the hypoplastic 8th nerve, particularly in the presence of a cochlea that would allow conventional cochlear implantation **(figure 9)**. The first question is how thin does the nerve have to be to preclude cochlear implantation (ie what proportion is vestibular) or indeed can a cochlear component of the 8th nerve been seen on detailed MR imaging entering the modiolus?

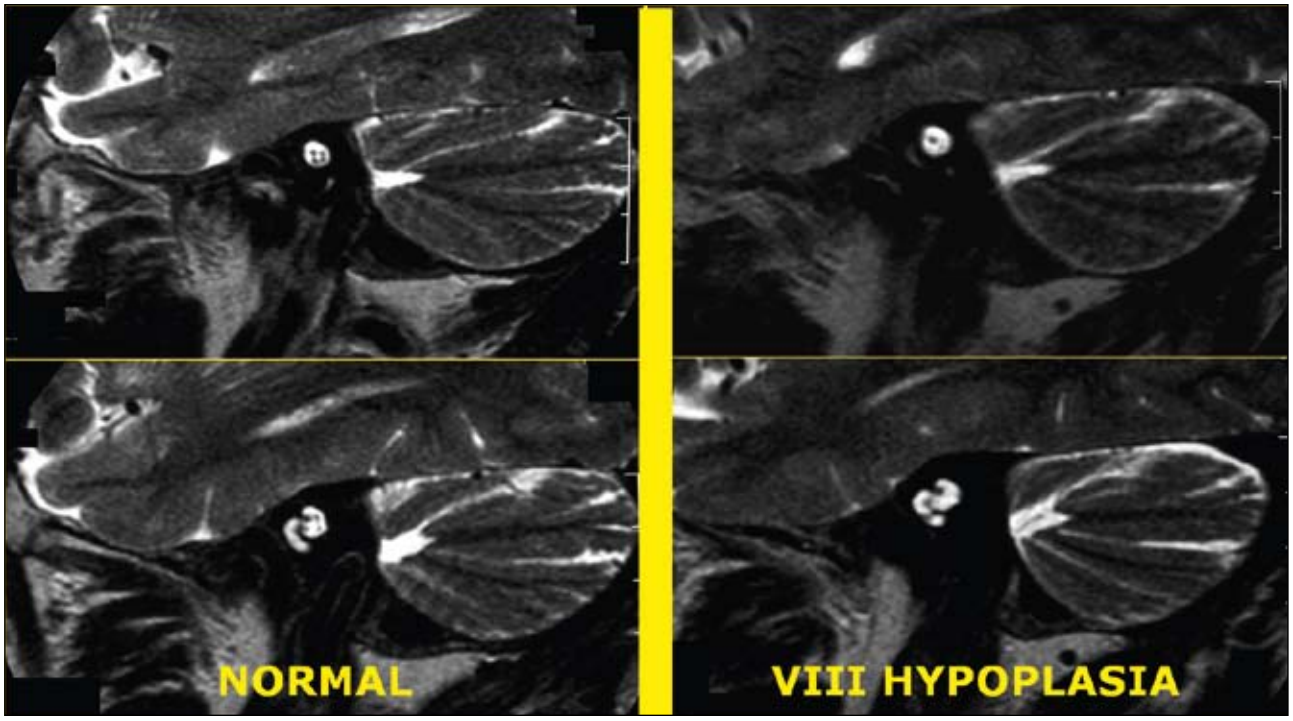

Figure 9: *Comparison of a normal and hypoplastic 8th nerve on T2 weighted para-sagittal. MR imaging. Note the 4 nerves in the internal meatus in the normal image and the facial nerve and hypoplastic 8th nerve on the right.*

The distinction is fundamental because it underpins the decision between a cochlear implant and an ABI. Historically, because the CI procedure is well established and significantly less invasive than inserting an ABI, children in this situation have often undergone cochlear implantation. The outcomes in these children have however have been mixed, ranging from no auditory perception at all, through limited benefit and slow progress in terms of speech development through to some children deriving significant benefit. In order to objectively quantify the "auditory" function of a hypoplastic 8th nerve several centres have evaluated the utility of round window electric evoked response audiometry as part of the decision making process as to whether a CI or ABI is indicated.

Acquired cochlear and audiovestibular nerve abnormalities

The second group of non-NF2 individuals in whom an ABI may be indicated are those patients in whom a cochlear implant cannot be inserted because of gross pathological or structural changes in the cochlea or 8th nerve. This represents an emergent group of ABI recipients as the global experience of this intervention has increased in NF2 cases. Whilst still relatively few in number, the underlying documented indications are considered below.

Meningitis

Profound deafness as a consequence of meningitis has historically been one of the commonest acquired indications for cochlear implantation. The outcomes however show a wide variation and are less consistent when compared to children with congenital deafness. The reasons for this are multiple and in part relate to the varying degrees of fibrosis or ossification that may occur within the cochlear lumen following meningitis. In the more severe cases of ossification, modified cochlear implant electrode arrays have been utilised in an attempt to confer some auditory benefit. The outcomes are often disappointing and this has acted as an impetus for using the ABI as an alternative. Currently there remains debate amongst some implant teams as to whether the totally ossified cochlea **(figure 10)** should be implanted with a split array CI in which two separate troughs are drilled in the position of the original basal and middle cochlear turns or whether such individuals should be offered an ABI from the outset, based on emerging evidence described below.

Otosclerosis

The majority of CI programmes will have accrued a number of adult CI recipients rendered severely deaf by end-stage cochlear otosclerosis. Whilst many of these individuals derive significant benefit from their implant, there is a high incidence of inadvertent electrical stimulation

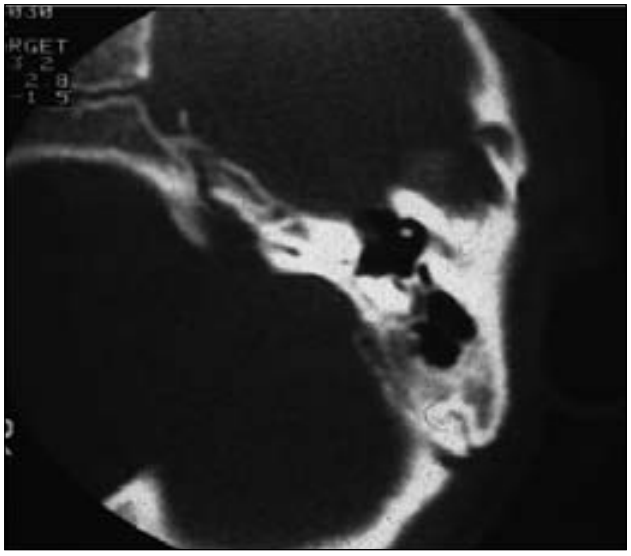

Figure 10: *Gross ossification of the cochlea following meningitis.*

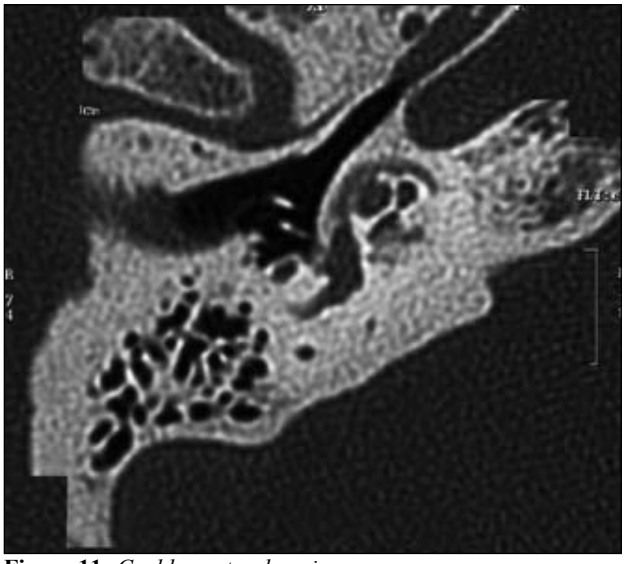

Figure 11: *Cochlear otosclerosis.*

of the facial nerve which often necessitates the offending electrode channels to be switched off (Rotteveel et al, 2004). Occasionally, the cochlear architecture is so deranged by the disease process **(figure 11)** that cochlear implantation would be impossible and in such instances an ABI has been shown to be a viable alternative.

Trauma

Bilateral skullbase fractures may rarely cause 8th nerve avulsion or cochlear haemorrhage with secondary complete ossification. In such instances an ABI may also be indicated.

Outcomes

The outcomes from *cochlear implantation* are one of the great success stories of modern otology: congenitally deaf children developing age-appropriate speech and language and adults with acquired deafness being able to track speech effortlessly and in many instances use the telephone. However such outcomes are by no means universal and CI recipients still struggle to hear in background noise, appreciate music or localise sound. In contrast the outcomes from the auditory brainstem implant are largely limited to enhancement of lip-reading skills and perception of environmental sound with the occasional exceptional user deriving speech discrimination. There are several reasons for this. Firstly, until fairly recently the ABI was almost exclusively utilised in individuals undergoing vestibular schwannoma removal in NF2.

Invariably these patients had significant distortion of the brainstem due to their large tumours and hitherto ill-defined effects on the cochlear nuclei. Secondly, unlike the bony anatomy of the cochlea, which allows a CI to attempt to emulate the tonotopic transducer arrangement of the cochlea, the tonotopic arrangement of the cochlear nuclei is tangential to their surface and the anatomy of the lateral recess of the 4th ventricle is variable and subject to the distortion described above. Thirdly, the proximity of other cranial nerve nuclei and the brainstem tracts to the site of electrical stimulation often leads to non-auditory stimulation which precludes use of all the active channels on the device. Finally, the NF2 ABI user may well have to cope with the consequences of other manifestations of their disease and the demands of auditory rehabilitation may become onerous.

In the report by Colletti and colleagues of 80 ABI recipients with at least 1 year follow-up, 32 patients had NF2 as the underlying diagnosis. Of these, the mean speech perception score was 10% with a range of 5 to 31% (Colletti et al, 2009). In contrast, the same group reported a mean speech score of 59% (range 10 to 100%) in 48 non-NF2 recipients. The latter group included patients with severe cochlear ossification or loss of 8th nerve function due to head injury. Similarly, the Melbourne group found that in their 10 ABI recipients, all of whom have NF2, the majority used their device for several hours per day, two patients became non-users and the remainder showed on-going improvement in performance with the device over many years (Maini et al, 2009). In attempt to overcome the issues around the tonotopic arrangement in the cochlear nuclei, the House Ear Institute group published the results of the penetrating auditory brainstem implant (PABI) which utilises between 8 and 10 penetrating microelectrodes in addition to 10 or 12 conventional surface contacts.

In 10 NF2 recipients, only 25% of the penetrating electrodes resulted in auditory sensations and this group did not gain additional benefit in terms of speech recognition (Otto et al, 2008). The observation that the NF2 ABI recipients fare less well than non-tumour cases was also reported by Grayeli and colleagues who found that the mean open-set word recognition score for the NF2 group was 33% with a high variation between individuals (Grayeli et al, 2008). The review by McCreery encapsulates the outcomes of the ABI against a backdrop of a global experience of over 500 cases: in NF2 recipients, the ABI provides little open-set speech recognition but does give useful appreciation of environmental sounds and importantly, improved speech perception with lip-reading (McCreery, 2008).

The more recent impetus in this field has been the use of the ABI in non-NF2 cases. As reported by Colletti's group, such recipients derive significantly greater benefit than the NF2 group (Colletti et al, 2009) and indeed he and his team have been strong proponents of utilising the ABI in children with congenital deafness in whom a cochlear implant cannot be used and children and adults with acquired causes as described above (Colletti and Zoccante, 2008). Others have followed suit. Sennaroglu and colleagues published their outcomes in 11 children with congenital deafness: all demonstrated improvement on the Meaningful Auditory Integration Scale with two children beginning to identify word pattern differences at 6 to 9 months post-implantation (Sennaroglu et al, 2009). Similarly Grayeli and co-workers and Sanna and his team have described positive outcomes of ABI in post-meningitis cochlear ossification and conclude that the ABI is a viable alternative to the limitations of cochlear implantation in such instances (Sanna et al, 2006, Grayeli et al 2007).

The outcomes and the limitations of the ABI in NF2 recipients are now well documented and having accrued this experience, implant teams working in this field are beginning to push the boundaries further in terms of the potential indications in non-NF2 patients, particularly congenitally deaf children in whom cochlear or auditory nerve abnormalities preclude cochlear implantation. In light of this development a group of doctors, scientists, therapists and rehabilitationists met in Istanbul recently to discuss the indications, assessment, surgery, safety and outcomes of auditory brainstem implantation in the non-NF2 group and propose to publish a consensus statement summarising this meeting in due course.

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Noise-induced hearing loss

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Abstract:
Noise Induced Hearing Loss (NIHL) is a sensorineural hearing loss caused by exposure to damaging levels of noise. This article reviews the aetiopathology and clinical features of NIHL. The medico-legal aspects of diagnosis and noise legislation are discussed. Management and preventative strategies for NIHL are also reviewed.

Keywords:
Hearing Loss, Noise-Induced; Legislation & Jurisprudence; Disease Management.

Introduction
For over a century is has been recognised that exposure to loud noise can cause deafness. This was often regarded as an unavoidable occupational hazard. In the early 20th century ear protectors were developed and used by some military personnel in the world wars. It has not been until the last 50 years that efforts have been made in industry to prevent Noise Induced Hearing Loss (NIHL). Even today the World Health Organisation describes NIHL as "the most prevalent irreversible industrial disease". In the United States it is estimated that 30 million adults are exposed to hazardous noise in the workplace and that a quarter of these will suffer permanent NIHL as a result[1].In Europe NIHL represents the largest single category of compensated occupational disease[2].

The one inner and three outer rows of hair cells of the organ of corti continuously convert mechanical energy from sound into electro-chemical energy. This is transmitted as nerve impulses to the brain. Excessive noise causes metabolic exhaustion, characterised by depletion of glycogen stores and eventual production of protein damaging free radicals[3]. Excessive noise exposure leading to metabolic exhaustion can result in reversible cessation of normal cell function known as a 'temporary threshold shift' (TTS). Over a period of 16-48 hours the cells can recover. If noise intensity is high enough, permanent injury, such as breaks in rootlet structures, mixing of endolymph and perilymph, hair cell apoptosis and degeneration of cochlear nerve fibres, may result[4,5]. This causes a 'permanent threshold shift' (PTS).

Clinically, NIHL begins with a TTS. The extent of the TTS is related to noise intensity, frequency and temporality. Levels greater than 80dBA have potential to cause damage. Noise levels less than 85dBA over an 8 hour working day are unlikely to cause NIHL except in a small minority of highly sensitive individuals. High frequency noise is more damaging than low frequencies. Continuous noise is more damaging than intermittent[6].The audiometric loss begins at around 4kHz. As noise exposure and damage continues, the 4 kHz notch widens and deepens. Various explanations for this characteristic notch exist including the inherent resonant frequency of the external auditory canal and the acoustic reflex protecting the ear at lower frequencies and the anatomical positioning at the basal turn of the cochlea.

Cochlear injury is directly related to noise intensity and duration. A doubling of sound intensity over half the period of time will result in a similar level of energy exposure **(Table 1)**. However when the elastic limit of the inner ear is exceeded, this relationship no longer exists. The level at which this occurs is unclear, but probably at levels greater than 140dB. Levels above this even for very short periods of time (<0.2s) may result in PTS.

TABLE 1

NOISE LEVEL	MAXIMUM EXPOSURE TIME
85 dBA	8 hours
88 dBA	4 hours
91 dBA	2 hours
100 dBA	15 minutes
115 dBA	28 seconds
139 dBA	0.1 second

Table 1 – *Noise of 85dBA over 8 hours may cause damage. This table shows maximum permissible exposure for continuous time weighted average noise. Every 3dB increase in sound correlates with a doubling of sound energy. Thus for every 3dB increase in sound exposure time must be halved.*

TABLE 2

NOISE SOURCE	TYPICAL NOISE LEVEL
Chipping weld on large aluminium structure	120dBA
Cut-off grinder cutting galvanized pipe	98 dBA
Router	93 dBA
Motorboats	up to 110 dBA
Lawnmowers	up to 96 dBA
Hunting weapons	143-173 dBA

Table 2 – *Some noise sources and their typical noise levels*

Clinical Assessment

History

The typical patient tends to be male and middle aged. However many female predominated industries such as knitting mill workers exhibit lower levels of NIHL.

Patients initially complain of lack of clarity of sound and find conversations more difficult, particularly in noisy environments. The television volume is often turned up to a level which is uncomfortable for other family members. Telephone conversation is usually un-impaired initially because telephones do not use frequencies above 3KHz. Tinnitus is also a common finding, especially if present just after the noise exposure. Post noise exposure tinnitus suggests a TTS and auditory system damage. The clinician should make a record of the impact any tinnitus has on sleep, mood and concentration. This will help to grade severity. Hyperaccusis is found in up to 40% of those with tinnitus.

As hearing levels worsen, patients may complain specifically of hearing loss and may become socially isolated because of hearing difficulty. Embarrassment, poor confidence, anxiety and depression can result[7].

The clinician should identify all noise exposures (occupational and recreational)[8]. The degree of NIHL is influenced by; noise intensity (dBA), the temporal pattern of noise (continuous, intermittent or transient), the noise frequency spectrum, the exposure duration (time weighted average – TWA) and the individuals' susceptibility. Generally, if the worker has to shout to be heard in the workplace, then noise levels are hazardous. Ask if ear protection was provided, what type it was and whether it was used. Also enquire for other potential causes of hearing loss such as previous head injury, meningitis, serious illness, aminoglycosides and strong family history etc.

Examination

Otoscopic examination is usually normal. Other visible ear pathology does not exclude the presence of NIHL. Some conductive hearing losses may even afford the patient some protection from noise exposure.

Investigations

A pure tone audiogram, with both air and bone conduction thresholds, should be performed. Three and six kilohertz should be tested in addition to the usual clinical frequencies. The classic 4kHz notch may not always be present, but significant loss below 2kHz is rare. Tympanometry should be performed to assess middle ear function.

If non-organic hearing loss is suspected, cortically-evoked response audiometry (CERA) may provide a more objective measure of hearing thresholds. Because CERA is recorded from a higher auditory level than electrocochleography or brainstem electric response audiometry, it is less influenced by other neurological disorders.

Significant asymmetry is unusual in NIHL. It is seen however in military personnel who fire weapons. Right handed shooting produces more hearing loss in the left ear. This is because the left ear faces the barrel and the right ear is protected by the head shadow effect. Greater than 10dB asymmetry at the same frequency will normally require an MRI scan to exclude an acoustic neuroma or other retro-cochlear cause[9].

Diagnosis

In an otherwise otologically well patient with a clear history of prolonged excessive unprotected noise exposure and an audiogram showing high frequency loss with notching at 4-6kHz and preservation of the low – mid frequencies, the diagnosis is straight forward. However the usual patient will be older with an element of age

related hearing loss. The noise intensity may not have been high and protection may have been provided.

In the pure clinical setting, the clinician need not worry too much about this. The management of the existing sensorineural hearing problems will remain the same, irrespective of the relative cause.

In the medico-legal setting, the relative contribution of each cause must be calculated. If ones assumes that a patient with possible NIHL will have a hearing loss composed of an age related component, a noise induced component and an idiopathic degenerative component, the clinician's task is to separate and calculate the relative contribution (if any) from each source.

The 'Black Book'[8] and the NPL tables[10,11] are used to help achieve this. The NPL tables describe average noise immission levels (NIL) for various hearing losses. Where there is a significant discrepancy between the required NIL for a hearing loss and the noise exposure supposedly responsible, the presence of an additional degenerative process becomes more likely. The effects of ageing can be estimated by reference to one or more of the many standardised reference tables detailing hearing thresholds with age for typical screened and un-screened populations e.g. The NPL tables[11], ISO 7029[12], ISO1999[13] or the National Study of Hearing[14].

A medical report should address all these points. A value should be attached to the noise-induced portion, and any other hearing loss components. Some attempt should be made to calculate the relative contribution of each noise source, if there is more than one[8]. Tinnitus, if present, should be graded for severity and the various contributions to its aetiology should be apportioned. Guidance for severity grading is available[15]. The report should also include comments on prognosis of the hearing loss and tinnitus. Comment should also be made regarding the current or future need for any hearing aids or rehabilitative treatment.

Management

NIHL is irreversible. This should be explained and advice given on optimising their acoustic environment. This includes reducing background noise and face to face conversation which enhances non-verbal cues.

A hearing aid may not help where the loss is predominantly high frequency, but will have a role in more advanced loss. The National Institute of Clinical Excellence supports the additional benefit of binaural aiding[16].
With more severe hearing loss, referral to a hearing therapist for a directed rehabilitation programme, including psychological counselling, can help the patient to understand and acknowledge their problem. Inclusion of, and support for the spouse should also be provided.17 Lip-reading classes can be extremely valuable. Practical measures may include television head phones, volume controllable telephones, and loud door-bells with an alternative alert system.

Tinnitus should be managed as part of the overall care package. Modern neuro-physiological methods (such as tinnitus retraining therapy) utilise a combination of cognitive, directive counselling and sound therapy (including hearing aids and/or white-noise generators) and report success rates in the region of 60-70%.18 Hyperacusis responds well to similar treatment methods.

Some authors suggest that smoking, cardiovascular disease, and diabetes mellitus exacerbate the resultant noise-induced cochlear damage. Thus optimising treatment of these co-existing factors may reduce progression of further NIHL in those still exposed to noise.

Some medical treatments have shown some promise in mitigating NIHL damage. These include anti-oxidants[19,20,21,22], Glutamate receptor antagonists[23], Neurotrophins[24], hyperbaric oxygen / steroids[25] and D-JNK Ligand-1[26].

Prevention & Noise Legislation

Avoidance of the noise exposure is key it its prevention. If this is not possible, then noise reduction and suitable ear protection should be used.

In 1963 a government sponsored report entitled "Noise and the Worker" was published. This document warned industries of the risk of hearing loss from noise exposure at work. In 1984, a landmark legal judgement (Thompson v Smith Ship Repairers[27]) ruled that industry as a whole had knowledge of the risk of NIHL from this 1963 document. Since ear protection was readily available at this time, employers could be liable for NIHL from this date onwards.

Cases from 1963 to 1989 were actioned either in common law or under the Factories Acts 1959 and 1961. These gave employers the responsibility to make the workplace as safe as practicable. In 1996 the Factories Act was repealed. A new statutory Instrument; the "Noise at Work Regulations (1989)" was implemented following a new European Directive. This was the first legislation to specifically deal with noise at work and to set noise limits[28]. From the 6th April 2006, these regulations were

updated by the "Control of noise at work Regulations 2005"[29]. These regulations cover noise in the workplace in the music and entertainment sectors as well as the manufacturing industry.

These regulations describe two action levels for daily, personal noise-exposure: a first action level at 80dBA and a second at 85dBA. At the first action level employers must conduct noise assessments and provide employee noise risk education and appropriate hearing protection. The use of this hearing protection is at the discretion of the employee until the second or peak action levels are reached, when it becomes compulsory. The employer is required to identify areas where hearing protection use is required. Regular hearing tests should be offered to employees where potential risks are recognised.

Unfortunately, given the known variation in susceptibility to noise damage, adherence to all the regulations does not guarantee to protect all employees. At 85dBA, 5% of the exposed population are at risk, at 90dBA that rises to 15%[30]. The risk of hearing loss at 80dBA though, is negligible.

Hearing protection can be achieved with earplugs, earmuffs or active noise reduction (ANR). Earplugs may be custom made or generic. The best earplug can perform as well as the best earmuff in terms of sound attenuation[31] but they are harder to fit correctly. Improper fitting in the workplace often means that adequate protection with earplugs is not achieved. Earmuffs are generally more reliable[32]. Earplugs and ear muffs give anywhere from 10-32dB of sound attenuation.

ANR is an electronic method of sound attenuation. It uses electronics to provide sound inside a set of earmuffs that is at antiphase with the ambient sound. This effectively cancels out background sound. ANR is an effective form of sound attenuation, particularly for lower frequencies and relatively constant noise, but the electronics required are expensive. It is frequently used in military and aircraft settings where additional communication devices are required and can be incorporated into the headset[33].

Conclusions

In the clinical setting, NIHL is essentially a sensorineural hearing loss of which the diagnosis and management is normally straight forward. In the medico-legal setting, the clinician has to separate out the different causes of hearing loss and apportion the relative causes. This can be a challenging task but also a rewarding one.

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Management of Otosclerosis: Current Opinions

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ABSTRACT
Otosclerosis is the commonest cause of progressive deafness in young adults. Patients should be offered the full range of treatment options available although the merits of the various treatments are subject to debate. Currently stapes surgery represents the gold standard in the treatment of otosclerotic fixation of the stapes footplate. While there is no universally accepted technique what is clear is that the most decisive factor for successful surgery is the skill of the surgeon: both surgical skill and experience using a specific microsurgical technique are required to produce reliably successful results. This article reviews the various treatment options available, uses recently published evidence to present the current controversies in performing stapes surgery and presents an algorithm for the management of otosclerosis.

Key Words
Otosclerosis, Management, Surgery, Stapedotomy

INTRODUCTION
Otosclerosis is the commonest cause of progressive deafness in young adults, with an equal sex distribution. Although usually inherited, isolated cases do occur. Incidence increases with age and the overall reported prevalence of clinical otosclerosis in adults is 2%. The process involves both ears in 70-90% of cases.

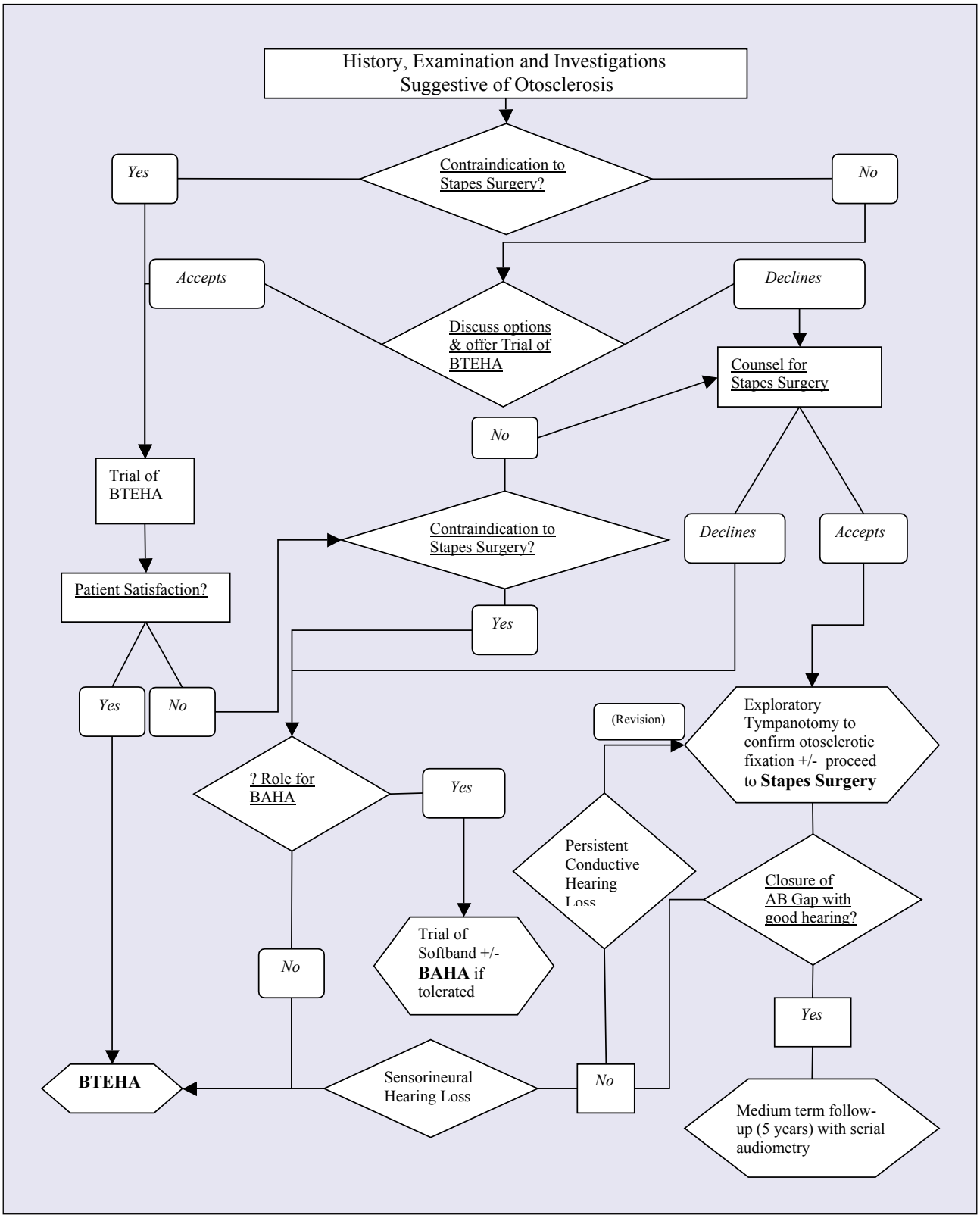
The condition affects endochondral bone of the otic capsule being characterised by disordered resorption and deposition of bone in association with localised vascular proliferation and a connective tissue stroma. The process occurs at certain sites within the otic capsule, the most common site being the area anterior to the oval window (80-95% of cases). Another common site is the round window niche where it can occasionally obliterate the round window niche and obstruct the round window membrane. In this circumstance stapes surgery would not be successful. The stapes footplate is involved in about 12% of cases.

MANAGEMENT OF OTOSCLEROSIS
Currently behind-the-ear hearing aids and stapes surgery, in isolation or in combination, are the most popular interventions in the management of otosclerosis. Bone anchored hearing aids (BAHA) are also used, however this practice is relatively confined to the UK. The use of cochlear implantation for otosclerosis is very much in its infancy but there has been some recent data to suggest that cochlear implantation may be a useful option in very far advanced otosclerosis. In current practice fluoride therapy is rarely, if ever, offered.

The merits of the various treatment options available for otosclerosis are subject to debate and the full range of options available should therefore be presented to the patient. This should be in a manner in which they can understand these, in order to allow fully informed consent for their chosen therapy.

Hearing Aids

Behind-The-Ear Hearing Aids
Behind-the-ear (BTE) hearing aids are an effective means of managing most cases of conductive hearing loss. Their



(Algorithm) Management of Otosclerosis: A possible treatment algorithm. It may be argued that a trial of Behind-The-Ear Hearing Aid (BTEHA) should always be recommended in order to allow fully informed consent to be acquired when counselling a patient for surgery. Bone Anchored Hearing Aids (BAHA) may be the most appropriate option in certain circumstances. Stapes surgery remains the gold standard treatment for otosclerotic fixation of the stapes footplate.

role may increase with ongoing technological development and it may be argued that all patients considering surgical treatment of otosclerosis should undergo a trial of BTE hearing aid to allow fully informed consent to be obtained. Given that stapes surgery carries a risk of injury to the chorda tympani and to the vestibule, patients whose vocation relies on efficient function of these (e.g. sommeliers, construction workers, professional drivers, acrobats) might prefer to avoid these risks at any cost and elect to use BTE hearing aids. While stapes surgery is commonly performed under local anaesthesia with sedation in North America and in some continental European centres, with the assertion that it is easier to assess the change in hearing and development of vestibular symptoms per-operatively, most UK surgeons prefer to perform the procedure under general anaesthesia with the belief that it facilitates tighter control of the heart rate and blood pressure thereby optimising the operative field. A patient who is at high risk from general anaesthesia might therefore elect to use a BTE hearing aid. However the relatively young population affected by otosclerosis makes aesthetic considerations particularly important and this is a distinct disadvantage of BTE hearing aids.

Progression over time can lead to a mixed hearing impairment the level of which may exceed that correctable by BTE hearing aids alone. Patients with hearing thresholds in excess of 100dBHL and no measurable cochlear reserve on speech discrimination may be suitable for operative intervention to enable them to utilise a BTE hearing aid, which previously would have been of little benefit. The extent of a patients hearing loss preoperatively does not affect the success from such 'bimodal' therapy which is reportedly successful in the vast majority of these patients[1].

Bone Anchored Hearing Aids

Bone-anchored hearing aids (BAHA) are recognised as a safe and effective option for managing conductive or mixed hearing losses[2], capable of producing audiological outcomes comparable to those from BTE hearing aids. A significant advantage of BAHA over stapes surgery is that it avoids the small risk of a dead ear resulting from stapedotomy. However aesthetic considerations are particularly important in the relatively young group of patients concerned and as with BTE hearing aids this is a significant disadvantage of BAHA. BAHA might be more reliable than stapes surgery in achieving full closure of the air-bone gap however an experienced stapes surgeon can achieve *adequate* closure of the air-bone gap (to ≤15dB of the contralateral ear) with relative reliability. Evidence for the role of BAHA in the context of otosclerosis remains limited and its use in this context is relatively confined to the UK as compared with the practice in continental Europe and North America. Nonetheless in certain situations, including an only hearing ear with otosclerosis combined with difficulty using a conventional hearing aid, or a post-fenestration cavity[3] BAHA may be the most appropriate management option.

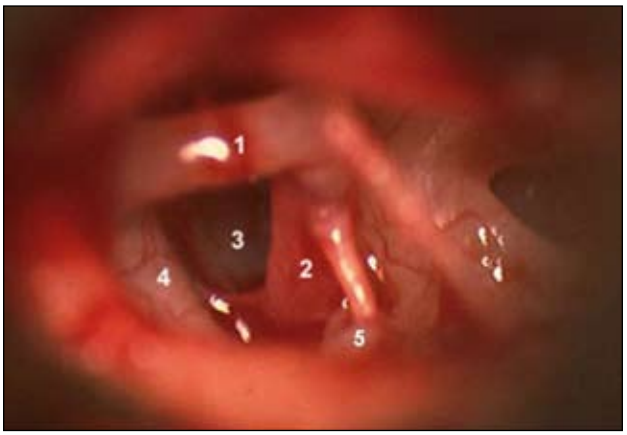


Fig 1: *Suggested required exposure in order to perform stapes surgery (1 long process of incus, 2 posterior crus of stapes, 3 oval window, 4 facial nerve, 5 pyramid)*

Stapes Surgery

Modern stapes surgery was pioneered in North America in the mid 1950's and has remained a successful intervention currently representing the gold standard in the treatment of otosclerotic fixation of the stapes footplate[4]. Closure of the air-bone gap to ≤10dB can be achieved in over 90% of cases[5]. While historically an air-bone gap of 20dB or greater was considered the minimum conductive loss to justify consideration of surgery, some experienced stapes surgeons operate on patients with an air-bone gap of

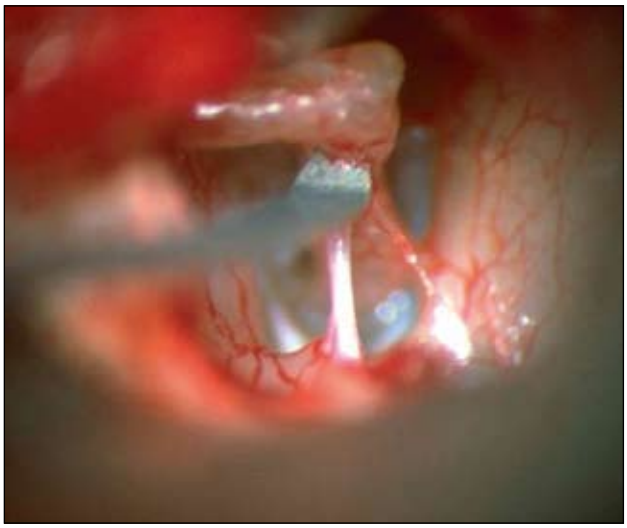


Fig 2: *Separation of the inducostapedial joint using a triangular joint knife*

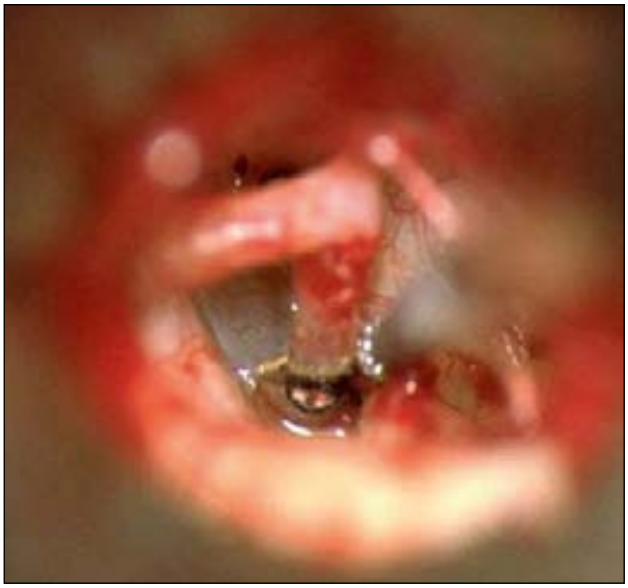


Fig 3: *Posterior crus of stapes following vaporisation with laser*

≤10dB knowing that in a high proportion the air-bone gap will be closed and with the assertion that there is the potential for a greater improvement in air-conduction thresholds than 10dB because of the Carhart effect. Some of these patients who undergo exploratory tympanotomy do not, however, go on to have stapes surgery, suggesting that diagnosing otosclerosis may be more difficult in this group. Since air-bone gaps of ≤10dB may also be artefacts of the audiometric assessment there should be other evidence of a conductive hearing loss, such as serial audiograms, absent acoustic reflexes or appropriate tuning fork test results prior to considering surgery. Local audits to investigate the frequency with which closure of the air-bone gap occurs in otosclerotic patients with larger air-bone gaps (≥20dB) should be performed before patients with small air-bone gaps are operated upon[6]. Adequate

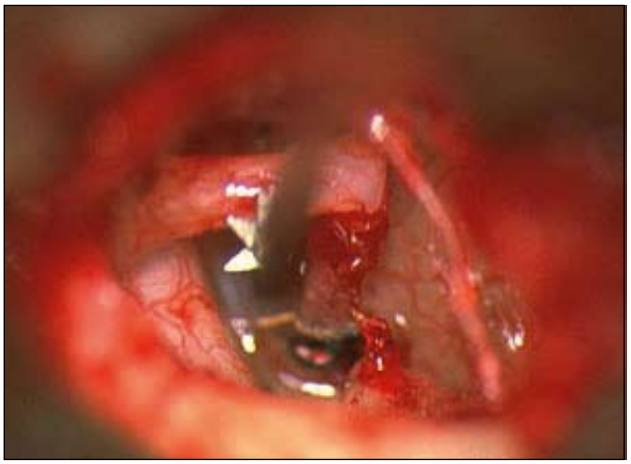


Fig 4: *Measuring device to establish the required prosthesis length*

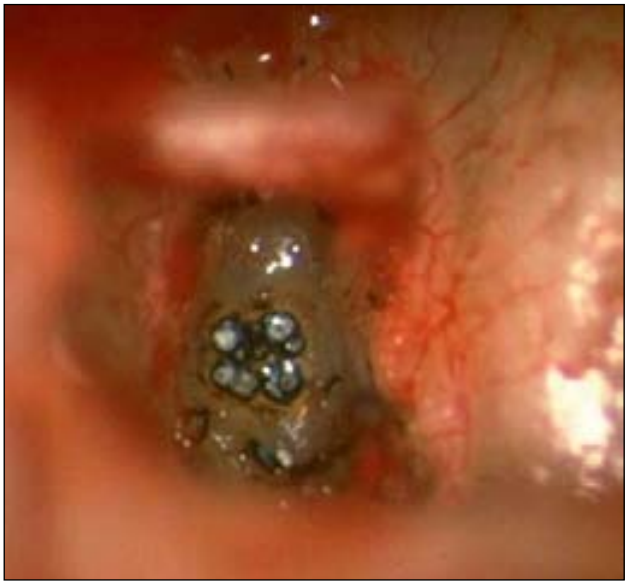


Fig 5: *"Rosette" on posterior half of footplate formed with laser*

cochlear reserve is also required when considering stapes surgery, with a maximum speech discrimination score in excess of 60% desirable.

Indications for and Cautions/Contraindications to Stapes Surgery

General contraindications to surgery relate to the patient's co-morbidities, fitness for anaesthesia and pregnancy. Specific contraindications to stapes surgery include poor Eustachian tube function, active middle or external ear infection, the only-hearing ear, active otosclerosis with positive Schwartze sign and Meniere's disease. Per-

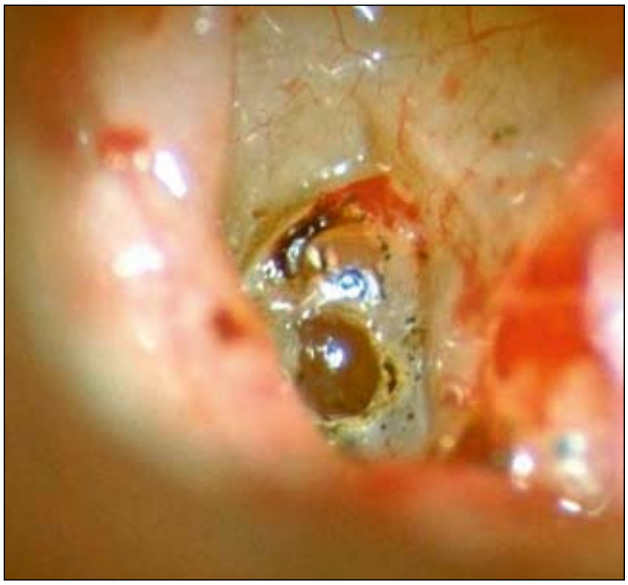


Fig 6: *Stapedotomy following completion with diamond dust burr*

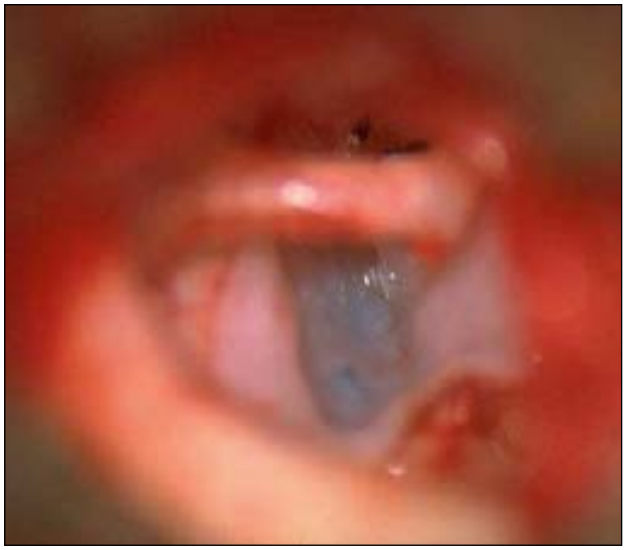


Fig 7: *Vein graft in position completely covering oval window and its immediate surrounds*

operative findings, including vascular and facial nerve anomalies compromising adequate surgical access may necessitate abandonment of the procedure.

Caution is required when considering surgery in children. This reflects the natural history of the condition and the efficacy of hearing aids in managing conductive hearing impairments. However in experienced hands closure of the air-bone gap to ≤10dB has been reported in over 93.5% of children with no observed cases of significant postoperative sensorineural hearing loss[5]. The same series reported that surgery in elderly patients (≥65 years) is successful, with closure of the air-bone gap to ≤10dB in 94.5% of cases.

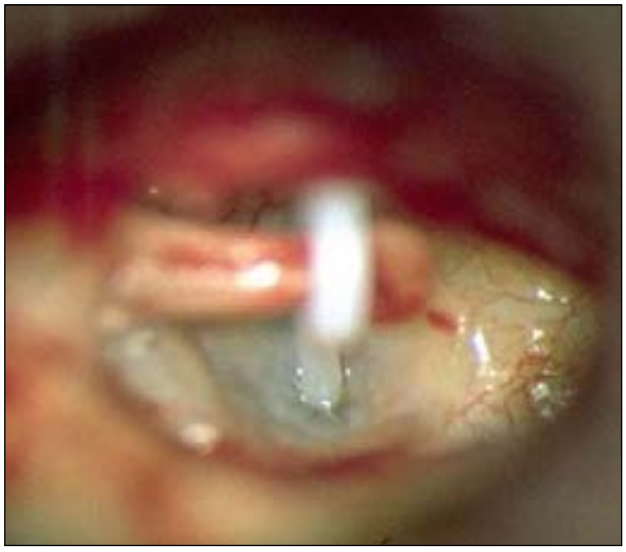


Fig 8: *Stapedotomy piston in position having been crimped around the long process of incus*

Fig 8: *Prostheses (from left to right): K-Piston (Titanium); Causse Piston (Teflon); àWenger CliP (Titanium); Richards bucket-handle prosthesis and Causse Piston*

Occupation and leisure activities predisposing to barotrauma have been cautioned in patients undergoing stapes surgery. There is, however, limited evidence that such activities bear any immediate relationship to otological difficulties following stapes surgery. Without a widely accepted means of assessing whether such activities can be safely performed there is no firm consensus amongst surgeons regarding advice to patients.

The presence of a history, examination findings and investigations suggestive of otosclerosis in a fully counselled and appropriately consented patient in whom there are no general or specific contraindications to stapes surgery would justify an exploratory tympanotomy, proceeding to stapes surgery if otosclerotic fixation of the stapes footplate is confirmed.

While both stapedectomy and stapedotomy techniques are currently employed the recent evidence has been in support of stapedotomy as the superior procedure, with fine fenestra stapedotomy believed to cause less trauma to the membranous labyrinth resulting in greater functional improvements (particularly in the high frequencies), fewer complications and a reduced rate of revision surgery[7,8].

Controversies in Stapes Surgery

Current controversies in stapes surgery include the technique employed for performing the stapedotomy (laser versus microdrill), the prosthesis used (material, diameter, crimping versus non-crimping and technique for crimping) and the use of interposed material between the tip of the prosthesis and the vestibule.

Laser v. Microdrill

Numerous authors have stated the advantages of laser stapedotomy over microdrill stapedotomy. Studies demonstrate equivalent or improved hearing results with reduced inner ear damage and vertigo. However a recent prospective randomised audiological analysis of 336 otosclerosis operations using the two different techniques to perform the stapedotomy (CO2 laser and microdrill)

found no statistically significant difference between the two techniques[9]. Both visible (Argon and KTP) and invisible, far infrared (CO2 and Er:YAG) laser systems have been supported for use in otosclerosis surgery. None of the available laser devices is perfect and at present there is no conclusive evidence to support one laser over the others although prospective comparative studies of results with different types of laser are currently in progress.

The use of lasers is strongly advocated in revision surgery where their use is associated with improved hearing outcomes[10]. They are particularly useful in clearing adhesions from the oval window, freeing ankylosed prostheses from the incus, to sculpt the incus and to control bleeding.

Prosthesis Material

A number of materials are currently employed in the manufacture of stapes prostheses including Teflon, metals (e.g. titanium, platinum, stainless steel) and composite materials (e.g. fluoroplastic-platinum). There are some published data to suggest that heavier pistons (steel, gold) may produce better results in the lower frequencies whilst lighter pistons (Teflon) may be better in higher frequencies however these differences are not statistically significant. Popular prostheses include the Causse Teflon loop piston, the àWenger Titanium CliP piston and the Smart Nitinol (nickel/titanium alloy) piston. The Richards "bucket handle" prosthesis can be utilised in cases where the lenticular process directly overlies the oval fossa. The published literature suggests that in the hands of an experienced stapes surgeon any one of these prostheses can be used to deliver a reliably successful outcome.

Prosthesis Diameter

A review of the literature shows a wide variety of functional results obtained when considering the 'optimum' diameter of the prosthesis. While a minority of studies show no difference in hearing outcome between different piston sizes, the majority appear to show a greater improvement in the post-operative air-bone gap with larger pistons (0.6-0.8mm), especially at lower frequencies and across the speech frequencies, when compared with narrower pistons[11]. The risk of a sensorineural hearing impairment however appears greater with a wider prosthesis4 and a smaller diameter piston is associated with ease of procedure and reduced risk of inner ear damage, particularly when inserted via a narrow laser stapedotomy. A 0.6mm piston might therefore be appropriate for a microdrilled stapedotomy, whereas a 0.4mm piston may be more appropriate for a narrower laser stapedotomy.

Crimping versus Non-Crimping Prostheses

Certain prostheses require crimping to secure their position on the long process of the incus. Manual crimping of the stapes prosthesis is a skill which can be confidently learned by an otologist, however the final shape and tightness of the crimp can be very variable and removal of this step has been suggested to be beneficial[12]. However a recent publication failed to show any significant difference between the hearing outcomes achieved with crimping (K-Piston Titanium) and non-crimping (àWenger Titanium CliP-Piston) prostheses[13]. When using a prosthesis which requires crimping and considering the crimping technique itself there is an increasing body of evidence that heat-activated-crimp prostheses (such as the Smart Nitinol piston) result in a better hearing outcome as compared with manual-crimping techniques[14-17]. This may reflect tighter fixation of the stapes prosthesis to the long process of the incus and thus improved sound-transmission efficiency. Longer term data are required, however, before conclusions can be drawn with regard to long-term loosening or incudial necrosis in association with heat-activated crimping.

Use of Interposed Material

Many otologists seal a tight-fitting stapedotomy with fat placed around the prosthesis whilst others interpose a vein graft. Connective tissue seals aid in preventing perilymph leakage and may reduce the risk of the prosthesis dislocating in the postoperative period. An interposed graft has the added advantage of reducing the risk of the prosthesis prolapsing into the membranous labyrinth and causing damage. Placing the graft and thereafter locating the prosthesis into the hidden stapedotomy, however, is a technically challenging exercise. Vein has been demonstrated to be the material of choice for interposition grafts[18].

The Learning Curve in Stapes Surgery

While controversies exist concerning the details of the technique employed, what is clear is that a good result can be achieved using any of the techniques currently employed. There is a strong association between experience and both technical ability and surgical outcome for stapes surgery and the most fundamental requirement for a reliably successful outcome is the surgeons experience in their chosen technique. The 'learning curve' for stapes surgery is suggested to be 70-80 procedures[19].

Cochlear Implantation

Cochlear implantation may be a management option for some patients with bilateral very far advanced otosclerosis in whom other modes of amplification have failed. Some studies report reliable improvement in speech discrimination

scores in patients implanted for very far-advanced otosclerosis[20,21] but it was also noted that some patients who underwent stapes surgery and were then fitted with hearing aids had comparable results to those who underwent cochlear implantation. Facial stimulation has been noted to be a significant problem in patients undergoing cochlear implantation for otosclerosis. This therefore remains an area of increasing research but data is limited and definitive conclusions cannot be drawn at this time.

Conclusions

Patients with otosclerosis should be fully counselled in the various management options available. Behind-the-ear (BTE) hearing aids should always be discussed as a treatment option and may be the only option in certain groups of patients, with bone anchored hearing aids an alternative in those experiencing difficulty with the use of BTE hearing aids. Stapes surgery for otosclerotic fixation of the stapes footplate is a successful surgical procedure and is the current gold standard treatment. There is no universally accepted technique and there are a number of surgical technicalities which remain controversial. Despite these controversies each of the techniques and prostheses under debate has been demonstrated to produce excellent results in the hands of experienced surgeons. Technical modifications and refinements of stapes surgery will continue in the future but ultimately the most decisive factor for successful surgery is surgical experience.

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Evidence Based Management of Bell's Palsy

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STRUCTURED ABSTRACT

Bell's palsy is a lower motor neurone palsy of the VIIth cranial nerve resulting in various degrees of facial paralysis. It is the most common diagnosis given to a facial nerve palsy, usually when all other causes have been ruled out. It has been thought that Bell's palsy is idiopathic, however there is increasing research which suggests a viral aetiology.

Management of Bell's palsy is mainly medical, using corticosteroids and/or anti-virals. There is considerable evidence to support the early use of steroids to shorten the time to recovery and reduce the risk of sequelae. Trials have been undertaken to assess the role of anti-viral medication, however reproducible conclusive benefit has not yet been demonstrated. Whilst medical treatment is underway, further measures such as eye protection should be instituted to prevent further complications.

KEY WORDS

Bell's palsy, facial palsy, management

Introduction

Sir Charles Bell (1774-1842) first observed facial muscle paralysis following damage to the seventh cranial nerve in 1821 and reported the true function of the facial nerve[1].

Sir William Gowers, a neurologist with an interest in the facial nerve subsequently coined the term Bell's palsy for a unilateral lower motor neurone paralysis of the seventh cranial nerve, in the late nineteenth century[2].

Bell's palsy is an idiopathic lower motor neurone facial nerve palsy. It is a common neurological condition that follows a common clinical course. However, a universal aetiology has yet to be identified.

There is ample evidence to suggest a viral aetiology, first proposed by McCormick in 1972[3]. Latent viral reactivation in the geniculate ganglion is believed to result in inflammation, oedema and compression, causing a subsequent entrapment neuropathy of the facial nerve within the bony canal. Hence management may include steroids and/or anti-viral drugs.

The main aim of treatment is to reduce the duration of facial palsy and prevent complications, which also includes psychological problems taking into consideration that 15% of one's self-esteem is derived from facial appearance[4].

Incidence

Seventy percent of facial nerve palsies are diagnosed as a Bell's palsy[5]. Epidemiological studies report the incidence as 11 – 40 new cases per 100, 000 each year, with the

30 – 45 year age group being most commonly affected[6]. There is little geographical variation in incidence between countries, however Japan has the highest reported rates[7]. There is an equal sex distribution of this nerve palsy[8]. Certain groups such as diabetics are at risk of recurrent episodes of Bell's palsy.

Clinical features

There are several features of this condition that remain fairly constant whilst others have a variable association with Bell's palsy **(table 1)**.

Table 1

Constant Features	Variable Features
Peripheral facial nerve lesion causing diffuse weakness to all branches of the nerve.	Viral Prodrome (31%)
	Facial or retroauricular pain (50%)
Acute and progressive course, with maximum weakness of facial muscles reached by 3 weeks from onset.	Hyperacusis (33%)
	Facial Numbness (40%)
Improvement in function within six months from onset.	Dysgeusia (33%)

The clinical course of untreated Bell's favours complete resolution of 71% at 1 year. The remaining 29% have complications such as residual paralysis, synkinesis and contracture[5].

Studies suggest an early onset of recovery gives a better likelihood of complete resolution. One hundred percent of patients who begin to recover within the first week go on to have a full remission, whereas this number reduces to 61% if recovery begins in the third week[5].

Incomplete palsy at first presentation is a good prognostic indicator of complete resolution, with 99% of patients with partial facial paralysis making a full recovery. If the facial paralysis is complete only 75% will completely resolve[9]. [9]

Diagnosis

Diagnosis of Bell's palsy is mainly clinical and insists upon exclusion of all causes **(table 2)**.

Table 2: Causes of Facial Nerve Palsy

Birth
Forceps delivery
Dystrophia myotonica
Möbius syndrome (facial diplegia associated with other cranial nerve deficits)
Trauma
Basal skull fractures
Facial injuries
Penetrating injury to middle ear
Altitude paralysis (barotrauma)
Scuba diving (barotrauma)
Lightning
Neurologic
Multiple sclerosis
Myasthenia gravis
Opercular syndrome (cortical lesion in facial motor area)
Infection
Otitis media
Mastoiditis
Chickenpox
Herpes zoster oticus (Ramsay Hunt syndrome)
Encephalitis
Poliomyelitis (type 1)
Mumps
Mononucleosis
Guillan-Barre Syndrome
Leprosy
Influenza
Malaria
Syphilis
Tuberculosis
Botulism
Lyme disease
Cat scratch
AIDS
Metabolic
Diabetes mellitus
Hyperthyroidism
Pregnancy
Hypertension
Acute porphyria
Vitamin A deficiency
Neoplastic
Parotid tumours
Cholesteatoma
Seventh nerve tumor
Glomus jugulare tumor
Leukaemia
Meningioma
Hemangioblastoma
Sarcoma
Toxic
Thalidomide
Ethylene glycol
Alcoholism
Arsenic intoxication
Tetanus
Diphtheria
Carbon monoxide
Iatrogenic
Parotid surgery
Mastoid surgery
Iontophoresis (local anesthesia)
Embolization
Idiopathic
Bell's palsy
Melkersson-Rosenthal syndrome (recurrent alternating facial palsy, furrowed tongue, faciolabial edema)
Autoimmune syndrome
Temporal arteritis
Thrombotic thrombocytopenic purpura
Periarteritis nodosa

Diagnosis must include a detailed history, a thorough neurological and ear, nose and throat examination. Further investigations should be selectively aimed at excluding other diseases or conditions implicated in the history and examination.

Grading

Several grading systems are in use but the most common is the House-Brackmann scale **(table 3)**[10].

Table 3

Grade	Definition
I	Normal symmetrical function in all areas
II	Slight weakness noticeable only on close inspection
	Complete eye closure with minimal effort
	Slight asymmetry of smile with maximal effort
	Synkinesis barely noticeable, contracture, or spasm absent
III	Obvious weakness, but not disfiguring
	May not be able to lift eyebrow
	Complete eye closure and strong but asymmetrical mouth movement with maximal effort
	Obvious, but not disfiguring synkinesis, mass movement or spasm
IV	Obvious disfiguring weakness
	Inability to lift brow
	Incomplete eye closure and asymmetry of mouth with maximal effort
	Severe synkinesis, mass movement, spasm
V	Motion barely perceptible
	Incomplete eye closure, slight movement corner mouth
	Synkinesis, contracture, and spasm usually absent
VI	No movement, loss of tone, no synkinesis, contracture, or spasm

It is a discontinuous grading system with six separate categories, I-VI, with I being normal and VI being a complete palsy. This grading system, originally described to monitor facial nerve recovery after acoustic neuroma surgery, gives a discrete score. It is the preferred standard of facial palsy grading by The American Academy of Otolaryngology-Head and Neck Surgery and Academy of Ophthalmology.

The other two common grading systems are the Sunnybrook and Yanagihara scales.

In 1996, Ross[12] proposed the Sunnybrook facial grading system. It assigns precise scores that are accumulated to a maximum of 100. The score reports facial weakness in a continuous manner, is more objective and has a wider response range in comparison to the House-Brackmann scale[13]. There is also good reliability within the system. There is good correlation between ratings given on Sunnybrook and other systems. The more gross categorizations of the House-Brackmann scale are not easily converted to a score on the Sunnybrook scale.

The Yanagihara grading system was first described in 1976 and is most widely used in Japan. It assigns a score of 0-4 to ten different aspects of facial muscle function, with a total maximum score of 40[14].

Amongst the three scales described, there is highest agreement between the Sunnybrook and Yanagihara[15]. There is moderate agreement between the Sunnybrook and House-Brackmann systems. These points must be borne in mind when evaluating the literature as trials will differ in the scale used, which has implications in comparative analysis of their results.

Evoked electromyography (EEMG) provides an objective tool for grading facial paralysis. It also serves as a powerful prognosticator. If used within the first 14 days on patients with Bell's palsy, and the patient achieves a score of greater than 25% of their predicted, only 2.6% will go on to have an unsatisfactory result (House-Brackmann III or IV). Whereas if they score less than 10% of their predicted, 68% will have an unsatisfactory outcome[9].

EEMG is both time consuming and expensive, this level of function stratification and prognostication is unnecessary for the vast majority of cases, but is a vital tool for patients who are not responsive to conservative measures and who may be candidates for surgery.

Pathophysiology

Research into the aetiology of Bell's palsy has focused on a viral aetiology[4] causing symptoms via inflammation[15,16], compression and subsequent ischaemia of the seventh cranial nerve[17,18].

The most likely virus has been Herpes Simplex (HSV) after early work done by McCormick[19] and Takasu[20]. However, it has proved difficult to conclusively demonstrate causality as there is a high prevalence of HSV

within geniculate ganglia but a disparately low incidence of Bell's palsy.

Yanagihara and his team (1996) made even greater strides by using polymerase chain reaction (PCR) on VIIth nerve endoneurial fluid and posterior auricular muscle of 14 patients with Bell's palsy, who were undergoing decompressive surgery for Bell's that was not responding to medical measures. The viral genome of HSV type 1 was isolated in 11 out of his 14 subjects but not in any of his two control groups. Their first control group comprised 12 patients who either had facial nerve paralysis secondary to temporal bone fractures and otitis media or those without facial nerve paralysis who were undergoing tympanoplasty for chronic otitis media. Yanagihara's second control group consisted of 9 patients with Ramsay Hunt syndrome[21].

They proposed that primary infection with HSV-1 resulted in the facial palsy, the secondary effects of oedema, nerve compression and ischaemia led to a more pronounced palsy.

Although the presence of HSV DNA does not prove that the virus was the causative agent, its presence in the endoneurial fluid and auricular muscle is quite convincing.

However, counter-arguments for HSV-1 as the causative agent are: (1) the poor evidence for use of anti-virals to date, (2) the seldom seen diagnostic four fold rise in antibody titre against HSV-1 in acute Bell's palsy and (3) the low incidence of Bell's palsy compared to other manifestations of HSV-1[22].

Treatment

The available options include steroids, anti-virals and facial nerve decompression.

The aim of treatment has been reducing the duration of the disability and preventing sequelae, particularly ocular complications. To this end it is agreed that prevention of corneal dehydration, abrasion and ulceration forms a cornerstone in the management of Bell's palsy. The risk of corneal ulceration can be reduced by diligent hydration of the eye – using drops, lubricants, and a protective eye chamber.

Working on the premise that the nerve palsy arises as a result of viral-mediated inflammation, medical treatment modalities have mainly been anti-inflammatory and anti-viral drugs. Research into the benefit of these drugs has provided disappointing results to date.

In 2006, a Cochrane Review of the role of anti-virals[23] in Bell's palsy found insufficient evidence supporting their role and recommended further randomised-control trials. However, there is considerable evidence to support the use of steroids in the treatment of Bell's palsy[24,25,26,27,28].

One of the most recent studies was carried out in Scotland by Sullivan et al (2008) which was a double-blinded randomized control trial of 551 patients referred within 72 hours of onset of Bell's palsy over a 2-year period[29]. The study investigated the benefit of prednisolone alone or with acyclovir against placebo.

Prednisolone alone was associated with a statistical higher rate of recovery at 3 months compared to placebo (83% vs. 63.6% respectively), this advantage was maintained at 9 months (94.4% vs. 81.6%). However, when adding acyclovir compared to placebo, the results at three months were 71.2% vs. 75.7%, respectively (non-significant).

Sullivan et al showed that treatment with prednisolone (25mg bd PO) results in 1 additional person with complete recovery at 9 months for every 9 patients treated[30].

The authors reported compliance at 69.5% (383/551). Without further breakdown on compliance failure it is difficult to draw definitive conclusions.

Also, of note is the choice of antiviral and the dose prescribed. The authors report this dose was chosen based on studies included in the Cochrane review[31]. Acyclovir was prescribed as a 400mg five times daily regime. This is half the recommended dosage for the treatment for herpes zoster and herpes simplex infections. Acyclovir is subject to first pass metabolism and has a subsequent low bioavailability in comparison to other anti-virals that are pro-drugs.

A large multi-centre randomized double-blinded placebo-controlled trial was undertaken in Sweden between 2001 and 2006. This randomized 839 patients to one of four arms: Placebo-placebo; prednisolone-placebo; prednisolone-valacyclovir and placebo-valacyclovir.

Primary outcome measure was time to full recovery, assessed by Sunnybrook scale within a one-year period. The results of this study were concordant with the Scottish study: Prednisolone reduced the time to recovery significantly, with valacyclovir having no statistical benefit[32].

Whilst the dose of valaciclovir used was large enough to inhibit HSV, it was not a large enough dose to treat

varicella zoster. Neither study excluded zoster sine herpete which has been implicated in 2.8% [33] -19%[34] of Bell's palsy cases. Failure to exclude this potentially large group from within their cohort could greatly change the results of their study.

A Japanese multi-centre prospective randomized placebo controlled trial evaluating valacyclovir-prednisolone versus prednisolone-placebo was published in 2007. The study excluded patients who were serologically proven to have zoster sine herpete. Using the Yanagihara grading system to evaluate complete resolution of symptoms on their cohort of 221 patients, this group reported a statistical advantage when adding valacyclovir to prednisolone compared to placebo and prednisolone[35]. This study has advantages over earlier research into anti-viral medication, as they chose valacyclovir, which is a pro-drug. It undergoes first pass metabolism when taken orally and at that point is converted to the active metabolite acyclovir, thereby reaching far higher, indeed three to five times higher levels of bioavailability in comparison to acyclovir which is metabolized to an inactive derivative[36].

More recently, a meta-analysis of combined corticosteroid and antiviral treatment for Bell's palsy has been published[37]. Eighteen studies were reviewed. It convincingly confirms the benefit of steroids in Bell's palsy management, with treatment of 11 patients required to provide resolution in 1 patient. The meta-analysis concluded that anti-virals as monotherapy was ineffective. However, using anti-virals with steroids demonstrated a possible increased benefit over steroids alone and a synergistic effect when the two classes of drugs are given in combination, although this was not statistically significant[37].

Conclusion

There is extensive research on this common neurological condition that frequently presents to otolaryngologists. Histological and radiological evidence supports the role of inflammation as the pathophysiological mechanism for the nerve palsy. Clinical research has shown that prednisolone reduces the course and severity of Bell's palsy, adding further evidence that inflammation is the physiological antecedent of the condition.

Although there is interesting scientific evidence that implicates HSV-1 as an important aetiological agent in Bell's palsy, the failure of anti-viral treatment has been disappointing.

The mechanism of action of the anti-virals is such that they prevent further replication of the virus by disrupting DNA polymerase. They do not destroy the virus itself and this may explain in part, why anti-virals have not always shown to be effective in treating Bell's palsy.

Early treatment is recommended, using oral corticosteroids. Pro-drug anti-virals (valacyclovir, famciclovir or ganciclovir) that have excellent bioavailability should be seriously considered although the evidence base is currently wanting.

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Autoimmune Inner Ear Disease (AIED)

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Abstract
Autoimmune Inner Ear Disease (AIED) is a rare disease that accounts for less than 1% of hearing loss or dizziness. Clinical course is of progressive, fluctuating, bilateral sensorineural hearing loss (SNHL) over a matter of weeks to months. Other symptoms may include vestibular effects (i.e. imbalance, ataxia and vertigo), tinnitus, and aural fullness. It is most common in females in their 3rd to 6th decade. Systemic autoimmune diseases coexist in 15-30% of patients. There is no specific test for diagnosis of AIED, but importantly, prompt treatment with steroids may reverse the hearing loss. Therefore, the diagnosis is made based on clinical criteria and response to steroids.

Keywords
Autoimmune, cochlear, vestibular, hearing loss

Introduction
AIED is a rare disease that accounts for less than 1% of hearing loss or dizziness. McCabe first described rapidly progressive, bilateral sensorineural hearing loss that improved with steroid treatment in 1979[1]. It is most common in females in their 3rd to 6th decade. Systemic autoimmune diseases coexist in 15-30% of patients and these patients may have a poorer prognosis.

Clinical Features
The clinical course of autoimmune inner ear disease (AIED) is a rapidly progressive, often fluctuating, frequently bilateral, sensorineural hearing loss over a period of weeks to months. This progression is too slow to be a sudden sensorineural hearing loss (within 72 hours) and too quick to be presbyacusis (related to ageing). Up to 50% of patients thought to have AIED initially present with vestibular symptoms[2], including imbalance, ataxia, true vertigo, or motion intolerance. Other symptoms can include tinnitus and aural fullness.

Background
There are many hundreds of reported autoantibodies, broadly divided into organ-specific and organ-non-specific. Autoantibodies are either directly involved with the pathological process (primary antibodies) or are markers for the disease process (secondary antibodies). There are multiple techniques for testing, and comparison between different assays is difficult. There is often no "gold standard" and results may vary between different laboratories. Western Blot analysis, lymphocyte migration assay and indirect immuno-fluorescence, are the most common techniques for antibody detection.

AIED implies antibodies to an inner ear antigen. Viral infection, trauma and vascular damage may be triggers for AIED. Perhaps antibodies or T-cells cause accidental inner ear damage because inner ear tissue (possibly type II collagen in particular), shares common antigens with potentially harmful substances. The normal cochlea does not contain lymphocytes. The hypothesis that the endolymphatic sac is the key organ in the immune response of the inner ear was proposed in 1974[3]. Macrophages, B cells and T cells have been demonstrated in the endolymphatic sac and the peri-saccular tissues , but it is not clear whether these are produced locally or are recruited from the systemic circulation[4], but it is not clear whether these are produced locally or are recruited from the systemic circulation[5]. Obliteration of the endolymphatic sac has been shown to reduce immune responses in the cochlea[6]. Immune mediated or autoimmune pathology of the endolymphatic sac may lead to endolymphatic hydrops.

Differential diagnoses
Although there are many possible causes of a sensorineural hearing loss, many patients do not have a clear aetiology (i.e. idiopathic).

Investigations
The pathophysiology of AIED is not well understood but the suggestion is that there are antibodies to an inner ear antigen. This hypothesis has stimulated research into organ-specific autoimmunity with the initial focus on the 68kD protein (previously thought to be heat shock protein-70)[8].

However, this is now regarded as incorrect, not specific, not sensitive and unhelpful in diagnosis of AIED[9,10,11].

Table 1 – Possible identifiable causes of sensorineural hearing loss[7]

Autoimmune	See Table 2
Infectious	Meningococcal meningitis, encephalitis, herpes virus, measles, mumps, rubella, HIV, syphilis, Lyme disease, toxoplasmosis
Traumatic	Temporal bone fracture, barotrauma, perilymph fistula, excess noise exposure, decompression sickness, surgery
Neoplastic	Acoustic schwannoma, meningioma, leukaemia, myeloma
Toxic	Aminoglycoside antibiotics, salicylates, loop diuretics, NSAIDs, platinum based chemotherapeutic agents, general anaesthesia
Circulatory	Micro-vascular disease, vertebrobasilar insufficiency, sickle cell disease, cardiopulmonary bypass
Neurologic	Multiple sclerosis, migraine, focal point ischaemia
Metabolic	Thyrotoxicosis, hyperlipidaemia, diabetes
Other	Meniere's disease

Table 2 - Autoimmune diseases

Non-organ specific autoimmune diseases	Wegener's granulomatosis Rheumatoid arthritis Polyarteritis nodosa Systemic Lupus Erythematosus Cogan's syndrome Sjorgen's Relapsing polychondritis Ulcerative colitis Antiphospholipid syndrome Sarcoidosis
Ear-specific autoimmune disease	Autoimmune Inner Ear Disease

A battery of non-specific antigen-screening tests may however, be useful as evidence of systemic autoimmune dysfunction, but this may not correlate with AIED[12]. Immunological laboratory tests suggested include; antinuclear, antineutrophil, cytoplasmic, antiendothelial cell, antiphospholipid/anticardiolipin, and antithyroid antibodies[13]. The more selective tests of ANA levels[14] and/or immuno-phenotype of peripheral blood lymphocytes[15] may be as helpful and far cheaper. The prognostic value of these tests is not clear and although they may help with diagnosis, it is likely that treatment will have been instigated before the results are available. There is no clear relation between these tests and steroid responsiveness.

Treatment

The current therapy is empirically based on the fact that steroids improve hearing in about 60% of patients thought to have AIED. Immunosuppressive therapy, usually in the form of oral corticosteroids, is suggested. A 1mg/kg course of daily Prednisolone, for a month, which is then slowly reduced to a maintenance dose, may be appropriate.

If there are adverse effects from the steroids or the hearing loss continues despite steroid use, then cytotoxic medications might be indicated. These drugs, such as cyclophosphamide[16] and methotrexate[17] have less clear benefits with significant toxicity and side effects. Transtympanic injections of chemotherapy have also been suggested.

A small study showed improvement in hearing and the ability to discontinue immunosuppressive medication after plasmapheresis[18]. Plasmapheresis removes antibody, antigen, immune complexes and mediators from the blood by extracorporeal filtration.

Cochlear implants may be of benefit in the long term.

Genetic factors are thought to influence susceptibility to hearing disorders. However, there is conflicting evidence as to the precise location of these genetic differences. In the future there may be scope for cell[19] or gene[20] therapy to treat the inner ear cell damage.

Conclusions

There is no specific test for diagnosis of AIED, but importantly, prompt treatment with steroids may reverse the hearing loss. Therefore, the diagnosis is made based on clinical criteria and response to steroids.

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Evaluation of the Dizzy Patient

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Abstract
Dizziness and postural instability are common symptoms that are treated in otolaryngology practices. Unfortunately, the population of patients suffering with these broad categories of symptoms frequently does not receive optimal evaluation and/or therapy. All too often, the less-than favorable evaluation and resulting therapy are due to the difficulty in obtaining a thorough—yet pertinent—history as well as a widespread perception that the physical examination is complex. Over the last 20 years, a standardized and user-friendly approach to evaluating the dizzy patient that also maximizes the clinician's time and efforts has been increasing utilized.

A thorough history is taken from the patient in two forms: (1) a specially-designed questionnaire completed prior to the patient's arrival at the appointment and (2) an interview using the answers on the questionnaire as a guide. During the physical examination, emphasis is placed on the following subtests: (1) spontaneous nystagmus; (2) central oculomotor function; (3) the vestibulo-ocular reflex battery-headshake, head impulse, dynamic visual acuity, and Dix-Hallpike positioning; (4) coordination; (5) posture; (6) gait; and (7) special examinations. This neurotologic examination is completed in about 10 minutes and is performed as a battery of tests following the routine otolaryngologic and/or neurologic examination. This test sequence is thorough yet easy to perform and, ideally, will demystify the examination of patients with symptoms that are challenging to evaluate and treat.

Key words
Dizzy, vertigo, nystagmus, examination

The Dizziness Questionnaire and Patient Interview
The dizziness questionnaire is mailed to the patient's home to be completed and returned prior to their appointment. The questionnaire is divided into five main sections:

1. **Description of symptomatic episodes**
2. **Accompanying symptoms indicative of peripheral etiology**
3. **Accompanying symptoms indicative of central etiology**
4. **Accompanying auditory complaints**
5. **General physical and emotional health**

For easy identification, "yes" and "no" options are placed in the left and right margins, respectively with instructions to circle the one that best matches their current state of health.

Description of the Symptomatic Episodes
Dizziness connotes different sensations and meanings to different patients. Therefore, it is imperative that the patient describe the sensations that they feel during the episodes without using the term dizzy. Once the stereotyped and overused concept of dizziness is removed from the process, each patient's distinct symptom pattern(s) can be assessed more accurately. The hallmark of peripheral dizziness is vertigo, which is defined as "the false sense of motion." Vertigo can present as a sensation or visual illusion that the external world is moving relative to an individual or that the individual is moving relative to space. Usually, patients describe the sensation or visual illusion as a "spinning" or "whirling" feeling; however, some patients feel as if they are rolling, rocking, bouncing or falling. For most patients with peripheral labyrinthine

Table 1: Symptomatology of peripheral versus central *dizziness*

Characteristic	BPPV	Ménière's	Peripheral PLF	SSCD	Lab	VN	MAD	Central Vascular / Cardiac
Vertigo*	+++	+++	+++	+++	+++	+++	++	+**
Light headed							+++	+++
Onset	acute	acute	acute	acute	acute	acute	gradual	varies
Intensity	severe	severe	severe	severe	severe	severe	varies	varies
Duration	< Min.	Min. - Hrs.	Sec.- Hrs.		Days	Days	varies	varies
Recovery	rapid	rapid	varies	varies	gradual	gradual	gradual	varies
Head Position	+++	++	++		++	++	++	+++
Tinnitus		+++	+++	++	++			
Aural Fullness		+++	+++	++				
Sound Sensitivity		++		+++				
Hearing loss		+++	+++	+	+++			
LOC								+++
Tullio Effect		++	++	+++				
Light sensitivity							+++	
Head Trauma Hx	++		+++	+++				
FNF (except CN VII)	-	-	-	-	-	-	++	++

* Perception of rotary motion

** brainstem stroke Abbreviations: BPPV, benign positional paroxysmal vertigo; CN, cranial nerve; FNF, focal neurologic findings; Hrs., hours; Hx, history; LOC, loss of consciousness; MAD, migraine-associated dizziness; Min., minute; PLF, perilymphatic fistula; Sec. = seconds, SSCD, superior semicircular dehiscence; VN, vestibular neuritis

disorders, the description is brief and focused on vertigo. Patients with acute central nervous system (CNS) dysfunction may or may not have sensations of vertigo, whereas chronic CNS, cerebrovascular, cardiovascular and metabolic causes of dizziness seldom produce true sensations of relative motion **(Table 1)**.

Symptoms Accompanying Peripheral Disease

Patients with peripheral vertigo have distinctive features of onset, duration, frequency and accompanying symptoms in relation to their dizziness **(Table 1)**. Peripheral vertigo occurs in episodes and usually lasts seconds (benign paroxysmal positional vertigo [BPPV]), minutes to hours (Ménière's disease), or hours to days (vestibular neuritis). Hearing loss, tinnitus and aural fullness are frequent symptoms of peripheral disease. It is important to establish if vertigo is induced by head position. For instance, BPPV should be suspected in cases of brief vertigo brought on by changes in head position, such as rolling over in bed. Symptoms may also be triggered by eating salty foods (Ménière's disease) or by changes in middle ear or intracranial pressure, such as sneezing, valsalva or loud noises (Superior semicircular canal dehiscence; SSCD)[1-9]. In most episodes, the onset is sudden; however, the episode's conclusion is less well defined. For the most part, patients feel normal between vertiginous episodes **(Table 1)**.

Symptoms Accompanying Central Nervous System Disease

Unlike peripheral vertigo, central nervous system causes of dizziness produce a more variable picture **(Table 1)**. The sensations patients experience may be described in a variety of ways: spinning, tilting, being forced to one side, lightheadedness, clumsiness, or blacking out. If loss of consciousness is documented, a peripheral etiology for dizziness is rarely—if ever—at fault. Each of the following neurologic-associated symptoms suggest a central etiology for dizziness: dysarthria, dysphagia, diplopia, hemiparesis, severe localized cephalgia, seizures, and memory loss. Compared to peripheral vertigo, the timeline of symptoms is more variable—ranging from minutes to hours—and sensitivity to changes of position is less predictable. Migraine-associated vertigo can last hours to days and is often associated with photophobia, phonophobia, a personal history of migraine, and/or a first-degree relative with migraine[10-12]. Females have a greater preponderance for migraine-associated vertigo than males[13-16]. The above symptoms lead the clinician to suspect brainstem or cortical rather than labyrinthine sources **(Table 1).**

Accompanying Auditory Complaints

The single most useful localizing symptom in a dizzy patient is a unilateral otologic complaint: aural fullness,

tinnitus, hearing loss, or distortion. By carefully evaluating these complaints, the clinician frequently can localize both the side and the site of the lesion before any examination or testing is performed. Frequent causes of unilateral auditory disease with dizziness include endolymphatic hydrops, perilymphatic fistula, labyrinthitis, vestibular neuritis (slight high-pitched loss with tinnitus), superior semicircular canal dehiscence **(Table I)**. While the classic presentation of autoimmune inner disease is decreased hearing accompanied by tinnitus, vertigo may be the presenting symptom in some patients.

General Physical and Emotional Health

Many medical conditions and emotional factors can create a sense of dizziness and imbalance. Hypertension, hypotension, atherosclerotic disease, cardiovascular disease, cerebrovascular disease, neurodegenerative disease, endocrine imbalances, and anxiety states are common causes of lightheadedness. Syncope and/or generalized instability rarely produce a sense of true vertigo. Side effects of medications as well as excessive intake of caffeine, nicotine, alcohol and other substances (legal and illegal) should also be investigated as possible sources of or contributors to the symptoms.

Performing the Physical Examination

After the history is complete, the clinician performs the full head and neck examination. This is important for two reasons: (1) dizzy patients frequently have other ear, nose, and throat pathology and (2) structural problems of the ear, nose, and throat may cause dizziness or indicate a more widespread process. Common findings on the routine examination related to dizziness include cerumen impaction, otitis media with effusion, chronic otitis with otorrhea, chronic sinusitis with nasal airway obstruction, and oropharyngeal findings consistent with sleep apnea. Certainly, congenital deformities of the face, external auditory canal, and pinna raise the question of labyrinthine involvement.

At the conclusion of the head and neck examination, the specialized examination for dizziness is performed. Patients are tested with their glasses or contact lenses in place for best corrected vision. The sequence of the examination is as follows:

1. Spontaneous nystagmus
2. Gaze nystagmus
3. Smooth pursuit
4. Saccades
5. Fixation suppression
6. Head Impulse Test (HIT)
7. Headshake Test
8. Dynamic visual acuity
9. Hallpike positioning
10. Static positional
11. Limb coordination
12. Romberg stance
13. Gait observation
14. Specialized tests

Spontaneous Nystagmus

Examination

Ask the patient to fixate on a stationary target in neutral gaze position with best corrected vision (if applicable, with glasses or contact lenses in place). Observe for nystagmus or rhythmic refixation eye movements. Repeat this sequence under Frenzel lenses to remove target fixation.

Interpretation

If nystagmus is observed, particular attention is paid to the amplitude, direction, and effect of target fixation. Lesions of the labyrinth and nerve VIII produce intense, direction-fixed horizontal-rotary nystagmus that is enhanced in the absence of visual fixation (e.g. Frenzel lenses). The nystagmus also intensifies when gazing in the direction of the fast phase (Alexander's law). In rare instances, the irritative phase may be observed (fast phase toward the affected ear) and destructive (fast phase toward the unaffected ear) lesions of the labyrinth, nerve VIII, or (rarely) the vestibular nuclei. In the majority of cases the examiner observes the destructive phase of the process. In contrast, lesions of the brainstem, cerebellum, and cerebrum cause less intense, direction-changing horizontal, vertical, torsional, or pendular nystagmus that may appear diminished under Frenzel lenses. Examples include periodic alternating nystagmus, congenital nystagmus, and lesions of the midline cerebellum (for further detail see Leigh and Zee 2006).

Gaze Nystagmus

Examination

Ask the patient to gaze at a target positioned 20° to 30° to the left, right, up and down of center, for 20 seconds each. Observe for gaze-evoked nystagmus or change in the direction, form, or intensity of spontaneous nystagmus.

Interpretation

The ability to maintain eccentric gaze is under the control of the brainstem and midline cerebellum, particularly the vestibulocerebellum (especially the flocculonodular lobes). When these mechanisms fail to hold the eye in the eccentric position, the eye drifts toward the midline (exponentially decreasing velocity). Refixation saccades toward the target follow the eye drift. Such gaze-evoked

nystagmus is central in origin and always beats in the direction of intended gaze. In contrast, enhancement of peripheral spontaneous nystagmus (linear slow component velocity) occurs without direction change when gazing in the direction of the fast phase (Alexander's Law). Causes of gaze-evoked nystagmus include drug effects (sedatives, antiepileptics), alcohol, CNS tumors, and cerebellar degenerative syndromes.

Smooth Pursuit

Examination

The examiner positions his/her finger 3 feet in front of the patient. The patient tracks the examiner's finger moving left, right, up, and down. Assure that the patient can visualize the target clearly with best corrected vision and is attentive to the task. The examiner should make certain that the target does not exceed 60° in total arc or 40° per second in velocity.

Interpretation

Normal eye tracking of a slowly moving object generates a smooth eye movement. Cerebellar or brainstem disease can cause saccadic eye tracking in which the patient repeatedly loses the target resulting in small resetting saccades. In most cases, abnormal pursuit is non-localizing within the CNS, although ipsilateral loss of pursuit can be ascribed to parietal lobe lesions. The examiner should be aware that smooth pursuit performance progressively deteriorates as a patient's age increases[17-20].

Saccades

Examination

Ask the patient to look back and forth between two outstretched fingers held 12 inches apart in the horizontal and vertical planes. Observe for latency of onset, velocity, accuracy, and conjugate movement.

Interpretation

Saccadic eye movements are refixation movements that involve the frontal and parietal eye fields, paramedian pontine reticular formation, medial longitudinal fasciculus, superior colliculus, and oculomotor nuclei III, IV, and VI. Important characteristics to observe during examination are amplitude, velocity, conjugate deviation, accuracy and latency. The midline cerebellum and fastigial nuclei control saccadic accuracy, whereas velocity, latency, and conjugate deviation are controlled in the brainstem and frontal eye fields. Small amplitude saccades are characteristic of myasthenia gravis or an abnormality in the orbit. Slow saccades are seen in cortical and brainstem disease. Progressive supranuclear palsy (PSP) is characterized by slow vertical saccades initially as well as slow and hypometric (undershoot) horizontal saccades. Olivopontocerebellar atrophy (OPCA) also known as spinocerebellar ataxia (SCA) is characterized by slow saccades, especially in the horizontal direction. Inaccurate saccades (especially hypermetria or overshoots) are associated with cerebellar vermis and fastigial nuclei lesions. Lesions of the frontal eye fields produce an increased latency for contralateral saccades. Pathology of the medial longitudinal fasciculus produce internuclear ophthalmoplegia (INO), which is characterized by disconjugate eye movements with slowing of the adducting eye and overshoots of the abducting eye. INO is frequently associated with multiple sclerosis.

Fixation Suppression Test

Examination

First, rotate the patient without fixation. Then look for nystagmus. Next, ask the patient to fixate on his/her own index finger held out in front at arm's length. Unlock the examination chair and rotate the patient up to 2 Hz while the patient stares at their finger moving with them. Notice whether or not there is a decrease in the visual-vestibular nystagmus that is evoked during rotation without ocular fixation.

Interpretation

The modulation of nystagmus invoked by rotation is a CNS phenomenon that is heavily dependent on the cerebellar flocculus. Failure of fixation suppression in the presence of adequate visual acuity implies floccular dysfunction. Although this test is performed at a higher velocity, it is similar in nature to the fixation suppression performed after caloric stimulation.

Head Impulse Test (HIT)

Examination

While the patient fixates on the examiner's nose, move patient's head 30° off midline. Thrust the patient's head rapidly (velocity >200°/sec, acceleration >2000°/sec2) to midline. Look for any movement of the pupil during the head thrust and a refixation saccade back to the target **(Figure 2)**. Either direct observation of pupillary movement or the use of an ophthalmoscope is employed to document eye movement.

Interpretation

The head impulse test was introduced by Halmagyi and Curthoys in 1988 and is based on the oculocephalic response. The HIT is described as a reliable sign of significantly reduced unilateral horizontal semicircular

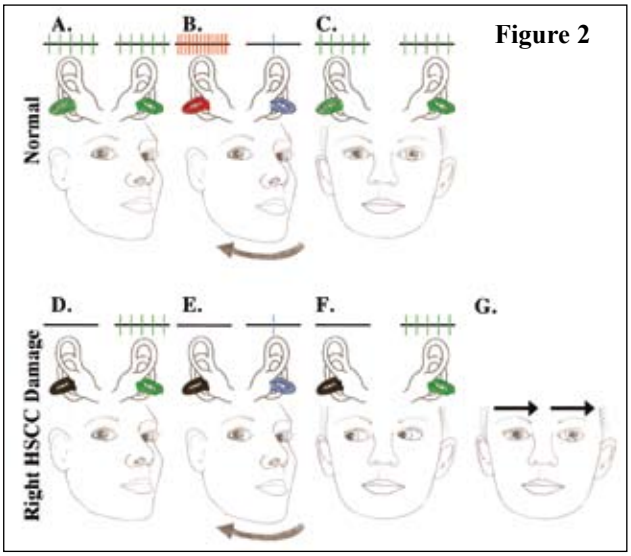

Figure 2

Figure 2. *Head impulse test (HIT) in normal and diseased subjects. The stages of the HIT are exemplified in a normal subject (A-C) and a patient with a damaged right horizontal semicircular canal (D-G). The test begins with the patient's head at 30°off midline while they fixate on the examiner's nose (A and D). A) In the normal subject at rest, the primary afferents of both horizontal semicircular canals (green) fire a resting basal rate. Since the input is symmetric, the brainstem detects no motion.* **B)** *In the normal subject, the examiner thrusts the head rapidly (<2000 deg/sec2) to the midline (from left to right). The discharge rate of the HSCC afferents ipsilateral tothe velocity vector increases (red, right). The discharge rate of the HSCC afferents contralateral to the velocity vector decreases (blue, left). The brainstem detects asymmetric input and, with an intact vestibulo-ocular reflex, the eyes are driven contralateral (left) to the higher firing rate (red, right).* **C)** *Visual fixation is maintained throughout the HIT and the HSCC afferents return to their basal firing rate.* **D)** *When one labyrinth is damaged, the firing rateof the afferents decreases (right, black).* **E)** *The head is thrust towards the damaged side (left to right). Although, the firing rate in the healthy HSCC afferents (blue, left) decreases compared to the resting position, the rate is higher than the damaged side (black, right).* **F)** *Therefore, the eyes are driven contralateral to the healthy sideand ipsilateral to the damaged side.* **G)** *In order to reset visual fixation, a saccadic eye movement is necessary. Abbreviations: HIT, head thrust test; HSCC, horizontal semicircular canal.*

canal function. The observation of eye movement during the maneuver is a sign of decreased neural input from the ipsilateral ear to the vestibulo-ocular reflex because the contralateral ear is inhibited during rapid contralateral movement and cannot supply enough neural activity to stabilize gaze. In such instances, the eye travels with the head during the high-velocity movement, and a refixation saccade is necessary to refoveate the target. Bilateral refixation movements are seen frequently in cases of ototoxicity. This test only detects horizontal semicircular canal dysfunction.

Post-headshake Nystagmus

Examination

Tilt the head of the patient forward 30° and shake the head in the horizontal plane at 2 Hz for 20 seconds. Observe for post-headshake nystagmus and note direction and any reversal. Frenzel lenses are preferred to avoid fixation **(Figure 3)**. The maneuver may be repeated in the vertical direction.

Interpretation

Post-headshake nystagmus is considered a pathologic sign of vestibular input asymmetry in the plane of rotation[21,22]. Typically, a peripheral cause is identified with the fast phase of nystagmus directed toward the stronger ear. A small reversal phase is sometimes observed. Signs of central etiology include prolonged nystagmus, vertical nystagmus following horizontal headshake ("cross coupling"), and disconjugate nystagmus.

Dynamic Visual Acuity

Examination

Ask the patient to read the lowest (smallest) line possible on a Snellen eye chart with best corrected vision. Repeat the maneuver while passively shaking the patient's head at 2 Hz, and record the number of lines of acuity "lost" during the headshake.

Interpretation

Dynamic visual acuity is also referred to as the dynamic illegible E test (DIE)[23]. An acuity decrease of more than two lines is abnormal. Excessive retinal slippage during head movement is a sign of vestibular dysfunction. In the clinical examination, the most frequent etiology is bilateral vestibular loss related to ototoxicity or aging. Poorly-compensated, unilateral dysfunction can also cause loss of dynamic visual acuity. However, using clinical testing, it is harder to identify a unilateral abnormality while assessing testing for dynamic visual acuity at the same time. During dynamic visual acuity assessment, it is important that the examiner shake the patient's head continually, avoiding pauses, during which the patient can see the target and unconsciously attempt to compensate for their dysfunction.

Dix-Hallpike Maneuver

Examination

With the examination chair unfolded, turn the patient's head 45° to one side while the patient is in a sitting position. Hold the patient's head firmly and rapidly, but carefully, recline the patient to a head-hanging position.

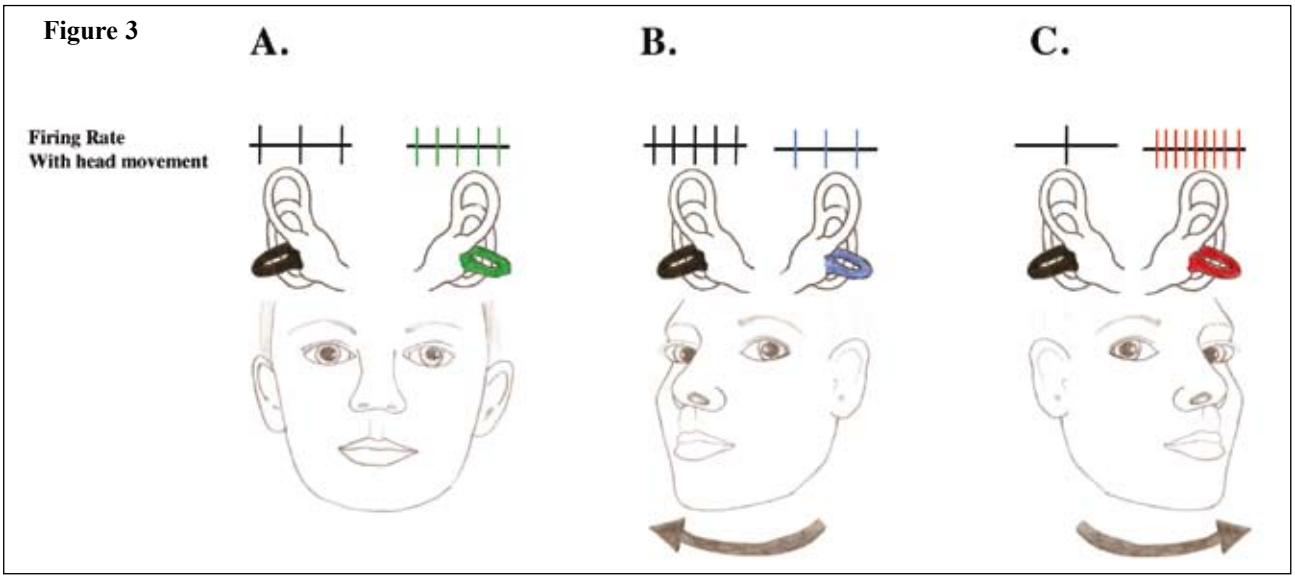

Figure 3. *The post-headshake nystagmus test in a patient with right labyrinthine hypofunction.* **A)** *When the head is stationary, the asymmetry in basal firing rates between the healthy labyrinth (left, green) and the hypofunctioning labyrinth (right, black) is minimal.* **B)** *With head turns toward the hypofunctioning labyrinth (right, black), a weaker than normal excitatory response is elicited. The firing rate of the healthy labyrinth decreases (left, blue).* **C)** *Turning the head toward the healthy labyrinth (left, red) produces a normal excitatory response. Each head rotation amplifies the asymmetry and the activity accumulates in the central velocity-storage mechanism. The nystagmus following head shaking reflects the discharge of the stored activity.*

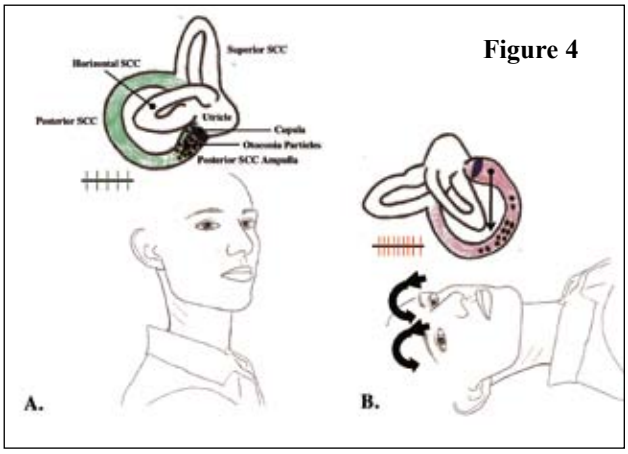

Figure 4. *The Dix Hallpike maneuver in a patient with right posterior semicircular canal benign paroxysmal positional vertigo.* **A)** *In a seated position, the calcium carbonate otoconia particles accumulate in the dependent portion of the right posterior SCC. The posterior SCC afferent fibers fire at the basal rate (green). The examiner turns the patient's head to the right 45°.* **B)** *The examiner moves the patient's head rapidly into a head-hanging, right-ear-down position while observing for eye movement. This maneuver moves the head in the plane of the right posterior SCC, causing the otoconia particles to move in an ampullofugal direction (straight arrow). This motion displaces the cupula and excites the posterior SCC afferent fibers (red). This results in a geotropic torsional nystagmus (curved arrows, fast phase of torsional nystagmus towards the ground). The examiner returns the patient to a seated position before turning the head to the left 45° and repeating the maneuver. SCC, semicircular canal.*

Hold this position for 30 seconds. Observe the eyes for nystagmus and, if present, note the following five characteristics: latency, direction, habituation (duration), fatigability (decreased nystagmus on repeated maneuvers), and reversal with rising to a sitting position **(Figure 4)**. Return the patient to an upright, seated position between head-hanging right-ear-down and left-ear-down positions **(Figure 4)**.

Interpretation

A positive maneuver is diagnostic for BPPV, which is thought to be due to otoconial debris either floating (canalithiasis) or fixed (cupulolithiasis) within the semicircular canal (SCC) (24). The posterior canal is affected more than 90% of the time followed by the horizontal SCC (6-8%), and rarely the superior semicircular canal (< 1%) (25, 26). For BPPV of the posterior SCC, a positive response is elicited when the affected ear is positioned toward the ground. Classic positioning nystagmus includes geotropic (towards the ground) torsional fixed direction, brief latency (5 to 20 seconds), < 30 seconds duration, and reversal nystagmus upon returning to a seated position, and fatigability with repeated positioning **(Table 2)** [24]. BPPV of the horizontal SCC is distinguished from BPPV of the posterior SCC by nystagmus in the horizontal direction (which can change from geotropic to ageotropic horizontal depending on the head position), shorter latency (0 to 3 seconds), and longer duration (30 to 60 seconds, Table 2). Nystagmus findings that do not fit

Table 2: Physical examination findings of peripheral, central, and systemic *dizziness*

Examination	Peripheral					Central*
	BPPV	Ménière's	PLF	SSCD	VN	
Sp. Nystagmus†	+++	+++	++	+	+++	+++
Gaze Nystagmus††	+++	+++	++	+	+++	+++
Smooth pursuit	-	-	-	-	-	+++ Saccadic eye tracking
Saccades	-	-	-	-	-	+++ Delayed, inaccurate, or disconjugate saccades
Fixation Suppression	-	-	-	-	-	+++ Failure of fixation suppression
HIT‡	+++	+++	+++	+	+++	-
PHSN§	+++	+++	+++	+	+++	+++
Dynamic Visual Acuity	+++	+++	+++	+	+++	-
Dix Hallpike^	+++	+	+	+	+	+++
Limb Coordination	-	-	-	-	-	+++ Dysmetria or dysdiadochokinesia
Romberg Stance						
Firm Ground	-	-	-	-	-	+++
Tandem Stance or 3" Foam	++	+++	++	+	+++	+++
Gait Observation	Occasionally, touches wall with hand for proprioceptive reference					+++ Various gait abnormalities
Unterberger / Fukuda Step test^^	++	+++	++	+	+++	-
Tragal Pressure	-	-	++	++++	-	-
Pneumatic Pressure	-	-	++	++++	-	-
Tuning Force	-	-	++	++++	-	-
Valsalva	-	-	++	++++	-	+++ Vertical downbeating nystagmus

* Central causes include multiple sclerosis, cerebrovascular accident, Parkinson's disease, normal pressure hydrocephalus

† In peripheral pathology, spontaneous nystagmus is enhanced by Frenzel lenses (decreases visual fixation) and is direction-fixed, horizontal-rotary nystagmus. In central pathology, spontaneous nystagmus diminished with Frenzel lenses and is direction-changing, horizontal, vertical, torsional or pendular nystagmus.

†† In peripheral pathology, gaze evoked nystagmus is enhanced when gazing in the direction of the nystagmus fast-phase. In central pathology, the nystagmus fast phase is in the direction of intended target.

‡ In peripheral pathology, the refixation saccade is observed when the head is thrust toward the hypofunctioning ear.

§ In peripheral pathology, during the primary phase, the fast phase of the PHSN is toward the healthy ear. In the secondary or reversal phase, the fast phase of the PHSN is toward the hypofunctioning ear. In central pathology, cross coupling occurs (vertical nystagmus is produced by horizontal headshake).

^ In peripheral pathology, the latency is 0-15s, duration is 5-30s, nystagmus is fatigable, direction is fixed (horizontal, torsional). In posterior semicircular canal pathology (with the hypofunctioning ear down), the nystagmus is fixed with the fast phase geotropic torsional, there is a brief latency (5-20s) and the duration is < 30s. In horizontal semicircular canal pathology, the nystagmus is horizontal (can change from geotropic to ageotropic horizontal), there is a shorter latency (0-3s) and a longer duration (30-60s). In central pathology, there is no latency, nystagmus duration is 30-120s, the nystagmus is direction changing and is vertical or horizontal.

^^ In peripheral pathology, the patient rotates > 45° toward hypofunctioning ear.

Abbreviations: BPPV, benign paroxysmal positional vertigo; dec., decreased; HIT, head impulse test; horiz., horizontal; PHSN, post-head shake nystagmus; PLF, perilymph fistula; Sp. Nystagmus, spontaneous nystagmus; s, seconds; SSCD, superior semicircular canal dehiscence; VN, vestibular neuritis.

these patterns may be due to BPPV of the superior SCC, or bilateral SCCs. The canalith repositioning maneuver is used to treat BPPV and is not discussed in this paper.

Positional Tests

Examination

Ask the patient to lie still in three positions–supine, left lateral, and right lateral–for 30 seconds and observe for nystagmus. Use of Frenzel lenses is recommended.

Interpretation

The presence of a static positional nystagmus is non-localizing by itself and must be interpreted in light of other physical findings. In general, however, vertical positional nystagmus is central in origin, implying a cranial-cervical or fourth ventricle origin.

Limb Coordination Tests

Examination

Ask the patient to perform a series of coordination tasks, such as finger-nose-finger, heel-shin, rapid alternating motion, and fine-finger motion (counting on all digits). Observe for dysmetria or dysrhythmia.

Interpretation

The presence of limb dysmetria or dysdiadochokinesia is a useful indicator of cerebellar cortical disease, which may or may not accompany midline or vestibulocerebellar oculomotor dysfunction.

Romberg Test

Examination

Have the patient stand with feet close together and arms at the side with eyes open and then eyes closed. Observe for the relative amount of sway with vision present versus absent.

Interpretation

The Romberg stance primarily tests somatosensation and proprioception functions and not the integrity of vestibular inputs. Patients compensating for bilateral vestibular loss are able to stand in the normal both eyes-open and eyes-closed Romberg position because of adequate proprioception from a stable support surface. There are two ways, however, to increase this test's sensitive to detect vestibular deficits: instruct the patient to 1) stand in the tandem stance and then 2) step onto a piece of 3-inch foam. In the tandem stance, the support surface cues are

sufficiently altered so that vestibular cues play a greater role in maintaining upright posture. Similarly, when the patient stands on a compliant support surface, such as 3-inch foam, somatosensory cues are muted and vestibular cues become more important.

Gait Observation

Examination

Ask the patient to walk 50 feet in a hall, turn rapidly, and walk back without touching the walls. Observe for initiation of movement, stride length, arm swing, missteps, veering, and signs of muscle weakness or skeletal abnormality (kyphoscoliosis, limb asymmetry, and limp).

Interpretation

"Vestibular gait" does not define any specific manner and/or type of movement. Indeed, broad array of characteristics can qualify a gait as abnormal. Furthermore, a number of causes can be the source(s) of the abnormal gait. If a patient suffers an acute unilateral loss of otolithic function, the patient will tend to veer toward the side of the lesion. However, a variety of central brainstem and musculoskeletal lesions also produce lateral deviation during ambulation. Difficulties with gait initiation and turns as well as decreased arm swing can be seen in extrapyramidal disease. Gait ataxia implies cerebellar dysfunction and is distinctly different from gait deviation associated with uncompensated peripheral vestibular disease. Finally, exaggerated hip sway, rhythmic deviations, and an excessive reliance on touching the wall during ambulation may constitute signs of a functional gait disorder.

Specialized Tests

Fukuda / Unterberger Step Test

Examination

Ask the patient to march in place with arms extended straight out and eyes closed for 1 minute. Note the degree of lateral rotation at the end of the maneuver.

Interpretation

The step test was first described in 1938 by Unterberger and later modified by Fukuda in 1959 (27, 28). Most normal subjects deviate less than 45° in rotation to one side during the step test, whereas some patients with uncompensated unilateral dysfunction deviate more than 45° toward the affected side. This finding alone, however, is not conclusive for otolith dysfunction.

Tragal Compression, Pneumatic Otoscopy, Tullio Phenomenon, Valsalva with pinched nostrils and closed glottis

Examination

With Frenzel lenses in place, observe for nystagmus or tonic eye deviations with symptoms of dizziness under four test conditions: (1) steady tragal compression to increase pressure in the external auditory canal, (2) positive and negative pressure applied with the pneumatic otoscope, (3) presentation of loud tones via tuning fork or impedance bridge, and (4) increased pressure during breath holding against pinched nostrils or closed glottis (Valsalva).

Interpretation

Consistent eye deviations or nystagmus during any of the preceding maneuvers implies abnormal coupling between either the outside atmosphere or the intracranial space and the inner ear. This can occur with abnormal connections between the labyrinth and the middle ear or middle fossa at the following sites: oval window (perilymph fistula, excessive footplate movement), round window (perilymph fistula), lateral semicircular canal (perilymph fistula), and superior semicircular canal (dehiscence). In particular, eye elevation and torsion away from the affected ear with loud sounds, pressure in the EAC (Hennebert's sign) or Valsalva maneuver against pinched nostrils suggests of superior canal dehiscence syndrome and has been described by Minor (1998). In addition, cranial-cervical junction abnormalities (Arnold-Chiari malformation in particular) produce vertical downbeat nystagmus with any maneuver that increases intracranial pressure.

Hyperventilation

Examination

Ask the patient to take 20 deep breaths, inhaling and exhaling in rapid succession. Observe for nystagmus under Frenzel lenses, and record symptoms.

Interpretation

Hyperventilation has two effects: (1) cerebrovascular vasoconstriction and (2) elevation of blood pH. Vasoconstriction causes lightheadedness and tingling of the hands and lips. Symptoms might be reproduced in patients with hyperventilation syndrome or anxiety. More specifically, irritative nystagmus (toward the affected ear) secondary to elevated pH and increased eighth nerve firing is seen in lesions affecting the vestibular nerve, such as petrous apex lesions, acoustic schwannoma, and eighth nerve demyelination.

Mastoid Oscillation

Examination

Place a vibration source on the mastoid tip and observe for nystagmus under Frenzel lenses. Note direction and waveform in addition to the effect of target fixation when the lenses are removed.

Interpretation

Nystagmus produced by mastoid oscillation in patients with vestibular asymmetry was first described by White et al in 2007[29]. Mastoid oscillation acts as an excitatory stimulus to both labyrinths and, in some cases of asymmetry, produces a horizontal-rotatory nystagmus toward the stronger ear. In a sense, this nystagmus is similar in origin to that produced by the headshake maneuver.

Conclusions

1. A thorough history and structured oculomotor and posture-gait examination is crucial in the evaluation of patients suffering with dizziness and/or imbalance.
2. The test protocol detailed in this review is a succinct—yet comprehensive—battery that can be added to the standard otologic or neurologic examination.
3. Laboratory tests for dizziness primarily play a confirmatory role and following a complete history and examination of patients afflicted with vestibular symptoms.

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Malignant Otitis Externa

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Abstract

Malignant otitis externa, or necrotizing external otitis, is a potentially lethal infection of the external auditory meatus and bony tympanic plate that may spread to the base of the skull and result in cranial neuropathies. The causative organism is usually *Pseudomonas aeruginosa*. It occurs typically but not only in elderly diabetic patients. The mortality rate is about 10 per cent.

Effective management involves early diagnosis, good glycaemic control in diabetic cases, and prolonged antibiotic therapy which may need to be given parenterally. Challenges in management include the emergence of antimicrobial resistance and determining the end point of prolonged and expensive therapy.

Key Words

Malignant otitis externa, necrotizing external otitis, skull base osteomyelitis

A search of Medline and EMBASE was carried out using the above MeSH headings.

Introduction

Malignant otitis externa is a potentially fatal osteomyelitis and periostitis of the external auditory meatus and bony tympanic plate, which may spread along the inferior surface of the skull base **(Fig 1)**. The condition occurs typically but not exclusively in elderly diabetic patients. *Pseudomonas aeruginosa* **(Fig 2)** is the causative organism in 90 per cent of cases[1].

The presentation is with severe unremitting otalgia, purulent aural discharge and granulations at the isthmus (bone-cartilage junction) of the external auditory meatus[2]. Single or multiple cranial neuropathies may develop. The facial nerve is usually affected first and most frequently. Complications include dural sinus thrombosis, meningitis and cerebral abscess.

In 1959, Meltzer and Keleman first described the condition in a patient with poorly controlled diabetes who died after protracted antibiotic therapy and repeated surgical debridement[3]. In 1968, Chandler published a series of 13 cases of which 11 had diabetes; all underwent surgical debridement, and six died[4]. Chandler named the condition *malignant otitis externa* because of its ominous nature; the condition is not neoplastic.

The reduction in mortality over the past fifty years, from 50 per cent to below 10 per cent[5,6,7], is attributable to the advent of modern antibiotic therapy, modern imaging and a greater awareness of the disease. Surgical debridement is now used infrequently.

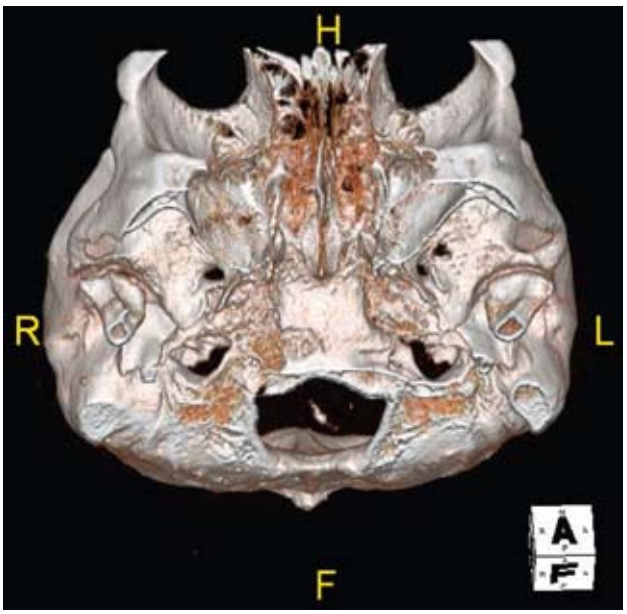

Fig 1: *Three-dimensional computed tomography reconstruction of the skull base showing erosion of the right petrous apex, hypoglossal canal and clivus.*

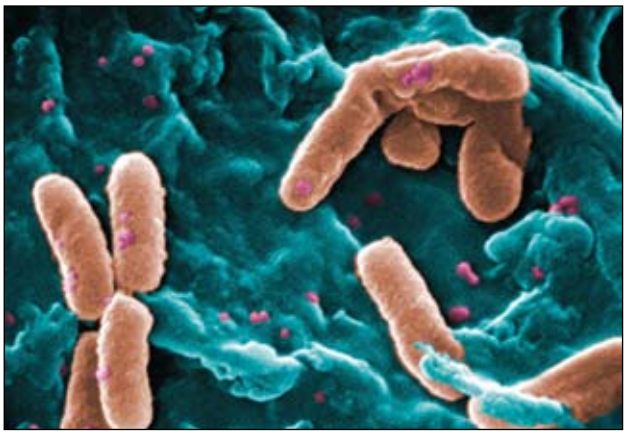

Fig 2: *Colorised scanning electron micrograph of Pseudomonas aeruginosa.* Content Providers: CDC / Janice Haney Carr (Wikimedia Commons)

Pathophysiology

Infection begins in the skin and cartilage of the external auditory meatus. Invasion into the adjacent tympanic plate leads to ulceration and granulation tissue at the isthmus. Infection spreads through the fissures of Santorini and the tympanomastoid suture to the skull base. Periostitis spreads along the under surface of the skull base to involve the stylomastoid foramen and then the jugular and hypoglossal foramina **(Fig 3)**. This can lead to facial and then glossopharyngeal, vagus, accessory and hypoglossal nerve palsies[2,4,8]. The otic capsule is not usually affected.[9] Trismus and inflammation of the temporomandibular joint have been reported **(Fig 4)**[10].

The high mortality is accounted for by old age, poorly controlled diabetes and complications such as septic dural sinus thrombosis, meningitis and cerebral abscess. Lower cranial nerve palsies are associated with poor nutrition and aspiration pneumonia. Acute infections can trigger exaggerated local inflammation in atherosclerotic coronary arteries[11], and systemic inflammation is a risk factor for arterial thrombosis[12]. In Chandler's series of 13 cases, four of the six deaths appear to have been cardiovascular and one cerebrovascular[4].

Identification of the organism is essential to tailoring antimicrobial therapy. *Pseudomonas aeruginosa* is the causative organism in more than 90 per cent of cases. Pseudomonas is a Gram-negative aerobic bacillus ubiquitous in water[13]. Fungi and other bacteria have been reported[1]. *Aspergillus fumigatus* is probably the second commonest causative pathogen reported, but other fungi have been isolated: *Aspergillus niger, Scedodporium apiosperumum, Pseudallescheria boydii, Candida ciferri* and *Malassezia sympodialis*. Other bacteria reported in cases of malignant otitis externa are *Staphylococcus aureus, Proteus mirabilis, Klebsiella oxytoca, Pseudomonas cepacia* and *Staphylococcus epidermidis* although it is unclear if these bacteria were true pathogens[14].

Diabetes may promote infection because of conditions in the ears of diabetic patients. Cerumen is less acidic, which may lessen its bactericidal action; microvascular disease may impede blood flow; and phagocytosis may be reduced.

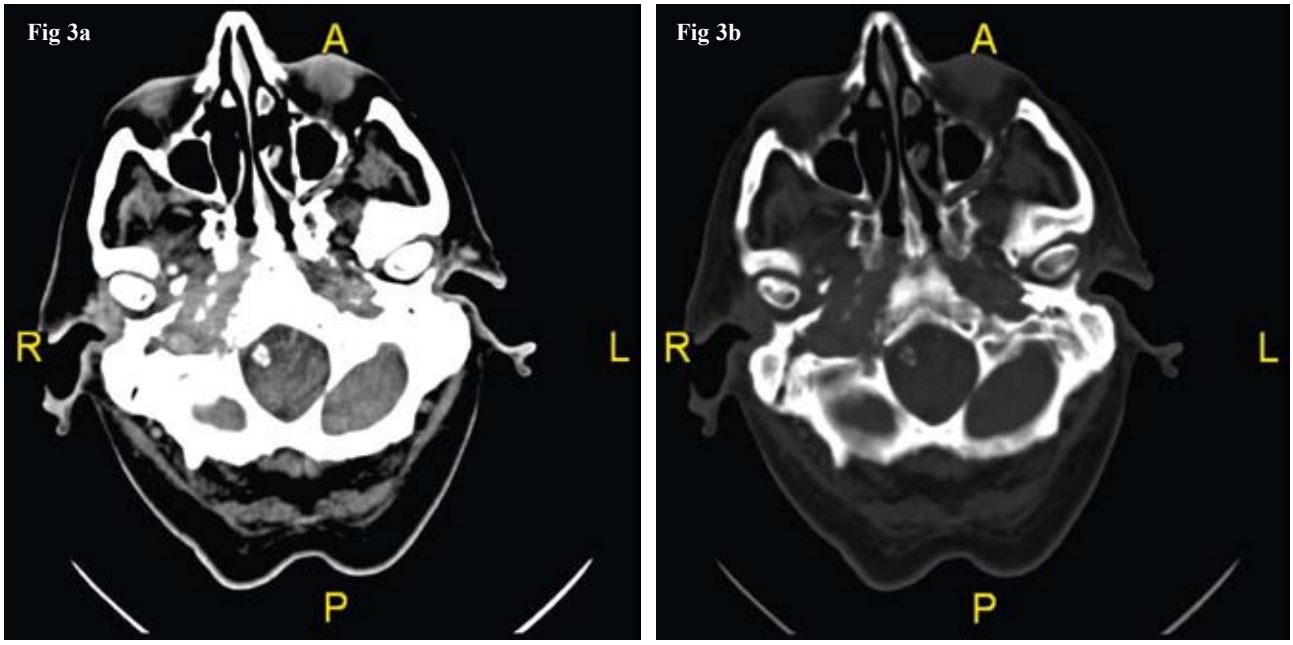

Fig 3: *Axial computed tomography showing extensive soft tissue changes in (a) and bone erosion involving the right temporal bone extending to the foramen magnum and involving the lower cranial nerves (IX, X, XI, XII) in (b).*

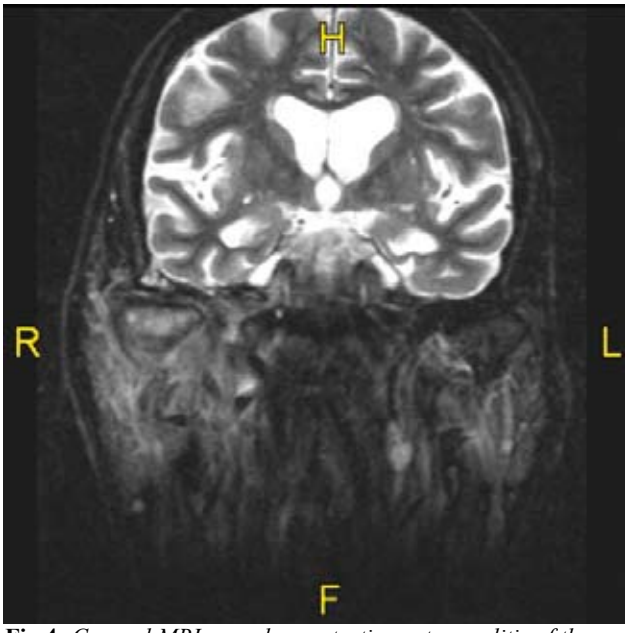

Fig 4: *Coronal MRI scan demonstrating osteomyelitis of the right skull base affecting the temporomandibular joint.*

With improved glycaemic control phagocytosis may improve, but normalisation of plasma glucose does not fully correct a defect in neutrophil and macrophage phagocytosis[15,16].

In one series, non-diabetic patients accounted for one third of cases[17]. Often there is no obvious predisposing disease, but in some cases there is immunocompromise from a condition such as acquired immunodeficiency syndrome (AIDS).

In children any immunocompromise is usually due to malignancy, and diabetes plays a part in less than a third of childhood cases[18]. Skull base osteomyelitis in children is most frequently caused by *Pseudomonas*; it tends to arise from otitis media and hence involves the facial nerve more often[19].

Aural syringing of cerumen is probably a risk factor for malignant otitis externa, because it involves irrigation and mild trauma to the skin of the external auditory meatus[20].

Diagnosis

Diagnosis of malignant otitis externa is made on clinical grounds. Otalgia, purulent otorrhoea, isthmus granulations and oedema of the external auditory meatus are typical. *Pseudomonas aeruginosa* may be grown from culture swab or fresh tissue biopsy and antibiotic sensitivity testing should include quinolones. The diagnosis can be confirmed with computed tomography, magnetic resonance imaging or technetium-99m labelled bone scanning. C-reactive protein and erythrocyte sedimentation rate are elevated, but the differential white cell count may be normal[1].

Table 1: Clinicopathological classification system for malignant otitis externa (Scott-Brown's Otorhinolaryngology, Head and Neck Surgery, 7th Ed.)

Stage	
1	Clinical evidence of malignant otitis externa with soft tissue infection beyond the external auditory meatus, but negative 99mTc bone scan
2	Soft tissue infection beyond the external auditory meatus with positive 99mTc bone scan
3	As Stage 2, but with cranial neuropathy
3a	single
3b	multiple
4	As Stage 2/3 with intracranial complication (meningitis, empyema, sinus thrombosis, brain abscess)

There is no widely accepted classification system for malignant otitis externa. A four-stage system published in Scott-Brown's Otorhinolaryngology, Head and Neck Surgery was produced by combining three staging systems published between 1985 and 1991 (see **Table 1**)[21]. However, this system of classification requires a 99mTc bone scan, which is no longer a standard investigation.

Imaging of malignant otitis externa has evolved over the decades. Technetium bone scan scintigraphy using 99mTc methylene diphosphonate is highly sensitive in malignant otitis externa at sites of osteoblastic activity. Scintigraphy may be abnormal before osteoporosis can be demonstrated by CT[22]. However, the specificity is low because bone scan activity is increased at sites of active infection and at sites of healing. Bone scan activity is also raised at sites of simple otitis externa, neoplasm, trauma and recent surgery. The increased scintigraphic activity with healing lasts many months, and weakens the use of scintigraphy in monitoring the response to therapy[14,23,24]. Diabetics may show impaired bone uptake of 99mTc[25].

Gallium scans (gallium citrate Ga67) are abnormal in both bone and soft tissue infections, because radioisotope is

incorporated into infiltrating leucocytes. However, there have been reports of normal gallium scans in cases of disease recurrence, and of abnormal uptake despite clinical resolution[14,23]. Gallium scanning combined with SPECT (single positron emission computed tomography) may be more effective for diagnosis and monitoring[26].

CT and MRI are anatomical scanning modalities and generally considered to be the gold standard in the diagnosis and monitoring of malignant otitis externa. CT may be more readily available in the acute setting and provides information on site and extent of bone erosion across the skull base. CT is not adequate alone to monitor disease activity according to a prospective study[27].

MRI may not be quite so readily available in acute cases but provides more information on the site and extent of soft tissue changes before bone demineralisation is evident on CT. Serial MRI provides information on soft tissue inflammation in monitoring disease resolution or treatment failure[27].

Imaging does not replace histological confirmation from biopsy. Squamous cell carcinoma and lymphoma of the nasopharynx and external auditory meatus may present in a similar way to malignant otitis externa. Squamous cell carcinoma of the temporal bone and malignant otitis externa have been reported to coexist[14,28].

The literature varies on the criteria required for a diagnosis of malignant otitis externa. There is no pathognomonic diagnostic criterion. The Cohen–Friedman (1987) criteria required isotope bone scanning before the widespread use of CT and MRI.29 We propose pathways for diagnosis **(Table 2)** and monitoring progress **(Table 3)**.

Table 2: Initial diagnostic pathway in malignant otitis externa

Clinical features	• Severe otalgia, granulations, older age, diabetes • Immunocompromised patient including child
Complication	Facial +/- other cranial neuropathy, dural sinus thrombosis, meningitis, cerebral abscess
Inflammatory markers	CRP, ESR
Imaging	• CT • (+ MRI) • (+ 99mTc bone scan / SPECT)
Microbiology	Culture of organism with antibiotic sensitivity including quinolones
Histopathology	EUA and biopsy

Treatment

The introduction of semisynthetic penicillins with anti-pseudomonal activity in the 1960s reduced the mortality of malignant otitis externa from over 50 per cent to 20 per cent[8]. The use of parenteral aminoglycoside and beta-lactam antibiotics required prolonged hospitalisation and could cause renal and vestibular toxicity. With the advent of the quinolone antibiotics in the 1980s, oral ciprofloxacin has become the mainstay of treatment for malignant otitis externa[14]. Ciprofloxacin is usually effective against *Pseudomonas aeruginosa* and gives good bone penetration and rapid accumulation. Ciprofloxacin is well absorbed by mouth and has a low toxicity profile[2,23].

In the late 1980s and early 1990s several case series of successful treatment of malignant otitis externa with oral ciprofloxacin alone were published[30,31,32,33]. These series demonstrated further improvements in morbidity and mortality despite treatment at home. In 1989, Hickey *et al*. reported two patients without cranial nerve palsies who after treatment with oral ciprofloxacin given for nine and ten weeks were free of disease five months later[30]. In response to Hickey et al., Fairley *et al*. (1989) reported a case of recalcitrant malignant otitis externa in a 54-year-old poorly controlled diabetic who developed facial, vagus and hypoglossal nerve palsies; after repeated courses of intravenous antibiotics over a period of 13 weeks the patient was discharged on oral ciprofloxacin for three months, after which the infection did not recur[34]. Levenson

Table 3: Monitoring progress in malignant otitis externa

Clinical features in monitoring	Severe otalgia, exudates, granulations
Serial inflammatory markers	CRP, ESR
Monitoring glycaemic control	Capillary blood glucose
Monitoring imaging	• MRI • (+ CT) • (+ gallium citrate scan / SPECT)
Complication	Facial +/- other cranial neuropathy, dural sinus thrombosis, meningitis, cerebral abscess, other

et al. (1991) reported 10 cases free of disease at 18 months after completion of oral ciprofloxacin given for a mean of 10 weeks.31 Zikk *et al*. (1991) reported a cure rate of 83 per cent with oral ciprofloxacin given alone in nine mild cases and 15 more severe cases[32].

Widespread use of quinolone antibiotics, particularly the community use of oral ciprofloxacin, has seen the emergence of resistance. Quinolone antibiotics inhibit two bacterial replication enzymes, DNA gyrase and topoisomerase IV; mutations in these enzymes confer resistance[35]. Bacteria may also adapt by producing a mucopolysaccharide coat, or biofilm, which impedes penetration of antibiotic into the bacterium[36]. In 2002, seven cases of malignant otitis externa unresponsive to ciprofloxacin were reported by Berenholtz et al., of which two occurred in the decade up to 1998 and five in the three years between 1998 and 2001[37]. After a 16-month period of observation ending in 2005, we reported a series of five cases of malignant otitis externa requiring hospital admission for intravenous antibiotic therapy because of a failure to respond to prolonged oral ciprofloxacin monotherapy. Only two of these cases had diabetes, and this was under good control[24]. Given the increase in antibiotic resistance, it is particularly important to isolate the organism and establish its antibiotic sensitivity profile.

Despite the concerns about antibiotic resistance, oral ciprofloxacin is still the first-line outpatient treatment for less severe cases of malignant otitis externa. Ciprofloxacin is given at full dose (750 mg twice daily) for six to eight weeks, as indicated for osteomyelitis[38]. It is important to monitor the response to treatment, because if oral quinolone treatment fails, there is now an urgent need to consider prolonged intravenous antibiotic therapy.

In severe cases, there may be a preference for intravenous therapy from the outset rather than risk wasting time on a potentially ineffective oral antibiotic. There is still a role for oral ciprofloxacin as maintenance therapy in full dose for six to eight weeks once such patients with initially severe malignant otitis externa have responded to parenteral antibiotic therapy.

Some experts now recommend parenteral antibiotics as first-line treatment, even in less severe cases[18,2,39,40,41]. Prolonged intravenous antibiotic therapy can be managed at home in some cases. *P. aeruginosa* may develop resistance to imepenem, ciprofloxacin and ceftazidime, so in the United States there is a vogue for dual antibiotic therapy in malignant otitis externa to try to prevent resistance.

Hyperbaric oxygen has been used as an adjuvant for recalcitrant cases in hospitals with access to hyperbaric chambers[42,43], but its effectiveness remains unproven. If the infection is fungal, amphotericin B is generally indicated for a period of at least 12 weeks[14].

Topical antibiotics are counterproductive in malignant otitis externa. There is a concern that topical antibiotics for a presumed simple otitis externa may interfere with the isolation of the pathogen when systemic therapy is needed for malignant otitis externa. Repeated short courses of oral or topical quinolones are associated with rapid emergence of resistant strains[2,14].

Other than biopsy for histopathological and microbiological diagnosis, surgery has only a limited role in malignant otitis externa, in that some centres may offer debridement in a few cases[14].

Outcomes

With the advent of modern medical management and a greater awareness of malignant otitis externa, the mortality has fallen from about 50 per cent in Chandler's original series to 20 per cent and now less than 10 per cent. Cranial neuropathies occur in 24–44 per cent of cases with the facial nerve being affected most commonly[44]. Among cases with cranial nerve palsies, the facial nerve is affected in 60 per cent[45]. If the disease can be controlled, the facial nerve palsy improves or resolves in a third of adult cases[4], but in children any facial palsy is usually complete and permanent[20,46]. Complications include dural sinus thrombosis, meningitis, cerebral abscess, aspiration pneumonia and death. Recurrence of malignant otitis externa arises occasionally a year or more after initial resolution[14].

Conclusions

We face renewed challenges in the treatment of malignant otitis externa. With an ageing population, increasing rates of diabetes, and increasing microbial resistance to quinolone antibiotics, a resurgence of malignant otitis externa may be underway.

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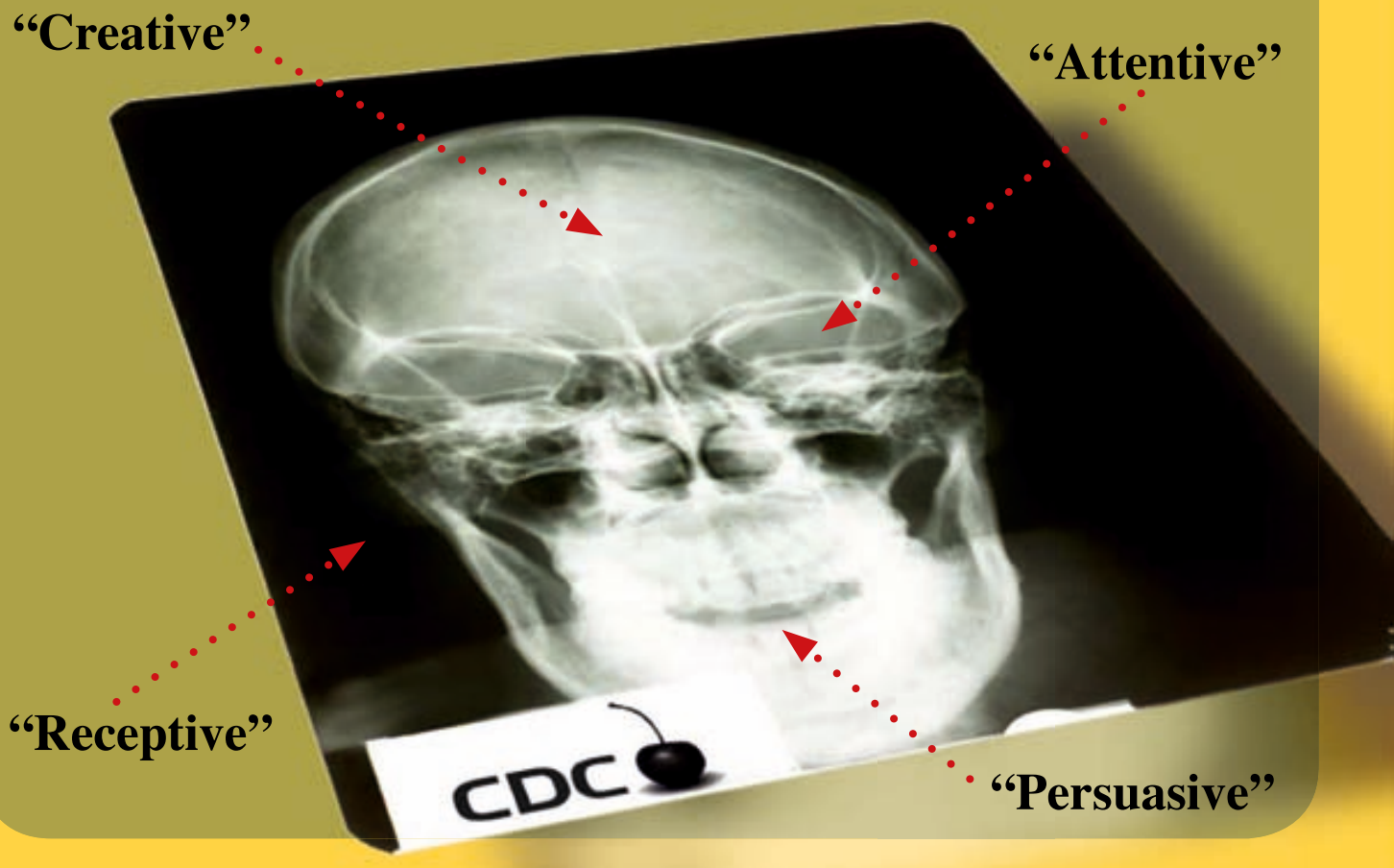

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