Image guided ablation of benign thyroid disease

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Abstract
Non-surgical management techniques have been described to manage thyroid nodules, ranging from high energy and chemical ablation to fine needle aspiration. We performed a review of recent literature of available non-surgical techniques, describing and assessing acknowledged image guided ablation interventions by mechanism of action, indication, effectiveness, limitations, contraindications and the appropriate level of anesthesia or analgesia required. All interventions were deemed safe alternatives to surgrey, and while not as absolute as surgery, can provide an appealing alternative to some patients. Interventions can further be tailored to the patient and nodule morphology.

J ENT Masterclass 2019; 12 (1): 4 - 12.

Key words
Ablation, benign, thyroid.

Background
Thyroid nodules are common in the population with reported rates of up to 65% having significant nodules at autopsy[1]. Nevertheless, the majority of these are not clinically relevant and most patients do not require any interventional treatment. Clearly patients with malignancy or toxic nodules require treatment in the form of surgery and / or Radioactive iodine. Currently patients with compressive symptoms (breathing or swallowing problems) from large or multiple nodules are treated surgically as previously there has been no good "Medical" treatment for this problem. The vast majority of patients with significant thyroid nodules are not malignant, so a treatment that symptomatically improves them whilst avoiding the inherent risks of surgical intervention at little risk in itself is the holy grail for managing these cases.

In recent years, non-surgical techniques have been described to manage thyroid nodules. From high energy and chemical ablation to regular aspiration, these have the potential benefit of providing symptomatic relief for patients without the risks of surgical intervention. Further, they can be cost-effective in comparison as many only require normal cohort of clinic staff compared to inpatient or day case staffing for surgery. A recent review by Nixon et al looked into the efficacy and complications associated with many image-guided ablation techniques, as well as its role in the current management of thyroid disease[2]. The purpose of this article is to expand on this recent review and describe acknowledged image guided ablation interventions by mechanism of action, indication, effectiveness, limitations, contraindications and the appropriate level of anesthesia or analgesia required. We will be focusing on benign thyroid disease as most reported data of these image guided techniques on malignant disease do not have longer term outcomes available, though much of that data is encouraging in low risk primary and recurrent disease[2].

High-energy techniques
High intensity focused ultrasound
High intensity focused ultrasound (HIFU) is a minimally invasive procedure that uses a focused US beam to a target area, inducing coagulative necrosis[3,4]. The target area is very small thus allowing for precision but requires a significant amount of time to cover any large area, particularly given that a cooling interval should be performed between each short sonification[3]. Typical treatment times range from 45 to 60 minutes and in larger nodules may need to be repeated. It utilizes piezoelectricity via a high-frequency amplifier. Software uses areas marked by the user and develops a treatment unit with safety margins[5].

The procedure can be performed under conscious sedation with the patient supine and neck hyperextended. Local anaesthetic can be used to alleviate pain during the procedure, this is infiltrated around the thyroid gland[4]. Some users advocate general anesthesia to avoid patient movement and the need for recalibration between treatment pulses, but the procedure has also been described without analgesia or sedation[6].

Reported studies largely focus on solid thyroid disease such as toxic nodules, benign thyroid nodules or multinodular goitres. Outcomes are reported as better with smaller volume thyroid nodules[2,7,8] but Lang et al further demonstrates larger nodules can be treated with sequential sessions[9]. It has also been used to treat persistent or relapsed Graves' disease with variable levels of success[10].

Many studies recently have reported an overall effective volume reduction in benign nodular disease from reported between 48 – 84%[2,6,11-13]. With sequential sessions on larger nodules (>20mls), the overall volume reduction at 6 months improved from 48% to 57%[9]. Further, 95% patients reported reduced overall symptoms (measured by a visual analogue score) at 24 months in a recent study by Lang et al[11]. When patient outcomes were looked at in comparison to open thyroid lobectomy surgery, the symptom reduction rate was comparable[14].

There is reduced efficacy as the treated nodule volume increases. Using a single session technique, Lang et al reports a reduction of 78%, 68% and 48% in small (<10 mL), medium (10–30 mL), and large (>30 mL) nodules demonstrating decreasing effectiveness with size[9]. Further, nodules that are close to the skin, carotid sheath, trachea, oesophagus or recurrent laryngeal nerve are difficult to treat as they are near these critical structures which are outlined in the safety margins during treatment[2]. It is advised to maintain safe distance of 1.1cm from the tracheoesophageal groove to prevent recurrent laryngeal nerve injury[4,15].

HIFU is typically more expensive than other high energy-ablative techniques[6]. Additionally, only one machine is available on the market presently that is able to deliver this technique and as it utilizes real time ultrasound in the planning it requires some end user familiarity with ultrasound[4].

As HIFU requires no needle or injected substance, it can be said to be nearly non-invasive. Despite this, some patients suffer side-effects to the procedure such as temporary vocal cord palsy (1-4%[4,10]), pain during session, transient skin erythaema, minor swelling, cough, skin blisters (12%[16]), hypothyroidism[4], horner's syndrome[14] and haematoma[5].

Radiofrequency ablation

Radiofrequency ablation (RFA) involves the insertion of a needle into a thyroid nodule that conducts electrical energy from a generator to induce coagulative necrosis[2]. This incurs a locally controlled temperature of up to 100 degrees Centigrade[3]. This can be done as either a cranial-caudal or trans-ithmic approach. Hydrodissection with 5% dextrose beforehand has been shown to help protect critical structures[3,17,18]). Pescatori et al advise using an 18-19 gauge needle as this allows for better maneuverability and thus better results and less complications, however, they do recognize that a larger (14 gauge) needle may be more effective in larger nodules[19]. The cost of the generator is around $25,000 and an electrode is about $750 for each session[20].

RFA is recommended as a non-surgical, minimally invasive technique for large thyroid nodules that are cosmetically undesirable or causing compressive symptoms. It is effective in solid benign thyroid nodules, toxic thyroid nodules and cystic nodules. The latter has been evaluated as second line treatment in cystic nodules refractory to chemical ablation[2,21-23]). There has been a further report by Hong et al of it being an effective non-surgical treatment in paediatric patients with compressive or cosmetically unsatisfactory thyroid nodules[24].

Perithyroid lidocaine is the advised method of analgesia. This is preferred to GA or sedation as it allows for constant assessment of nerve function and will alert the clinician to any proximity to the trachea as the patient will begin to cough and ablation should be immediately ceased. Further, it allows the patient to swallow cold fluids to help prevent oesophageal injury during the procedure[23].

In benign nodules, a response rate of up to 91% has been reported with an effective (>50%) reduction of volume[2,25,26]). A recent UK study on 31 nodules demonstrating an average volume reduction of 67% at 6 months[27] and recent prospective Austrian study on 277 patients demonstrating similar results at 6 months (68%) and a reduction of 82% at 12 months[28]. Deandrea et al demonstrated that RFA is more effective on spongiform nodules when compared to mixed or solid patterns on Ultrasound findings (76% vs 67 and 66% respectively – P =<0.01)[29]. Patient satisfaction scores are high, with Jung et al, demonstrating 98% therapeutic success rate and an 95% volume reduction at 60-months in a prospective multicenter study on 345 patients[30].

In Toxic Nodules results are variable with 24-82% normalization of thyroid function according to recently published Korean guidelines on RFA[23].

In Cystic Nodules Sung et al demonstrated no significant difference in effectiveness to percutaneous ethanol in cystic nodules compared with RFA[31], and thus the consensus to utilize RFA as a secondary technique as it is less economical than percutaneous ethanol.

Toxic nodules that are larger than 20ml can have a reduced response to RFA[23,32] and nodule volume appears a significant predictor in efficacy in these nodules[33]. Similarly, in large volume benign lesions, a second session may be required to manage patient symptoms and achieve adequate reduction[2,34,35]. Further, in nodules with heavy calcification, adequate ablation can be technically difficult[23]. Caution is advised with pregnancy, serious heart conditions or patients with pre-existing contralateral vocal cord palsy[20].

In the hands of an expert service, RFA has a very low side effect profile (overall complication rate of 2-5%[20, 23,30]). Major complications including nerve injury (recurrent laryngeal (2%[36]), cervical sympathetic ganglion, brachial plexus (<1%[37]) and accessory nerve), nodule rupture (<1%[37]), permanent hypothyroidism (<1%[37]), abscess (<1%[37]) thyroid storm[18] and haematoma (1%[7]) have been reported[2,23]). Other minor complications include vomiting (<1%[37]), skin burn (<1%[37]), transient thyrotoxicosis[28], lidocaine toxicity, voice change (1%[37]), hypertension and pain (2.6%[37])[23]. Sim et al has demonstrated in a long-term follow-up nodule regrowth can occur in up to 24% of nodules at an average of 40 months post procedure[38].

From an economic standpoint, RFA is more expensive than radioactive iodine treatment (for toxic nodules) but comparable in expense to surgery[23,39,40].

Microwave ablation

Microwave ablation (MWA) is non-invasive technique that operates by transferring up to 100W (typically 30-50W) of energy at a via frequency (2,450MHz) along a cable into an inserted needle (antennae). This results in rotation of molecules and an increase in temperature as a result of increased kinetic energy[2,3]. Hydrodissection has been reported to be helpful in protecting critical structures – similar to other thermal techniques[41,42].

Local anaesthetic, usually in the form of lidocaine, is injected in the perithyroid space. Peri-procedural cardiac and observation monitoring is recommended.

For benign disease, being a relatively new technique, there are less reported studies on the use of MWA. These predominantly focus on solid benign thyroid nodules.

In reported studies on benign solid nodules, the volume reduction ranges from 45-90%[3,41-44]. A recent meta-analysis on MWA reports a 12-month reduction rate of 88.6%[45]. Vorlander et al demonstrated that results of MWA on benign solid nodules were comparable to RFA (54% and 51% respectively)[46]; this matched a further study that included a HIFU arm as well with all three being effective and without statistical significance in efficacy[47]. Further, a prospective trial by Zhi et al demonstrates MWA to be an effective alternative compared to surgery with a lower side effect profile and overall greater patient satisfaction[48].

At present, there is little research in the application of MWA to benign thyroid disease other than solid benign nodules. As it has been reported as effective as other thermal techniques in this regard, there is scope to assess its efficacy in other pathologies, such as toxic nodules.

Complication profile is similar to other thermal ablative techniques with reported overall complication rate of 6.6%[45]. Reported complications include subcapsular haemorrhage (40%[49]), pain (70%[49]), fever (30%[49]), voice change (3-9%[49]), recurrent laryngeal nerve injury (9% [49]), horner's syndrome[46], skin burn and thyroid dysfunction[3,5]. Nodule regrowth has been demonstrated by Wang et al with 16 of 110 patients experiencing this complication[50].

Laser ablation

Laser ablation (LA) is a thermal ablative minimally invasive technique that utilizes laser light to heat up local tissue to temperatures between 46C – 110C and, depending on the temperature used, induces a combination of carbonization, coagulative necrosis and subsequent fibrosis of thyroid tissue[3,51]. This is achieved by inserting an optical fibre into the target tissue through a needle under US guidance and energy is delivered by Nd:YAG laser or laser diode[3]. It can be operated with single needle or multiple but needles should be more than 1cm apart if the lesion is large enough to necessitate multiple needles[5,25]. The needle should be parallel to the long axis of the thyroid nodule[51].

Due pain associated with the procedure, it is typically performed with a combination of sedation and local anaesthetic. Local anaesthetic alone may be inadequate[2,52]). Despite this, some have suggested that no anaesthesia allows the operator to better monitor proximity to critical structures[51].

LA has been demonstrated as an effective treatment alternative of benign thyroid nodules and toxic nodules[53]. It has also been used in conjunction with aspiration in mixed or cystic nodules[54,55]. While a systematic review demonstrated that RFA may be superior to LA in nodule reduction[56], LA appears to be more effective in large volume nodules[2,57]. It has been reportedly used effectively in nodules that did not respond to other thermal ablative techniques[58].

Volume reduction is reported to range from 47-84% in solid benign disease[2,3,5,51,59]. The effectiveness can vary based on the ultrasound appearances of the nodule. Negro et al report a 5 year nodule reduction of 59.7% with solid nodules versus a 78.6% reduction in spongiform nodules[60]. In mixed and cystic nodules, aspiration combined with subsequent LA has been shown to result in an average nodule size reduction of 92% and a loss of the cystic component in 75% at an average of 45 months[61]. Oddo et al further reported that there is a significantly positive perception of the procedure in patients who have undergone it. 100% of patients stated their symptoms of discomfort had improved and there was a significant reduction of goiter symptoms using a validated thyroid patient reported outcome questionnaire (ThyPRO)[62].

Toxic nodules can be treated with LA but results show only 50% of cases achieving normalization of TSH[63]. There appears to be a correlation to reduction of volume and normalization of thyroid function[64], this improves to 87% with multiple cycles of LA, though this value is still less than what is observed with RAI[65]. Single session appears to be adequate in most cases for nodules under 5ml in volume, with Gambelunghe et al reporting about 90% of these patients were able to come off their methimazole[64].

Similar to RFA, there is suggestion that LA can be used in combination with RAI for the treatment of toxic nodules. In large nodules, a combined approach may have greater control of symptoms compared to only RAI (2, 66). Using this technique, Negro et al demonstrated in large volume nodules, both surgery and a combination of RAI and LA were comparable in efficacy of restoring normal thyroid function and both resulted an overall improvement in quality of life for patients (67).

From an economic standpoint, A solitary diode or Nd:YAG laser source costs between $15,000 – $20, 000 with the deposable components factoring in at $400 per session[20]. A further limitation is that nodules close to critical structures are more likely to be undertreated and subsequently experience regrowth[68].

A large volume retrospective study reports an overall complication rate of 0.9% (0.5% major and 0.5% minor complications[51,69]) but if considering only minor complications, a recent review collates this to be much higher at 38.3% those this is significantly higher than other reported complication rates[5,69]. The predominant reported complication is pain (10.6% - 13.4%[51,64]), both during (12%[69]) and after (5.4%[69]) the procedure[5]. Other reported complications include fascial effusion (3%[70]), skin burns (<1%[59,69]), hypothyroidism, cough (<1%[69]), dysphonia (<1%[69]), haematoma (<1%[69]), vocal cord palsy (1.6%[70]), pericapsular bleeding, pseudocysts (5%[70]), fever (6-7.7%[64,69]) and vasovagal reaction (<1%[69])[2,5]. Dossing et al has postulated that more serious complications may be more likely when more than one fibre is used during the ablation[61]. Nodule regrowth occurs in 5% of nodules[51].

Non-thermal Techniques: Aspiration

Therapeutic fine needle aspiration (TFNA) of a thyroid cyst is a well-established, minimally invasive procedure to treat benign thyroid disease for many decades[71]. It involves using large bore needle (18 – 27 gauge) into a cystic thyroid lesion. Initially diagnosed and treated on clinical suspicion of cyst[71], the development of US allowed the operator to ensure the cyst is evacuated, ideally, to dryness. Further, US allows good control of the needle by the operator to avoid vascular structures and is now considered mandatory[3].

Aspiration requires there to be a completely cystic or a thyroid nodule with a cystic component. Further, this method also allows for the operator to send off samples of fluids and tissue by means to FNA or core biopsy if there is still diagnostic uncertainty. Lastly, as previously described, it can be used as an adjunct with other non-invasive image guided therapies.

The range of reported effectiveness is highly variable. In 1966, Crile et al described clinical success in 94% (absent or significant reduction on clinical examination) of patients after up to two aspirations. With the advent of US assessment of therapy, this number is more likely between 14% - 89%[72-80.]

TFNA should avoided in hot nodules on scintigraphy or patients with coagulopathy[5]. Further, some reported studies required as many as 17 repeat aspirations, which can represent a significant burden both to patient and service[73].

The complication profile of TFNA is minimal, with infection, bleeding and haematoma (0.01%[81]) being the most commonly reported[44]. The largest issue is the rate of eventual recurrence after aspiration. This has been reported as high as 90%[2,82] and can result in a larger cyst[83].

Needle aspiration is well tolerated and cost effective[3]. It can often be done in a clinical setting and rarely requires any analgesia.

Percutaneous chemical ablation

Percutaneous chemical ablation (PCA) involves the use of a sclerosing agent injected into the cyst or nodule to invoke a thrombotic, coagulative necrotic and fibrosing response to the target tissue or cyst[2]. Most research describes the use of tetracycline or ethanol as the sclerosing agent. Other agents have been used, including hydrochloric acid[78], polidocanol[84] and arginine hydrochloride[85]. Current guidance advises the used of percutaneous ethanol in cases of relapsing and symptomatic benign cystic nodules[3]. While most studies used between 30 – 70% of the fluid extracted volume of ethanol[3,8], Halenka et al demonstrated injecting 20% worth of initial cyst volume in 95% ethanol achieves adequate response[86].

It is often performed in a similar manner to US guided FNA, with an added step of sclerotic agent injection. As such, it rarely requires formal anesthesia or more than simple analgesia. Lidocaine or saline can be injected before final withdrawal of the needle[54].

PCA has been predominantly described as a method to treat benign cystic thyroid disease. Percutaneous ethanol injection (PEI) been also used to treat solid and toxic nodules. PEI has also been described without US guidance in large cysts but the authors note this is more appropriate in the limited resource setting[87].

Resolution of the cystic nodules through the use of ethanol has been reported to range between 72% - 100%[75,78,80,82,86,88-91]. Comparatively, tetracycline, has a cure rate of 43% - 97%[75,79,89,92-95]. This demonstrates how the former has become the standard agent used in practice today for PCA. Further, it has reported that there was no statistical significance in resolution of cysts when comparing tetracycline and injected isotonic saline (43% and 47% respectively)[93], and in similar studies comparing ethanol and isotonic saline there was a significant difference of 77%-82% cure rate with ethanol and 36% - 48% with isotonic saline[96,97].

Other sclerotic agents have been mentioned including: hydrochloric acid a 37.5% cure rate[78], polidocanol with a 93% - 100% cure rate at 12 months[84,98], arginine hydrochloride had a 100% response rate after up to 3 treatments[85]. A further study by Gong et al demonstrated while no significant difference in cure rate was evident comparing polidocanol and ethanol, complication rates were higher with ethanol[99]. As previously stated, compared to RFA, several studies do not report any difference in volume reduction, symptoms or cosmesis[3,31,100].

Table 1. Suggested Optimal Minimally Invasive Treatment Based on Efficacy

Benign nodule type	Suggested Treatment
Solid nodule	RFA/MWA/HIFU
Large solid nodule	LA
Spongiform nodule	RFA
Mixed nodule	Aspiration + LA
Cystic nodule	Aspiration
Recurrent cystic nodule	1st line PEI. 2nd line RFA
Toxic nodule	RAI. RAI + RFA/LA in large nodules (>20mls)

Solid nodules treated with PEI have had smaller response rates to cystic thyroid nodules but still with response rates around 62.5%[101]. Zbranca et al describes the used of PEI on 6 patients with toxic nodules in which all patients were cured after 1 to 9 injections[75]. This matches initial previous work by Mazzeo et al[102] however long term follow-up has suggested that this value was closer to 80% in this series with a further 16% having a partial response[2,103]. While it may result in a lower rate of hypothyroidism, RAI remains more effective and as such, the preferred non-surgical treatment[2].

PEI may make any future surgery more wdifficult due to periglandular fibrosis[72] and this should be recognised should any future surgical planning take place. Economically it is very cost effective with the items required to perform PEI valued at between $50 - $100[20].

Reported complications with PEI include pain (21 - 73%[97,99,101,104]), ethanol toxicity 10% - 24%[90,99,104], bruising (2.5%[101]), temporary dysphonia (3 - 5%[97,101]), vocal cord palsy (<1%[2,103,105]) and horners syndrome (2.5%[101]). Severe complications related to extravasation from the nodule have been described, including peri-glandular fibrosis, laryngeal and skin necrosis[106], jugular vein thrombosis (3%[107]), graves' disease and graves' orbitopathy[10]. A Cochrane review has suggested that side effects were more likely in treatment of solid nodules as opposed to cystic[72].

Conclusion

Non-surgical management of benign thyroid nodules is feasible and there are a variety of options available that may be more appropriate given a certain nodule morphology or clinical picture (Table 1). It is important to recognise that these treatments aren't as absolute as surgical intervention, which is well tested and regarded as safe, but may be more appealing to or more appropriate for certain patients. Surgery has the benefit of not requiring potential further intervention for the same nodule as it is

Table 2. Complication Rates of Non-surgical Intervention Treatments of Benign Thyroid Nodules							
Complication	**HFUS**	**RFA**	**MWA**	**LA**	**FNA**	**PEI**	**Surgical lobectomy**
Pain	73	2.6	6.5-70	10.6 - 13.4	NR	21-73	?
Fever	NR	NR	30	6 - 7.7	NR	NR	NR
Infection/abscess formation	NR	<1	NR	NR	*	NR	0.5
Skin Blistering/burn/ erythaema	1-12	<1	2	<1	NR	NR	NR
Hypothyroidism	*	<1	1.3***	*	NR	NR	14
Hamatoma/bleeding complication	*	1	3-40	<1	0.01	NR	0.8
Voice change/dysphonia	NR	NR	3-10	<1	NR	3-5	5.3
Recurrent laryngeal nerve injury/vocal cord palsy	1-4	2	1-9	1.6	NR	<1	0.01
Nodule/cyst recurrence	NR	24	14	5	90	NR	NR
Estimated cost	NR	$750**	NR	$400**	Minimal	NR	$5617
Overall complication rate	10.8	2-5	6.6	0.9 - 38.3	Minimal	NR	2.6

*reported but no values given
**for disposable items only
***reported as 'thyroid dysfunction'

definitive and removes the fear of misdiagnosis by giving definitive histology on the nature of the lesion. Complications comparing each intervention and those of surgery are in Table 2. Cost for non-surgical intervention should be considered before being adopted by a health board. Surgical treatment cost can vary between countries with a hemithyroidectomy being charged as much as $30,000[20] in the USA but this includes pathology costs and staff time that is not included in the other treatment costs.

There remains further scope for research in terms of further robust direct comparison of these minimally invasive interventions. Further, some complication data can appear skewed when not wholly reported or in small number trials and as such, a meta-analysis of the available databases in reported studies would help sharpen these values.

By tailoring the intervention to the lesion and the patient, healthcare boards will be able to effectively offer non-surgical management options to patients with benign thyroid disease. While it may be unreasonable for each individual trust to be able to provide every intervention, utilizing a national framework would help address this issue.

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