
# Consensus Guidance on Routine Practice for Differentiated Thyroid Cancer in Scotland

May 2020

National Thyroid Cancer Project

# Contents

# Introduction

In the United Kingdom, we are very fortunate to have a strong culture of evidence-based guidelines on which we can shape our clinical practice. Guidelines for the management of thyroid cancer were first published by the Royal College of Physicians of London in 2002, updated in 2006/7 and revised again in 2014 under the auspices of the British Thyroid Association. I found the 2014 recommendations particularly helpful in my personal practice and they paved the way for pretty radical changes in the way thyroid cancer services are delivered. This included the introduction of personalised decision making around radioactive iodine, follow-up of lobectomy-only patients and the 'U' ultrasound grading system for thyroid nodules.

However, like any piece of evidence-based medicine, grey areas in the guidelines meant that certain recommendations were open to interpretation by clinicians. There was also a subjective element to assessment in certain areas of practice. On speaking with colleagues across the country who ran thyroid cancer services, the variation in practice became very clear to me and was particularly marked between certain centres in Scotland. I did however sense a real appetite among thyroid cancer clinicians for greater collaborative working, in order to reduce variation and spread examples of best practice across Scotland.

In 2017, we received funding from the Scottish Government to establish a 'Scottish Thyroid Cancer Project Board'. Our initial meeting in February 2018 took place in a very small room at the Perth Royal Infirmary. On arrival, I was really quite taken aback by the number of people in attendance, the diversity of specialities and the breadth of geography represented. It took a while to get things up and running but we were very fortunate to appoint Micol Salvetto as our Project Manager. Micol came to us via Italy, Spain, Nicaragua and New Zealand. In the first two months of 2019, we both visited the regional thyroid cancer services. This was an extremely rewarding experience and allowed us to understand their organisational structure, delivery and governance.

We held our first Board meeting in February 2019 which included a representative from all specialities involved in thyroid cancer at the three cancer networks in Scotland. We were also delighted to welcome Kate Farnell, CEO of the Butterfly Thyroid Cancer Trust. At this meeting we established the basic structure of the project, including specific subgroups in surgery, pathology, radiology, radio-active iodine and nuclear medicine, long-term follow-up and oncology. Our patient material subgroup was established at a later date. In the intervening months, these groups have met regularly to discuss the key areas of variation in practice. There seems to have been a genuine 'esprit de corps' and I really do believe that healthcare professionals from the different disciplines and our patient representative, have enjoyed meeting and discussing these topics.

The purpose of this report is to present the work of the individual subgroups and to highlight areas of both consensus and areas where work still needs to be done. We hope that this document will act as a framework to allow centres in Scotland to have a more common approach in their management of people with thyroid cancer. Of course, it is natural that there will remain variations in practice for very legitimate reasons, including the structure of services, available resources and the lack of a clear evidence base.

An enormous amount of hard work has gone in to producing the areas of consensus that are reported in this document. I would like to thank the Chairs and members of the individual subgroups for all their support, commitment, enthusiasm and input. I would also like to extend my thanks to Kate MacDonald and Rachel Russell from SCAN who supported the initiative from the beginning, were integral in securing initial funding and helped establish our work. My biggest thanks however are reserved for Micol, who has been the beating heart of the whole project. She has cajoled us and held us to account but most crucially, she has provided enormous practical and common-sense support to ensure that the project has been an unqualified success. Thank you so much Micol! We can all be very proud of what we have achieved.

It is regrettable that we had to cancel our final meeting in April 2020 because of the COVID-19 crisis but I hope that we will be able to organise another national meeting later in the year. I know there is a real desire for us to continue with this whole process. There is still lots to do, including setting up audit procedures, providing ongoing education and producing patient information. Practice will of course evolve as we gain new evidence. We also need to understand and explore what improvements can be made in paediatric, anaplastic and medullary thyroid cancer practice. As many of you know, we have submitted an application to National Services Scotland in the hope that in 2021, we will be re-born as the Scottish Thyroid Cancer Network. I look forward to what is to come.

Best wishes,

**Professor Mark Strachan**

Chair - Scottish Thyroid Cancer Project Board

# 1. RADIOLOGY GROUP

## Group members

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| **Claire McArthur (Chair)** | Consultant Radiologist | NHS GG&C |
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## Introduction

This has been a welcome opportunity for us to discuss wide reaching, common issues in thyroid cancer imaging, while identifying differences in practice across the country and between professional groups. Discussions have prompted several audits and observational projects.

Our aim is to assist in diagnosis and inform how thyroid cancer can best be managed through imaging. Preventing over-diagnosis and unnecessary treatment is also crucial to our work.

There is a huge reservoir of clinically silent, impalpable nodules. Up to 67% of the population who are examined using an Ultrasound Scan (US) will have an incidental thyroid nodule (Cronan, 2008), while incidental thyroid nodules are found in up to 18% of cross-sectional imaging studies (Uppal, et al., 2015).

It is well recognised that despite a threefold increase in the incidence of papillary thyroid cancer over the past 30-40 years, the mortality rate is stable. This rise in cases is largely due to an increase in papillary microcarcinomas (≤1cm).

The rate of detection of latent papillary thyroid cancer at autopsy has not changed (up to 35.6% in one series (Harach & Wasenius, 1985)) but rather the increase in newly diagnosed cases is a result of improved diagnostic detection. This includes the ever-increasing use of US, Computerised Tomography (CT), Magnetic Resonance Imaging (MRI), Positron Emission Tomography-Computed Tomography (PETCT) and image guided FNA. Today, more patients receive a diagnosis of thyroid cancer after evaluation of an incidentally found thyroid nodule than after evaluation of a symptomatic or palpable nodule (Brito, Morris, & Montori, 2013).

Conversely, despite the high-resolution capability of US and detection of nodules as small as 2-3 mm, it would seem that many of the papillary microcarcinomas (PMCs) found histologically are

incidental or not seen or suspected with pre-operative US. A recent study using whole specimen mapping found that in 45% of patients, PMCs were occult on US (Park, et al., 2015).

Moreover, there is evidence to support an active surveillance approach in patients with low risk PMCs as first line management, without increase in morbidity or mortality (Miyauchi, Ito, & Oda, 2018).

Our aim as radiologists therefore is not to detect all thyroid cancers but rather to adopt a pragmatic approach, diagnose biologically relevant disease, target FNA appropriately and recognise the limitations of US.

We looked at a number of issues which were generated through dialogue at the subgroup level and included several matters following Board debate. Many of the topics are inescapably entwined.

## Ultrasound of the thyroid

### Nodule classification

There are a variety of sonographic classifications which can be used for thyroid nodules, categorising them as benign-looking or with incremental levels of suspicion for potential malignancy. Classification systems are largely similar, with different thresholds for FNA. It was recognised that not all thyroid US reports provided across Scotland at present include a formal grading or opinion on malignant potential of nodules found. The British Thyroid Association (BTA) (Perros P, 2014) system is most widely used in Scotland at present. At least one centre in GG&C is also using the American College of Radiology (ACR) Thyroid Imaging Reporting and Data System (TI-RADS) (Tessler, et al., 2017). There has been discussion in the international radiology community regarding the development of a universal TI-RADS whereby there are currently several versions. If applying a TI-RADS, clinical judgement and individual patient circumstances – such as long and inconvenient travel in some of the regions or a patient having stopped oral anticoagulants for the appointment – would be taken into consideration and perhaps lower the threshold for FNA rather than structured follow-up US. In cases of a multinodular thyroid it was deemed reasonable to adopt a pragmatic approach and use a grading to apply to multiple nodules (particularly those with benign appearance) whilst still obviously noting any specific suspicious nodules.

### Report structure

The group agreed that thyroid US reports should have a degree of organisation, including surgically/clinically relevant information about findings in each lobe. There should be clarity on the location and size of assessed nodules to facilitate any future US follow-up, aid surgical planning and allow correlation with any subsequent histology. This includes use of a published and recognised nodule grading system. The group were not in favour of using a reporting template as this would be difficult to implement at a national level due to differing IT interfaces.

### Image acquisition

When reviewing image acquisition, the group felt there was no need to be too prescriptive here so long as saved images represented what was seen and reported, allowing for follow-up US assessment if relevant.

### Thyroid assessment on unrelated request

The group also discussed whether thyroid interrogation in neck US should be included for other clinical indications. A significant proportion of US neck requests are for suprahyoid or non-thyroid related concerns from maxillofacial surgery, oral medicine, dermatology and plastic surgery specialties, as well as primary care. It was generally felt that this would lead to detection of many incidental nodules and inadvertent screening. Conversely, there are scenarios where thyroid assessment would be relevant - including evaluation of cervical lymphadenopathy or parathyroid adenoma. Sonographers are less likely to omit the thyroid US assessment during neck US as they feel this would require a clinical judgement. The consensus was that thyroid assessment on neck US takes place at the professional discretion of the operator.

Recommendations

- *Use a nodule grading system and specify which system has been applied (a prefix may of course suffice e.g. "U" if using BTA)*
- *In addition to nodule grading, use of the correlating terms "benign", "indeterminate" or "suspicious" for malignancy whether mild, moderate or high would be at the discretion of the operator*
- *Record nodule size – suggest longest diameter in a chosen stated plane – and location to facilitate follow-up assessment, surgical planning and correlation with any subsequent histology*
- *It would be helpful to include information on opinion on composition, echogenicity, calcifications/echogenic foci, border, shape (internal vascularity-if using BTA)*
- *In a suspected malignant nodule, a comment should be made if extra thyroidal extension is evident (this is implicit with ACR-TIRADS)*
- *Confirm that both lobes (and isthmus) have been assessed*
- *Document assessment of cervical lymph nodes – assess central compartment and lateral cervical chains*

## GP referral for thyroid US

The BTA does not support direct referral for ultrasound (US) of a thyroid mass from primary

Recommendations

*The acceptance of direct primary care referral for thyroid US is dependent on local trust arrangements and whether robust mechanisms are in place to ensure an appropriate referral pathway, with no delay to definitive management. This will differ by site.*

## Requirements for practice

A large number of operators are performing thyroid US across Scotland. In some centres, a number of sonographers are completing this procedure without on-site specialist radiologist input (Western Isles and Dumfries) which is not optimal. This often results in patients either having to re-attend at a more central department for repeat assessment or their images being reviewed remotely. There is often significant inter-observer disagreement. As an aside, the majority of subgroup members were not in favour of reviewing US images on PACS and would advise that where there is dubiety, the patient should be brought back for repeat US.

Radiologists and sonographers performing thyroid US should have gained prior expertise, with subspecialist interest encouraged. Sonographers should also receive additional training, as part of their service requirement needs. It was unanimously agreed that those performing thyroid FNA should self-audit their biopsy results and Thy1 rate.

Recommendations

*Those performing thyroid US +/- FNA should:*

- *Have dedicated lists of neck/thyroid US or at least see cases regularly*
- *Use a nodule grading system and provide a surgically/clinically effective report (See US Thyroid section)*
- *Maintain a professional interest in thyroid US with relevant CPD*
- *Perform regular audit of FNA results and Thy1 rate*
- *Ideally be able to access specialist Radiologist input (Sonographers)*
- *Be welcomed in thyroid cancer MDT discussions and attend if/when feasible*
- *Avoid reviewing "cold" US images on PACS where possible*

## Nodule size threshold for FNA

Across the country there is evidence that U3 and above (when using BTA) nodules <1 cm are being targeted for Fine Needle Aspiration (FNA) and it was consistently agreed that this should be discouraged in the majority of cases. BTA recommends not FNA-ing suspicious nodules less than 1 cm unless there are high risk clinical features, adenopathy or until MDT discussion has taken place. ACR TI-RADS does not advocate FNA of TR-3 nodules <2.5 cm, TR-4 nodules <1.5 cm or TR-5 nodules less than 1 cm, but they do get US follow-up depending on size. The American Thyroid Association (ATA) (Haugen, et al., 2016) and European Society of Medical Oncology (ESMO) (Filetti, et al., 2019) also do not promote sampling of nodules <1 cm. High risk features which might alter this approach include associated lymphadenopathy (in which case the malignant node may be a preferable target), ipsilateral vocal cord palsy, extra thyroidal extension, substantial interval growth, significant family history or history of head and neck or whole-body irradiation. Ultimately it was felt that a case would actively need to be made for FNA of any nodule <1 cm rather than FNA being the default course of action in ≥ U3 nodules.

Recommendations

*Do not perform FNA of nodules <1cm (this is implicit with ACR TI-RADS) even if sonographically suspicious. Factors that may change this approach include:*

- *Associated lymphadenopathy (in which case the pathological node may be a preferable target)*
- *Ipsilateral vocal cord palsy*
- *Extra thyroidal extension*
- *Substantial interval growth*
- *Significant family history of thyroid cancer*
- *History of head and neck or whole-body irradiation*

*There should be discussion or prior understanding with the local surgical team before embarking on FNA in these cases.*

## FNA technique and performance

The decision to use Fine Needle Aspiration (FNA) is guided by the classification system. If proceeding to FNA, we would ideally have an excellent diagnostic rate. To date, the Thy1 rate nationwide is approximately 25% (this data was obtained from the national audit and supplied by the pathology group). The Royal College of Pathologists recommend a Thy1 rate of 15% or less. However it is not clear whether this proposal encompasses current radiology practice, where a high proportion of small impalpable nodules are being targeted with US, or if it refers to practice where on-site cytology input is provided. . The Royal College of Radiologists recommend a rate of 30% or less. This was something we discussed in depth and the perceived high Thy1 rate was felt to be multifactorial. This includes nodule selection, targeting of sub-centimetre nodules, operator technique potentially having an impact during the FNA acquisition or slide preparation and variable leeway in sample acceptability and interpretation by the cytopathology team. The case-mix may also affect this result i.e. some operators may be more likely to have a proportionally higher number of return/repeat patients with a previous Thy1 result. GG&C data tell us that in those with a Thy1 cytology result there is only a 1/3 chance of a definitive result on repeat FNA (i.e. not Thy1 or Thy 3a). It is important to note that the cytology result should be considered as part of the larger picture and in the context of clinical and sonographic appearances, rather than the achievement of diagnostic cytology being an end in itself. It was agreed that efforts should also be made to avoid alienating those currently providing the service, instead looking to foster a supportive environment.

The group debated whether it may be beneficial to have a biomedical scientist (BMS) or cytopathologist onsite for FNA. Some subgroup members had experience with both. It was

recognised that ensuring a cytopathologist is on-site to assess specimen adequacy is the gold standard for FNA, whereby Thy1 rates don't appear to improve when just a BMS is in attendance. However, current variation in local practice makes it unrealistic for all departments to aim for this and the group therefore agreed that there was no mandate for this change to be implemented across the board at present.

Recommendations

- *Those performing thyroid FNA to take on board advice from the pathology subgroup (Appendix A) on slide preparation and the preferred medium for sample delivery, implementing this in line with local arrangements*
- *Regular interaction and collaboration between radiologists/sonographers and cytopathologists, including specialty trainees*
- *Reducing FNA of nodules <1 cm will also likely have an impact (see nodule size threshold for FNA)*
- *FNA operators to audit their Thy1 rate and ideally compare this with colleagues in the same department or Board. If rate is an outlier, operators to consider what factors may have a role and seek advice accordingly (see requirements for practice and audit sections)*

## Core biopsy

In carrying out a core biopsy it is not possible to differentiate between a follicular adenoma and carcinoma - or sometimes even a benign hyperplastic nodule. The role of this procedure is therefore relatively limited.

Recommendations

*The group agreed that there were exceptions, including:*

- *Suspected lymphoma*
- *Suspected anaplastic thyroid cancer*
- *Inconclusive FNA, particularly if patient does not require an up-front diagnostic hemithyroidectomy but with awareness and patient consent to note that core biopsy results may not be definitive*
- *Case discussed at MDT meeting and a core biopsy felt appropriate/necessary*

## Audit

Ideally it would be relatively easy to correlate US nodule grading with cytology and/or histology. However currently this is rather impractical. Histology may not be available for

many months, if at all, and there is no reliable way of following up on cytology results of graded nodules that are not FNA'd by the same operator. Furthermore, the histologically discovered cancer (usually papillary microcarcinoma) is sometimes sonographically occult and incidental to a symptomatic benign nodule that is graded at US. It is therefore imperative that we do not assume that the US scoring was incorrect in such a case.

Regarding the audit of Thy1 rates, the pathology department only have data on the referring surgeon or clinician, as opposed to the operator. This is an area that needs further work to support audit. The group were in support of a database or register which could collect this type of data.

Recommendations

*No specific recommendations here beyond those in other relevant sections.*

## CT for staging in thyroid cancer

It became clear during the course of discussions at our Board that the threshold for staging Computed Tomography (CT) in Differentiated Thyroid Cancer (DTC), varies across the country. In some centres, staging CT is only performed to assess bulkier tumours while elsewhere all cancers, including incidental papillary microcarcinomas, are CT staged.

US will generally perform better than CT regarding detection of extra thyroidal extension. However in more extensive tumours, CT or MRI will of course provide a better overview of disease extent and relationship to adjacent structures. A previous study demonstrated that while the addition of CT to US does not increase sensitivity for detection of central nodal metastases in papillary microcarcinoma, it does in papillary carcinoma. The study also showed that addition of CT does not significantly improve sensitivity for lateral cervical nodal metastases (Choi, et al., 2009). The added diagnostic benefit of CT will therefore depend on how closely the US operator pays attention to the presence of extra thyroidal extension, how diligently metastatic nodes are sought out with US, and local surgical practice in terms of managing the central compartment.

In a GG&C retrospective audit of differentiated thyroid cancers (n=92), staging CT added very little in terms of additional findings regarding nodal staging beyond the US assessment or in detection of haematogenous metastases. However, the overall number of cases with involved nodes or distant disease was small. In the few cases where further adenopathy or distant disease was found, cancers were all >4 cm. Furthermore, a sizable number of incidental abnormalities were found on CT, often requiring additional dedicated imaging studies and separate lines of clinical follow-up. They were occasionally serendipitous but often caused increased patient concern with limited clinical benefit. In those with early cancers, using a staging CT has the potential to cause more harm than good and there is a high chance of incidental finding.

The Board therefore suggests using a CT scan for surgical planning, particularly if lateral nodal disease is suspected. They otherwise advised that there was no benefit in using a routine CT scan for staging purposes.

The use of iodinated contrast and potential for delay regarding administration of adjuvant radioactive iodine (RAI), was also discussed. The use of contrast will significantly improve the diagnostic value of the CT, unless pulmonary metastases are present. This did not appear, at least in the West of Scotland, to limit the rate and the reduction in unnecessary post-operative CT will further moderate this concern.

Recommendations

- *Staging CT does not offer any additional benefit in papillary microcarcinoma and is not indicated*
- *CT scan may be utilised for surgical planning, in particular if lateral nodal disease is suspected, but otherwise there is no role for routine CT scan for staging purposes.*

## US follow-up in hemithyroidectomy DTC

Patients with low risk Differentiated Thyroid Cancer (DTC) can be treated using hemithyroidectomy alone i.e. smaller unifocal papillary carcinoma in younger patients without nodal disease or smaller follicular carcinomas in younger patients in the absence of vascular invasion or extensive capsular invasion. For such low-risk patients, with no structural evidence of disease on initial surveillance US, routine screening US is more likely to identify false-positive or indeterminate results than clinically significant structural disease recurrence.

The ESMO recommendation is for patients to undergo a treatment response US at 6-18 months and, if structurally clear, to use clinical follow-up and thyroglobulin (Tg) trend/Tg antibodies to direct need for further US. The subgroup was entirely in agreement with this and suggested a similar approach, prior to knowledge of the ESMO guidelines. The risk of inadvertent population thyroid screening was once again highlighted, if the practice of regular and unsystematic US follow-up was adopted.

Analysis of two years of consecutive data on hemithyroidectomy-only DTC in GG&C with 4-5 years of follow-up data indicated no clear benefit from repeated or indiscriminate US follow-up in these cases. The group also noted that there is increasing evidence to show that many of the papillary microcarcinomas found on histology are sonographically occult. A recent study using whole specimen mapping found that in 45% of patients with US-identified "solitary" papillary carcinoma, multifocal PMCs were found histologically (Park, et al., 2015). Furthermore, in the above-mentioned GG&C audit, papillary microcarcinomas were the only contralateral cancers detected in those patients who had up-front completion. In over half of these cases, no or only small benign looking nodules were seen on the preceding US.

Recommendations

*We recommend that patients with lower risk thyroid cancer who have undergone lobectomy-only should receive neck US around one year after surgery (6-18 months). This is to assess the contralateral lobe and for neck adenopathy. The patient should, as in standard procedure, have been assessed pre-operatively also. If no structural abnormality, we suggest clinical and biochemical follow-up. If any contralateral nodule(s) are present then this must be classified and FNA/follow-up to take place as appropriate. The radiology group are not in support of annual arbitrary US follow-up of hemithyroidectomy cancer cases.*

## MDT to include Radiologist

The group agreed that radiology input in the Multi-Disciplinary Team (MDT) setting is vital, particularly for indeterminate or difficult cases. There is some discrepancy in radiology representation at MDT groups for thyroid cancer across the country. In SCAN and NOSCAN, radiology input is integral. The group wondered if the West of Scotland (WoS) thyroid cancer MDT, which has no formal systematic (non-Nuclear Medicine) radiology input at present but the capacity for review of relevant imaging, could operate more effectively with such input. The Royal College of Radiologists suggest that Clinical Radiologists are considered core members of cancer MDTs, stating: "the presence of both a radiologist and pathologist has been mandated to ensure that the meeting is quorate."

The Board were unanimous in their support of the West of Scotland's quest to ensure a radiologist forms part of their thyroid cancer MDT going forward. Some members went so far as to state that they are unwilling to discuss cases in the absence of radiology input.

Recommendation

*Radiologist should form part of all Thyroid cancer MDTs, providing crucial input.*

## Incidental thyroid nodules on CT and MRI

Incidental thyroid nodules are found in up to 18% of cross-sectional imaging studies but the way in which they are reported varies across Scotland. At present, where they are reported, the default approach tends to be thyroid US. US referrals therefore tend to be made by non-ENT/ endocrine specialists, who have less experience with the nodule grading pathway.

Clinical evaluation of incidentally found nodules on CT/MRI is recommended in BTA guidelines: "In the majority of cases, no further assessment/investigation will be required. However, if there are suspicious findings on CT (extra thyroidal extension, tracheal invasion,

associated suspicious lymphadenopathy), the patient belongs to a high-risk group or there is significant clinical concern, US assessment is recommended."

In recent NICE guidance (Filetti, et al., 2019), the committee noted that many referrals for thyroid US are based on incidental findings obtained through other types of imaging (e.g. CT scans performed for other indications). The group therefore agreed that thyroid US should only be performed when full assessment indicates a likelihood of malignancy. "Thyroid ultrasound of incidental findings should not be the default option because most incidental findings are not malignant and further investigation may cause harm in terms of the adverse effects of testing and patient anxiety". The American College of Radiology White Paper recommends further investigation of nodules over 1.5 and 1cm in those over and under the age of 35 respectively (Hoang, et al., 2015).

Recommendations

- *Report nodules on CT/MRI if >1.5 cm and patient over 35 years old or > 1cm for those under 35 years old. Check this has not been previously investigated by US.*
- *Do not recommend US assessment in the first instance, but instead suggest clinical assessment so long as considered appropriate*
- *Ideally the US request, if required, should come from the ENT/endocrine team*

## Incidental FDG-avid nodules on PET-CT

Although the rate of malignancy is quoted at 1/3 for 18F-FDG-avid thyroid nodules (Bertagna, Treglia, Piccardo, & R, 2012), this is relatively low in the absence of specific suspicious ultrasound features (Beech, et al., 2016) (Foo, O'Neill, & McArthur, 2019). This suggests that US can be used to further stratify an 18F-FDG-avid thyroid nodule. When there is more than one nodule found in the relevant lobe during ultrasound assessment, it can be difficult to co-register with the avid focus on PET-CT. Sonographic assessment of each nodule would be made and, where appropriate, FNA targeted at the more suspicious nodule.

Overall survival with 18F-FDG-avid thyroid incidentaloma is relatively poor because of the prognosis associated with the underlying malignancy. This therefore must be considered before investigation of 18F-FDG-avid thyroid nodules and any aggressive treatment.

Recommendations

- *US nodule grading should be taken into account when dealing with incidental 18F-FDG-positive thyroid nodules, rather than blanket policy FNA*
- *Consider prognosis from other cancer prompting the PET-CT*

## Dissemination of recommendations

There was good geographical representation on the subgroup which should aid dissemination of recommendations to the large number of individuals in Diagnostics, who are involved in thyroid imaging.

*Dissemination of recommendations should be via Clinical Leads and Clinical Service Managers at each site.*

*Dr Claire McArthur*

Chair, Scottish Thyroid Cancer Radiology Group

# 2. PATHOLOGY GROUP

## Group members

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## Introduction

Thyroid pathology encompasses diagnostic Fine Needle Aspiration (FNA) cytology and histopathology of resected lesions for diagnostic confirmation. It also covers the reporting of histological parameters of prognostic relevance that will guide further management of the patient.

In most centres in Scotland, thyroid cancer pathology reporting is undertaken by histopathologists who are specifically interested and have experience in this area. In smaller centres, all pathologists can report thyroid cases but only one takes on the role of lead and attends Multidisciplinary Team (MDT) meetings. The overall number of pathologists reporting thyroid cases is relatively small. To date, there has been no formal network of thyroid pathologists to identify areas of inconsistency and discuss best practice. The Pathology Group above represents all centres reporting thyroid cancers.

Several issues relating to thyroid cancer pathology were identified by pathologists and by clinicians in the other groups.

## Optimising the quality of FNA

Fine Needle Aspiration (FNA) is the principle method of cellular diagnosis of thyroid neoplasia. Most FNAs are performed by a radiologist under ultrasound (US) guidance. When an FNA has to be repeated due to an unsatisfactory Thy1 result, it constitutes a cost in terms of additional time and resources for the pathology laboratory, radiologists who have to repeat FNA and patient who needs an invasive test repeated. Pathologists in the UK use the Royal College of Pathologists (RCPath) standardised reporting system (Thy1-5, Thy 1 being non-diagnostic). Although the RCPath does not currently give a specific standard for an acceptable rate of Thy1, current guidance (Paul Cross, 2016) recommends support for individual aspirators with Thy1 rates greater than 15%.

Recent data gathered from most Scottish laboratories found that the average unsatisfactory rate across Scotland is 23%, ranging from 20-29%. Although UK Thy1 rates are high overall, rates of 8-15% have been achieved elsewhere (Poller DN, 2020). Centres report variable impact of attendance by or assistance of a pathologist or BMS. The Radiology Group considers the RCR standard of 70% of FNAs to be acceptable, leaving a much larger margin for Thy1 rates. However, this group agreed to continue to uphold 15% as the standard which teams should aim for, given the key role of FNA in thyroid diagnosis.

Despite the lesions aspirated by radiologists often being challenging to sample, the group unanimously agreed that poor sample preparation was a significant factor - limiting both adequacy and diagnosis. The group agreed that laboratory staff with experience in sample preparation should provide training to support radiologists, including how to utilise the direct spreading technique. This may include BMS/pathologist attendance depending on local circumstances. To facilitate this, we have produced detailed guidance on thyroid FNA sample preparation (Appendix A) for distribution to radiology colleagues.

The RCPath believes it is essential for thyroid cytology reporting categories and outcomes to be audited. The group agreed that ongoing routine cytology data is needed to ascertain and monitor Thy1/all Thy category rates in Scotland and to support a dialogue with colleagues in radiology. As it is not possible for pathology departments to monitor Thy1 rates for individual operators, we recommend that FNA sample takers monitor their rates on an individual basis.

Recommendations

- *Thy1 rates of around 15% are achievable and should be aimed for*
- *Each laboratory should continue to monitor and compare Thy1 rates over time*
- *Individual radiologists should find a way to monitor their own Thy1 rates*
- *Ongoing training in slide preparation should be offered to aspirators at all centres*
- *We encourage you to share our group's guidance with clinicians performing thyroid FNA*

## Histopathology reporting - potential additional minimum dataset items

The Royal College of Pathologists has published histopathology reporting guidance and minimum cancer datasets for all systems, including reporting proformas. Pathologists are familiar with this process, allowing the group to conclude that histopathology reporting across Scotland is already largely consistent. Nevertheless, the current RCPath thyroid cancer pathology dataset 2014 (Johnson, February 2014) does not include all the parameters listed in the American Thyroid Association (ATA) recurrence risk stratification algorithm. This algorithm helps to inform decision making around patient management by MDTs. The International Collaboration on Cancer Reporting (ICCR) has recently published a thyroid dataset (Ghossein, et al., 2019) which captures additional information, specifically on documenting lymph node involvement. This group piloted the use of the dataset for four months during this project, including a template reporting proforma in the format of the dataset.

We concluded that the new ICCR dataset items were an improvement on the RCPath dataset. It therefore recommends that, in the absence of an updated RCPath minimum dataset, the ICCR dataset should be implemented across Scotland with a few very minor amendments. The dataset is supported by comprehensive guidance notes but to address ambiguity and communicate the amendments, the group will circulate a consistency note (Appendix B). The ICCR dataset includes a non-core section on ancillary tests which may include molecular testing. We identified that molecular reports are often not available when histology reporting takes place and these results may be reported separately by the pathologist or molecular pathology laboratory.

Group members had different views on the ease of use of the ICCR dataset proforma. The main criticisms were that it is complex to read out to MDTs and does not allow for reporting of multifocal tumours where more than just the largest tumour have features requiring documentation. It was agreed that, provided all the agreed core data items are included on the report, centres could continue to use a format that suits their MDT setting and laboratory IT system. If however there is future resource for a national thyroid cancer database, report forms could be modified to facilitate data extraction.

The project Board requested that pathologists consider including an ATA risk score on the report. Group members were unanimous in the view that they were not in a position to do this, as they felt that determining risk of recurrence was a decision for the MDT. We did however recognise the importance of including all required histological information.

The ICCR dataset includes clinical information that should be replicated on the histology report. The group agreed that the core clinical information covers the basics and is helpful but acknowledged that adequate clinical information is rarely supplied. This was raised with the surgery subgroup who agreed to supply clinical details but would like the pathologist to provide a form for this. Given the variation in sample requesting mechanisms/forms across the laboratories, it was agreed that group members would liaise with their local surgeons to facilitate provision of core clinical details and additional information where possible.

Recommendations

- *The data items included in the ICCR Dataset (Dec 2019) should be included in thyroid cancer histology reports, with minor amendments*
- *Either the ICCR format or a report format convenient for an individual centre is acceptable*
- *The ATA risk category should be determined by the MDT, with histological data items made available to allow this*
- *Pathologists will work with local surgeons to encourage submission of relevant clinical information*
- *The group supports the development of a national thyroid cancer database*

## Consistency of reporting

Within the field of thyroid histology, there are several areas that are diagnostically challenging and/or new or evolving. At the project Board, the group discussed and explored anecdotal evidence of variation in reporting of vascular invasion across Scotland. In doing so, they identified the following areas where pathologists found criteria uncertain or difficult to apply, often questioning their consistency in reporting.

## Vascular invasion

Reporting of vascular (angio) invasion has implications for surgical management of patients, whereby its presence means patients are deemed to be at intermediate risk of recurrence, according to the ATA. The group has outlined these definitions in the consistency note (Appendix B).

## NIFTP, FTUMP and WDTUMP

Non-invasive Follicular Thyroid Neoplasm with Papillary-like nuclear features **(**NIFTP) is a relatively new diagnostic entity, resulting from reclassification of diagnostic features, previously within the category of Encapsulated Follicular Variant of Papillary Thyroid Carcinoma (EFVPTC). This is challenging as the features are uncommon and interpretation is subjective. The group shared recent publications on NIFTP (Kakudo K, 2018) (Lloyd RV A. S., 2018) (Rossi ED, 2018), including revised criteria. The group originally considered drawing up a consensus document. However, the Birmingham group - tasked with updating these definitions for the BTA guidelines - have reviewed the available literature on this topic extensively. We are therefore happy to use their descriptions and recommendations when published, as a consensus guideline.

## TCV of PTC

Group members were not clear on Tall-Cell Variant (TCV) criteria and there was variation in the extent to which minor components were reported. We agreed to follow the World Health Organisation (WHO) definitions, whereby tall cells are two to three times taller than they are wide (Lloyd RV O. R., 2017). As tall cell areas are frequently found in otherwise conventional

Papillary Thyroid Carcinoma (PTC), a diagnosis of TCV should only be made when the percentage of tall cells is > or equal to 30%. In some centres, a minor tall cell component (<30%) is also recorded and the group agreed that this is good practice, hence recommended for inclusion in reports. It was however noted that the definition of TCV as above, for ATA purposes, is stringent.

With respect to measuring consistency of reporting in the above areas, we identified two mechanisms: audit and establishing a slide club/consensus meetings in which slides are discussed. These are explored further below.

Recommendations

- *A guidance note on vascular invasion has been agreed by the group and can be found in Appendix B*
- *Pathologists should refer to the document drafted by the Birmingham group in relation to NIFTP*

## Routine audit of thyroid cytology and histology

As outlined above, audits may provide data on frequency and consistency of reporting. Different methods and opportunities around data capture exist due to variation in pathology IT systems across Scottish laboratories, limiting the value of these findings.

The group agreed that despite being time consuming, it is important, to follow RCPath guidelines, audit Thy rates and outcomes. The RCPath template has therefore been circulated. The continuation of this network would act as a forum for cytology outcomes to be compared between centres and against any current national data (e.g. on risk of malignancy for Thy categories). Going forward, Thy 3a outcomes are an area of interest.

During the course of this project, we attempted to collect prospective data on frequency of reporting for NIFTP, vascular invasion and tall cell components. Unfortunately, there were too few cases recorded to detect any variation in practice. More focused audits, either retrospective or for a longer prospective period, may be a feasible option. It is felt that continuation of this group would help to promote ongoing audit. Pathologists also support the creation of a resourced national database.

## Thyroid pathology networking

### Second opinions in cytology/histology

Given the diagnostic challenges and importance of accurate classification and reporting of therapeutic/prognostic criteria, gaining a second opinion is invaluable. In the larger centres where several reporting pathologists regularly see thyroid cancer cases, this can be done internally. However at the smaller centres where there are fewer cases and/or pathologists with a thyroid interest, a second opinion from colleagues in another centre is required. Professionals at the UK Endocrine Pathology Society (UKEPS) have established a database of pathologists who are willing to give a second opinion but the number is currently small. As a

result of this project, more willing pathologists have been identified and shared their contact details. The larger centres have also offered to provide a second opinion when required.

### Consensus meetings

Alongside a system which allows pathologists to gain additional opinions on a specific case, the group agreed that establishing a forum to discuss difficult cases and review diagnostic criteria is another way in which consistency can be assessed and sought. Examples of such forums which already exist in other pathology specialties include the East of Scotland Lymphoma group and the SIN group for Oral Pathology. All group members are enthusiastic and support the establishment of a slide club, alongside continuing to meet to assess and update consensus views. Members are in the process of investigating the logistics of both digital and glass slide circulations and as this will require resource, are exploring potential sources of funding. It is hoped that the group will next meet in autumn 2020.

Recommendations

- *Scotland wide consultations for second opinions are ongoing and will continue to take place. This project has allowed pathologists to establish links with colleagues across the country, so that such consultations are possible.*
- *The group is keen to maintain a network for ongoing consensus discussions, in which changes to practice can be agreed*
- *The establishment of a Scottish endocrine pathology slide club for thyroid and parathyroid pathology would be a desirable outcome of this group. Logistics are being considered and funding sought.*

## Molecular testing for BRAF gene mutation and TERT promoter mutations on histology and cytology samples

Research has shown that the combined association of Telomerase Reverse Transcriptase (TERT) promoter mutation with BRAF V600E mutation, has a synergistic impact on aggressive outcomes in PTC (Liu R, 2016). As this is also recognised in the ATA's risk stratification, the project Board asked for the group to address the use of molecular testing.

We discussed current testing and confirmed that funding was available for BRAF testing of thyroid cancers. Following discussion at the Board, it was agreed that all laboratories will routinely test all papillary carcinomas >1cm (pT1b). A team in Glasgow are also undertaking a project to test tumours smaller than 1cm. The group will follow guidance from the Radioactive Iodine (RAI)/nuclear medicine subgroup to ascertain whether smaller cancers should be tested. The use of BRAF immunohistochemistry was also explored, but we considered this to be inferior to molecular testing.

The group reviewed the application of BRAF testing in the diagnostic setting. In cases where the differential is NIFTP/WDUMP or PTC, BRAF testing may be useful. In cytology, Thy4 cases can be resolved using BRAF testing but there is rarely sufficient material for full analysis.

The Pathology Consortium Group have submitted a proposal to NHS National Services Scotland (NSS) for TERT promoter mutation testing to be performed on TC samples, along with RAS testing for malignancy and indeterminate nodules. If this is approved, all labs in Scotland who can carry out these tests will receive funding to do so. Some labs may opt to send samples away for testing but they will still receive funding. Results are currently pending.

Recommendations

- *All centres will request BRAF testing on histology of papillary carcinomas >1cm*
- *BRAF testing can be used in diagnosis of cytology and histology cases where papillary carcinoma is in the differential*

## Microscopic lesions – papillary or suspected microcarcinomas

The group addressed variation between centres in the reporting and ancillary investigation of microcarcinomas. It was agreed that it is good practice to report any histological features that may indicate an ATA intermediate or high risk. The use of immunohistochemistry (e.g. CK19) to characterise suspected microcarcinomas has not yet been discussed by the group. With respect to molecular testing, we will await guidance from colleagues in the RAI and Nuclear Medicine Group.

*Dr Louise Smart*

Chair, Scottish Thyroid Cancer Pathology Group

# 3. SURGICAL GROUP

## Group members

| | | |
|---|---|---|
| **Richard Adamson (Chair)** | ENT Surgeon | NHS Lothian |
| **David Smith (Co-Chair)** | General Surgeon | NHS Tayside |
| **Iain Nixon** | ENT Surgeon | NHS Lothian |
| **Ashley Hay** | ENT Surgeon | NHS Lothian |
| **Sonia Wakelin** | General Surgeon | NHS Lothian |
| **Gavin Browning** | General Surgeon | NHS Lothian |
| **Karol Pal** | General Surgeon | NHS Borders |
| **David Walker** | ENT Surgeon | NHS Fife |
| **Richard Townsley** | ENT Surgeon | NHS Ayrshire & Arran |
| **Omar Hilmi** | ENT Surgeon | NHS GG&C |
| **Sebastian Aspinall** | Breast and Endocrine Surgeon | NHS Grampian |
| **Muhammad Shakeel** | ENT Surgeon | NHS Grampian |
| **Aidah Isa** | ENT Surgeon | NHS Highlands |
| **Carol Watson** | General Surgeon | NHS GG&C |
| **Fiona MacGregor** | ENT Surgeon | NHS GG&C |
| **Louise Clark** | ENT Surgeon | NHS GG&C |
| **Anne Hitchings** | ENT Surgeon | NHS GG&C |
| **Jenny Montgomery** | ENT Surgeon | NHS GG&C |
| **Murray Stewart** | ENT Surgeon | NHS GG&C |
| **Alison Lannigan** | General Surgeon | NHS Lanarkshire |
| **Swee Keong Kang** | ENT Surgeon | NHS Lanarkshire |
| **Iain Smillie** | ENT Surgeon | NHS Lanarkshire |
| **Andy Chin** | ENT Surgeon | NHS Lanarkshire |
| **Michail Winkler** | General Surgeon | NHS Forth Valley |
| **Iain Muir** | General Surgeon | NHS D&G |
| **Micol Salvetto** | Project Manager | SCAN |
| **Kate Farnell** | Patient Representative | Butterfly Thyroid Cancer Trust |

## Introduction

This subgroup brings together surgeons who deliver thyroid surgery for cancer patients in Scotland. We identified individuals through the British Association of Endocrine and Thyroid Surgeons (BAETS) and word of mouth.

Our remit was to develop advice on all aspects of the surgical pathway which a thyroid cancer patient would come into contact with. We also seek to identify what standard services in Scotland should meet.

We were keen to ensure that all surgeons had access to the appropriate clinical networks and an acceptable level of equipment, both diagnostic and surgical. We performed an email survey and demonstrated that this was the case across all centres.

We subsequently identified key areas where we felt group discussion was needed and met on two occasions. The attendance at these meetings was excellent and I am grateful to the group members for their commitment. The outcomes are discussed below.

## The referral pathway

The thyroid is currently not included in the Scottish Urgent Suspicion of Cancer (USOC) referral pathway. We therefore identified a number of proforma to help identify higher risk thyroid patients. The Newcastle proforma (Appendix C) was felt to be an excellent tool and we recommend that it is used in Scotland. The group also felt that those patients identified as high risk should be seen within two weeks of referral, as for other USOC patients.

Patients should be seen in either a dedicated thyroid nodule clinic or a neck lump clinic. Having immediate access to ultrasound (US) scanning and US-guided FNA biopsy is desirable.

Recommendations

- *A structured proforma should be used to stratify GP referrals*
- *High-risk patients to be seen within two weeks at an appropriately resourced clinic*

## The pathway to surgery

The group acknowledge that proceeding to surgery as quickly as possible is the best way to reduce anxiety for the patient. However, we also recognised that the nature of well-differentiated thyroid cancer is such that short and likely unachievable targets, would not improve clinical outcomes.

We felt that all patients with a high-likelihood of cancer (Thy4+) should be operated on within four weeks of the diagnostic biopsy result. We also felt that this target should be the aspiration for Thy3 patients. It was clear that in certain centres there is significant delay in diagnostic tests and to advocate for shorter targets at this stage would be unrealistic.

The target time for completion surgery is controversial. The group acknowledged that a large number of external factors can influence this and that no evidence exists to suggest that rapid completion ultimately improves patient outcomes. We did however acknowledge that patient anxiety increases and RAI therapy is delayed, when there are undue delays in completion.

On balance we felt that completion thyroidectomy should always be performed so that patients can receive RAI therapy within six months of their primary surgery, with an aspirational target of three months.

Recommendations

- *To operate on high-risk patients (Thy4+) within four weeks of their diagnostic biopsy result*
- *Aim to operate on Thy3 patients within 4 weeks*
- *To always perform completion thyroidectomy so that RAI therapy can be given within six months of primary surgery*

## Pre-operative assessment

Access to the following investigations is mandatory for the adequate work up of this patient group.

| | |
|---|---|
| **Radiology:** | Ultrasound<br>Ultrasound guided FNA biopsy<br>Ultrasound guided core biopsy<br>CT neck/chest |
| **Clinical:** | Vocal cord function assessment<br>Endocrine MDT |
| **Laboratory:** | Thyroid Function Test (TFT)<br>Serum calcium<br>Parathyroid Hormone (PTH) Test – ideally same day<br>Serum vitamin D<br>Serum calcitonin<br>Cytology |

Please note that the majority of patients will not require all of the above tests.

The group endorsed the Butterfly Thyroid Cancer Trust's pre-operative information for patients and recommend that this, or an equivalent, is routinely provided to thyroid cancer patients. We also felt that all Thy4+ patients should be discussed at an MDT. In many cases this discussion can take place after initial surgery. Pre-operative discussion of Thy3 patients can take place at local discretion. All surgeons should be able to attend and discuss any case at an MDT meeting.

Recommendations

- *Access to investigations as indicated above is mandated*
- *The Butterfly Trust patient information, or an equivalent, to be used for all patients*
- *Surgeons able to discuss all Thy4+ patients with their MDT*

## Surgical practice

It was felt that the current BTA guidelines provide appropriate guidance on the best surgical approach for actual and suspected thyroid cancers. The group are therefore in favour of following these guidelines. For cancer cases, it was stressed that there is no benefit in performing any near or sub-total surgery.

Recommendation

- *BTA guidelines used to guide appropriate surgical intervention*

## Perioperative management

All centres should have a clear protocol for the management of post-operative calcium. We felt that this can be agreed locally rather than the use of a standardised proforma being made mandatory. A national UK proforma may however be available soon. We would envisage adopting this protocol once it is published.

The identification and management of post-operative hypocalcaemia should be included in the induction for junior doctors and information they receive, along with education provided to nurses. .

The identification and management of post-operative bleeding, particularly during airway emergencies, should also be part of our junior doctors' induction, information and nurse education.

All units are expected to be able to demonstrate appropriate training as above. It is desirable for post-operative laryngoscopy to be performed for all patients.

Recommendations

- *All units must have protocols and training in place for management of hypocalcaemia, bleeding and airway emergencies*
- *For routine post-operative vocal cord function assessment to take place where possible*

## Governance

It is a General Medical Council (GMC) requirement that surgeons collect and audit their outcome data. The UKRETS database is currently the only national tool that is regularly used for this and so the group recommends that its use must be made mandatory for all surgeons undertaking thyroid surgery for cancer patients in Scotland.

The group also recommends setting up a forum for discussion of difficult cases. Interested surgeons could, for instance, communicate via an email group.

We also felt that there should be an annual meeting which would include review of surgical audit data.

Recommendation

- *All surgeons should submit their outcome data to the UKRETs database*

## Paediatric thyroid surgeries

It was agreed that a small group of surgeons should perform all thyroid surgery for paediatric patients in Scotland and that this could include Mr Iain Nixon in the South-East, Mr Omar Hilmi in the South-West and Mr Sebastian Aspinall for the North.

*Mr Richard Adamson*

Chair, Scottish Thyroid Cancer Surgical Group

# 4. RADIOACTIVE IODINE AND NUCLEAR MEDICINE GROUP

## Group members

| | | |
|---|---|---|
| **Kathryn Graham (Chair)** | Consultant Clinical Oncologist | NHS GG&C |
| **John Davidson (co-Chair)** | Consultant Nuclear Medicine | NHS Tayside |
| **Prakash Abraham** | Consultant Endocrinologist | NHS Grampian |
| **Victoria Bassett-Smith** | Consultant Medical Physicist / SRPA Representative | NHS Lothian |
| **Lisa Black** | Clinical Nurse Specialist | NHS Lothian |
| **Lorna Bracken** | Clinical Nurse Specialist | Macmillan |
| **Colin Brown** | Consultant Medical Physicist | NHS GG&C |
| **Dave Colville** | Consultant Nuclear Medicine | NHS GG&C |
| **Kate Farnell** | Patient Representative | |
| **Fraser Gibb** | Consultant Endocrinologist | NHS Lothian |
| **Alex Graveling** | Consultant Endocrinologist | NHS Grampian |
| **Fergus McKiddie** | Consultant Medical Physicist | NHS Grampian |
| **Dilip Patel** | Consultant Radiologist & Nuclear Medicine | NHS Lothian |
| **Micol Salvetto** | Project Manager | NHS Lothian |
| **Mark Strachan** | Consultant Endocrinologist | NHS Lothian |

## Introduction

Evolving paradigms in the management of Differentiated Thyroid Cancer (DTC) propose a more conservative approach. For example, performing a lobectomy (L) rather than near total thyroidectomy (TT) for patients with tumours <4cm and with no high-risk features, is considered the best course of action. However, the number of patients requiring Radioactive Iodine Ablation (RAIA) across Scotland has not varied over the past five to ten years. This may reflect a gradual move towards simply prescribing more low-dose activity (1.1GBq), compared with the standard activity of 3.7GBq. This is either a consequence of the non-inferiority randomised Hi-Lo trial (Dehbi, et al., 2019) or indicative of an increase in incidence. It has been noted that diagnostic rates of both low-risk microcarcinomas and higher risk tumours are on the rise in the UK, and indeed worldwide (Pellegriti G., 2013).

According to the American Thyroid Association (ATA) 2015 guidelines, the risk of relapse for patients who have the highest risk strain of the disease may be over 50% (Haugen, et al., 2016). In such cases, the diseases expresses itself as widely invasive follicular thyroid cancer with extensive vascular invasion, papillary thyroid cancer with gross extra-thyroid extension and/or bulky lymph node involvement >3cm and/or extracapsular spread. As a result, there will always be a cohort requiring repeat treatment with RAI to control local and/or systemic recurrence. Even in those patients who eventually develop iodine refractory disease, the role of molecularly targeted agents is currently under the spotlight in an attempt to reverse RAI resistance and allow further RAI therapy. It is therefore unlikely that the number of patients requiring RAI ablation or therapy in Scotland will significantly drop over the next decade.

To that end, it is imperative that each of the four regions have the appropriate facilities and infrastructure to deliver RAI in a timely and efficient manner. This is particularly important as

novel radionuclides are entering standard practice for other malignancies, such as lymphoma, prostate, and neuroendocrine tumours. This may impact on availability of radiation isolation suites in the regional centres.

## RAIA/therapy activity

### Ablation

The current British Thyroid Association (BTA) 2014 guidelines indicate that Radioactive Iodine Ablation (RAIA) is advised following Total Thyroidectomy (TT) for DTC in the following clinical contexts: tumour measuring >4cm in maximum diameter; macroscopic residual disease; and/or metastatic disease. Conversely, RAIA is not indicated for sub-centimetre tumours. In all other cases, personalised decision making is recommended. The majority of patients fall into the latter category and it can prove challenging for both the clinician and patient to arrive at a decision. The ATA guidelines published the following year provide a more robust risk profile based on individual clinicopathological data. However, the diagram does not take into account multiple risk factors and is not easily integrated into the multidisciplinary tumour Board process. In addition, molecular markers - namely BRAF and TERT - have been incorporated into the profile, neither of which is performed routinely across Scotland or the UK.

There was unanimous agreement that an algorithm would be an invaluable tool to aid the decision making process, taking into account the BTA and ATA recommendations. This would encompass the optimal activity of I-131 to be administered, along with whether ablation is required. Recent years have seen de-escalation of therapy, specifically the introduction of 1.1GBq for lower risk DTC. Minimising radiation exposure and any subsequent late toxicity, which poses a small risk of second cancers such as leukaemia, tends to be advantageous in the majority of patients. Yet this must be balanced against insufficient treatment and potential recurrence.

Firstly, a consensus was reached that I-131 activity would be standardised across all regional centres and 1.1GBq or 3.7GBq utilised in the post-operative ablative setting. This is in line with the two dose regimens from the Hi-Lo (Mallick U, 2008 ) and ESTIMABL-1 (Schlumberger M, 2018 ) clinical trials. Prescribing an alternative activity is still permitted in extenuating clinical circumstances. Secondly, the literature was reviewed in order to address if there were any specific clinical or pathological factors that would favour one activity over the other. With the exception of the ATA highest risk group already outlined above (T4/R2/node >3cm/ECS), a case could be argued for either activity in most other scenarios. For the ATA highest risk group, we would recommend 3.7GBq. And for the BTA low risk group of T1-T2 (Nx or N0) DTC with no adverse pathology or vascular invasion, we would recommend 1.1 GBq so long as personalised decision making advocates RAIA. In particular, T3 tumours (>4cm) were excluded from ESTIMABL-1 and comprised only 15% of Hi-Lo participants, leading to speculation over categorisation as low or intermediate risk. Also, N1b nodal involvement has traditionally been managed with standard dose ablation and was excluded from both low dose trials. However, the ATA guidelines differentiate between size and number of involved lymph nodes, as

opposed to anatomical location in the central compartment (N1a) versus lateral neck (N1b). On balance, the resultant algorithm tries to reflect the multitude of competing clinical and pathological features including age, pathological subtype, multifocality, nodal status, lympho-vascular invasion and resection margin; all of which the clinician must take into account.

As research provides further clarity on the significance of molecular diagnosis and stratification of DTC, mutational analysis will almost certainly enter clinical practice and not be restricted to academic centres. Although the precise role of BRAF has proven controversial (Yasuhiro ITO, 2009 ), it does appear to be associated with more locally advanced disease and can prognosticate for nodal spread (Kim TH, 2012). Even more interesting is the ability of TERT promoter mutations to predict distant disease (Gandolfi, et al., 2015). This platform represents an unparalleled opportunity to introduce testing for BRAF and TERT across Scotland. The data generated will not only provide important epidemiological information that can be compared with international literature, but can also be integrated into the decision making tool on an individual patient basis - as per the ATA model. All of the above relies on obtaining a fully comprehensive report from pathology. A detailed minimum data set and reporting template is in development by the pathology subgroup.

At the request of the surgical subgroup, an optimum timeline for delivery of RAIA was considered. There is limited data on this topic and recent work from an international centre suggests that a delay of six months or more has no detrimental effect on low/intermediate risk DTC (Matrone, et al., 2020 ). However, liaison with patient advocacy networks indicates that such a delay would be unacceptable to the vast majority of patients. Where possible, RAI should be administered within three months of TT, especially in high-risk disease and assuming the patient has adequately recovered from surgery.

### Therapy

Historically, a standard ablative activity of 3.7GBq is delivered even in the presence of metastatic disease. Thereafter, activities of 3.7GBq – 8GBq are given no more frequently than every six to twelve months, although practice varies significantly worldwide. The role of individualised dosimetry based prescription is under investigation but remains experimental and should not be performed outside of a clinical trial. At present, there is no definitive evidence that higher activities are more efficacious. It was therefore agreed that 5.5GBq was a suitable therapeutic activity for patients with loco-regional recurrence and/or metastatic disease. I-131 therapy can be repeated at intervals with a minimum gap of six to twelve months, depending on thyroglobulin level and radiological response on axial imaging. A topic for further study is the timing of therapeutic I-131. A retrospective analysis of long term outcomes could be performed in order to determine whether there is a trend of improved survival, when patients receive repeated treatments over a shorter interval.

The BTA 2014 guidelines advise caution to be exercised when cumulative activity of I-131 exceeds 20GBq, based on theoretical increased risk of leukaemia. There will be a small proportion of patients who continue to have I-131 uptake and display ongoing disease response, when this threshold has been reached. An absolute cap of 20GBq will not be enforced and personalised decision making is advised, taking into account individual factors and availability/suitability for alternative treatment options.

Recommendations

*Ablation*

- *I-131 ablation activities of 1.1GBq and 3.7GBq will be adopted as standard practice*
- *Alternative activity is permitted in extenuating clinical circumstances*
- *RAI algorithm (Appendix 1) to aid decision making process on the following:*
  - *Is RAI required?*
  - *What is the optimal activity of RAI?*
- *A standardised pathology template for reporting with minimum dataset has been requested*
- *BRAF and TERT pilot studies to be requested with a view to national implementation*
- *Aim to administer I-131 within three months of TT*

*Therapy*

- *3.7GBq I-131 will be administered as initial ablation activity*
- *Repeated therapeutic activity of 5.5GBq I-131 can be administered at six to twelve monthly intervals, depending on response (assessed by thyroglobulin level and radiological imaging)*
- *Further I-131 therapy after cumulative activity of 20GBq can be considered as part of personalised decision making*

## Preparation for RAIA/therapy

The traditional approach prior to I-131 ablation/therapy is withdrawal of thyroid replacement hormone - levothyroxine at four weeks or liothyronine at two weeks - and a low iodine diet for up to three weeks prior to treatment. It is well recognised that thyroid hormone withdrawal leads to temporary impairment in quality of life and may exacerbate underlying medical and psychiatric conditions. The Hi-Lo trial demonstrated that Recombinant Thyroid Stimulating Hormone (rTSH) led to equivalent rates of successful ablation in patients with low/intermediate risk disease (Dehbi, et al., 2019). As a result, the BTA guidelines recommend rTSH in T1-T3, N0/Nx DTC. However, the use of rTSH is now becoming ubiquitous, even in patients with high-risk and metastatic disease. There is increasing literature to support this trend (Klubo-Gwiezdzinska J, 2012) (Klubo-Guriezdzinska J, 2013) (Tu J, 2014) and rTSH has the additional advantage of more rapid clearance of iodine. This can potentially result in shorter hospital isolation and a reduced period of restrictions. It is important to be mindful of a potential disadvantage of rTSH: tumour flare is a small but distinct possibility and in the context of airway compromise or impending spinal cord compression, thyroid hormone withdrawal is strongly advised.

There is no randomised data on the value of a low iodine diet and some centres in the UK have chosen to no longer instruct patients on dietary restrictions. The low iodine diet is

probably more relevant in areas of the world where nutritional intake is high in iodine. In view of geographical movement of patients and changing patterns in diet, the consensus was that a low iodine diet would remain in force. A period of one week was suggested, due to a recent study from a high iodine region of South East Asia illustrating that one week following a low iodine diet, in preparation for RAI ablation, was as efficacious as two weeks (Chung, 2013). In order to minimise patient anxiety, a simple and concise information leaflet should be prepared and distributed nationally.

Recommendations

- *Low iodine diet to be restricted to one week*
- *A simple and concise patient information leaflet should be produced (information subgroup)*
- *rTSH should be universally adopted for I-131 ablation and/or therapy unless c/i:*
  - *Residual disease encroaching on or invading airway*
  - *Spinal cord compression*

## RAI suite

Isolation is often the most daunting part of the patient journey following a diagnosis of DTC. It is therefore important to ensure that everything is done to reduce distress where possible. A pre-assessment visit to the unit is advised, unless geography is a deterrent, so that the patient can be introduced to the team. This is also a useful time to confirm specific arrangements for rTSH injection and re-iterate radiation protection issues. The isolation suite should be comfortable and equipped to reasonable standards, with access to electronic entertainment equipment. The Butterfly Thyroid Cancer Trust (BTCT) will contribute to the upgrading of one isolation suite per regional centre. Although the suite does not need to be solely for the administration of I-131, it should be a dedicated area that is utilised for radioisotopes which has associated radiation protection rules governing location, sterilisation, and maintenance.

To reduce radiation exposure for nursing, nuclear medicine and ancillary staff, 24-hour video surveillance of the isolation suite is recommended. If video surveillance would breach patient confidentiality, then telephone contact is acceptable.

Recommendations

- *At least one dedicated RAI suite per regional centre should be equipped to minimum standards*
- *BTCT will contribute to the upgrading of one suite per regional centre*
- *Patient observation by 24-hour video surveillance (or telephone if confidentiality is an issue)*

## Radiation protection

There is currently significant variation across Scotland in terms of the isolation period following I-131 ablation or therapy and the instructions relayed to patients on the length/intensity of restrictions that will be imposed afterwards (from less than one to four weeks). The overwhelming consensus is that there should be a standardised approach, alongside the production of a supporting national information leaflet.

At present, it has been agreed that there is no reason why the isolation period for in-patient admission cannot be streamlined. Unless there are social and/or medical reasons (e.g. renal impairment, large residual remnant or extensive metastatic disease) that require a more prolonged stay in hospital, isolation should take place as follows.

| I-131 activity | Isolation period |
|---|---|
| **1.1 GBq** | 24 hours |
| **3.7 GBq** | 48 hours |
| **5.5 GBq** | 48 – 72 hours |

This is of course dependent on residual activity, as regulations mandate this to be <800MBq. There are various methods to calculate dose rate but the most consistent and reliable is a ceiling monitor, which BTCT is willing to fund the installation of.

Several centres now perform individualised restrictions based on calculated dose rate at 24 or 48 hours but this is not yet established at a national level and a historical period of four weeks may be stipulated in some regions. In liaison with the Scottish Radiation Protection Advisory (SRPA) committee, there are on-going discussions with the common goal of standardising restrictions across all centres.

However, concerns have been raised over increased contamination rates, if earlier restrictions are enforced. A study has been proposed that will address these issues. More importantly, the updated Medical and Dental Guidance Notes on Ionising Radiation are anticipated to be released imminently. There are also reservations about developing Scottish guidelines now which may need to be immediately revised on the basis of over-riding legislation.

Recommendations

- *Proposed isolation period following I-131, subject to residual activity <800MBq at discharge*
  - *1.1 GBq – 24 hours*
  - *3.7 GBq – 48 hours*
  - *5.5 GBq – 48 – 72 hours*
- *Ceiling dose rate monitor to be installed in each isolation suite*
- *Restriction period of two weeks maximum*
- *Audit of excretion to be performed*
- *Further liaison with SRPA following publication of Medical and Dental Guidance*

## Nuclear medicine imaging

An essential component of RAI ablation or therapy is calculating the iodine uptake and distribution on I-131 Whole Body Scan (WBS). This can be performed between one to ten days post treatment. There is no gold standard for the timing of this procedure and in a number of centres the scheduling is fixed by availability of the g-camera scanner. It was not deemed necessary to specify a timeframe for imaging, especially if mandating a scan slot means a longer stay in hospital or a return visit to the nuclear medicine department from a significant geographical distance. There is no appetite at present to perform routine Single-Photon Emission Computerized Tomography (SPECT)-CT imaging in all patients but this can be requested if additional anatomical information will aid management.

In the era of Dynamic Risk Stratification (DRS) - where neck ultrasound (USS) and highly sensitive Tg level is recommended at nine to twelve months post ablation to estimate the risk of recurrence and direct appropriate follow up - there is diminishing need for a diagnostic I-131 WBS to assess the response to ablation. An audit of diagnostic WBS may provide useful information on current practice and help to formulate future guidelines. At present, there are no plans to withdraw this imaging tool but it should not replace DRS. Both I-123 and I-131 can be utilised for WBS and the selection of radioisotope is at the discretion of the individual nuclear medicine department. rTSH is the preparation of choice.

PET-CT is currently permitted within the Scottish PET guidelines to investigate patients with a rising Tg level and no visible disease on USS or axial CT imaging. Experience informs that PET-CT may also prove useful in delineating the extent of disease in RAI refractory DTC. It may also be instrumental in ruling out distant or widespread disease in patients being considered for radical radiotherapy to the neck and upper mediastinum, in the case of locoregional recurrence/inoperable disease or to sites with solitary/oligometastatic deposits. This is likely to become a more pressing issue in the advent of Stereotactic Ablative Radiotherapy (SABR) for oligometastatic disease. Similarly, adequate and thorough staging information is imperative if surgical metastatectomy or Radio Frequency Ablation (RFA) is planned. As yet, there is no strong evidence to support rTSH stimulation prior to PET-CT imaging and this practice is not recommended. It is clear that PET-CT can provide additional staging information in many situations that are not explicitly delineated in the Scottish guidelines. If the detection of metastatic disease - or more widespread disease beyond the definition of

oligometastatic - will significantly alter management, then a PET-CT should be requested. This does not require an alteration to the current PET-CT guidelines.

Recommendations

- *Post ablation/therapy I-131 WBS to be performed as standard*
- *SPECT-CT at ablation/therapy may provide additional anatomical information*
- *Diagnostic WBS (rTSH preferred) is permitted on individual patient basis (I-123 or I-131)*
- *PET-CT (rTSH not indicated) to be considered in the following scenarios:*
  - *Rising Tg levels with no visible disease on USS neck and CT NCAP*
  - *Prior to radical external beam radiotherapy for loco-regional recurrence*
  - *Prior to radical external beam radiotherapy/SABR/surgery/RFA for metastatic or oligometastatic disease*
  - *Prior to commencing tyrosine kinase inhibitor in RAI refractory disease*

## Future topics to be addressed

### Radiation restrictions following I-131

As outlined previously, work is ongoing to establish Scotland-wide consensus on the duration and intensity of radiation restrictions following I-131 ablation or therapy. The Radioiodine and Nuclear Medicine subgroup are grateful to SRPA for their input and guidance to date. We look forward to further discussions following the release of updated Medical and Dental Guidance Notes, with a view to formalising guidelines on restrictions that can be implemented nationwide.

### Outpatient ablation

It has been noted that a small number of units in the UK practice outpatient ablation (1.1 GBq only). There is enthusiasm towards introducing outpatient based delivery of low dose I-131, when each unit can reliably pinpoint a suitable location that would meet all of the radiation protection requirements. This is a service to strive for in the future, when all of the suggested recommendations as outlined above have been fulfilled.

### Post-operative risk stratification

It was recognised that deciding whether to offer RAIA can be more challenging than selecting the activity. Several Phase III trials currently recruiting (ION and ESTIMABL-2) aim to answer this question but the reporting of results are still some years away. There is a small body of literature that proposes risk stratification in the post-operative setting by performing neck USS and stimulated Tg (or unstimulated Tg) 3 months after surgery (Momesso DP T. R., 2014) (Orlov S, 2015) (Momesso DP V. F., 2016). However, there is no fixed threshold at which RAIA is definitely not indicated. ION and ESTIMABL-2 will also address this issue, so randomised data is pending. Meanwhile, this approach is an option for selected patients as part of

personalised decision making, providing it has been made clear that this method of risk profiling has not yet been fully validated and that a defined follow up process will be adhered to.

## Conclusion

At the start of this process, the preparation and indications for I-131 ablation, duration of isolation and post treatment restrictions were widely divergent across Scotland. There is now significant agreement on almost all of the key elements that constitute robust and efficient delivery of I-131, based on high level evidence where available. The group will continue to work in tandem with SRPA to establish guidelines on post treatment radiation restrictions and aim to implement these as soon as is safe and practicable.

*Dr Kathryn Graham*

Chair, Scottish Thyroid Cancer RAI and Nuclear Medicine Group

# 5. LONG-TERM FOLLOW-UP GROUP

## Group members

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## Introduction

The purpose of this group was to attempt harmonisation of follow-up strategies for clinicians across Scotland involved in longer term follow-up of thyroid cancer. Radioiodine (RAI) for thyroid cancer is offered in Edinburgh, Glasgow, Dundee and Aberdeen. There was significant variation in follow-up strategies between centres, partly due to the different ways in which treatment pathways have historically evolved in each area. The longer term follow-up of patients is led by different specialties, Surgery, Endocrinology and Nuclear Medicine, in different parts of the country. There were variations in the use of US, Tg assays (each centre has different sensitivity assays) and duration of follow-up. All centres expressed a desire to harmonise the way in which follow-up was planned, with some minor variations and transitional arrangements required to account for what patients have been counselled to expect from previous follow-up strategies. The recent ESMO guidelines (Filetti, et al., 2019) and draft Birmingham/BTA consensus statements, formed the basis of many of the recommendations for the group.

Although this group made progress towards standardising some elements of follow-up, we were unable to reach firm conclusions on several of the other important issues addressed. This was due to a concomitant discussion on the same topics by the Birmingham group, who are still trying to reach consensus on these. The Birmingham group, led by Dr Kristien Boelaert, has been tasked with updating the 2014 BTA Guidelines for the Management of Thyroid Cancer. Members of the long-term follow-up group were unanimous in their belief

that once such recommendations are available, consultants across Scotland will adopt these in their clinical practice. Until then, follow-up methodologies may continue to vary across the country, depending on historical cohorts of patients and current clinical practice.

## Tg and TgAB assessment based on DRS

Thyroglobulin (Tg) is a sensitive and specific marker of thyroid tissue remnant after total thyroidectomy. Tg is a marker of normal and malignant thyroid tissue. Its use in patients who have not had remnant ablation or received treatment through lobectomy alone, remains a subject of some debate. The trend in Tg over time, along with the absolute value, is considered to be a useful marker and has been included in recent guidelines (ESMO, (Filetti, et al., 2019)). Thyroglubulin Antibody (TgAB) is present in approximately 25% of patients and can interfere with Tg measurement, resulting in false negative values. In these situations, the TgAB trend is valuable due to the levels decreasing over time. An increase in TgAB levels could indicate tumour recurrence, prompting further evaluation (Matrone, et al., 2018).

Tg and TgAb are processed in four laboratories across Scotland. Only two of these laboratories have a high sensitivity Tg assay but the others are currently in the process of upgrading their assays. Recent guidelines (ESMO/Birmingham consensus) have accepted the evolution of Tg assays and the availability of high sensitivity Tg assays would remove the need for thyrogen stimulation, therefore saving costs. This practice is already undertaken in one of the NHS Health Boards where a high sensitivity Tg assay is available. All four laboratories in Scotland should be able to provide a functional TG sensitivity of ≤0.2ng/ml by the summer of 2020. This level of functional sensitivity is deemed acceptable in the recent ESMO guidelines. The group also established that trends in increase or decline of serum Tg are more important in follow-up, than values of any single measurement. In the event that the remaining laboratories do not succeed in moving to high sensitivity Tg by the summer of 2020, we recommend that they explore sending the Tg to other Health Boards, so that the process is harmonised across Scotland. This would also save costs by reducing Thyrogen use.

It should be noted that results produced by different laboratories may not be directly comparable. Patients should be monitored at the same laboratory wherever possible.

The group agreed that quantitative reporting of TgAb would be useful, whereby trends have the power to influence treatment decisions. This is due to the fact that TgAb typically decline over time and their increase may suggest tumour recurrence. All four laboratories now undertake quantitative reporting of TgAb.

Although there will be method specific variation in Tg and TgAb results, the group aims to harmonise the laboratory aspects of thyroid cancer follow-up - with regard to high sensitivity Tg assay and quantitative TgAb – and see this as within its remit. If the group could achieve this, it would be an extremely positive result.

Recommendations

- *DRS to be adopted across Scotland as per the 2014 BTA guidelines*
- *All laboratories in Scotland to have functional sensitivity for serum Tg ≤0.2ng/ml*
- *High sensitivity Tg ≤0.2ng/ml to be accepted as equivalent to thyrogen stimulation, for risk assessment in DRS*
- *All laboratories in Scotland to report TgAb in a quantitative, as opposed to qualitative, manner*
- *If all laboratories processing serum Tg and TgAb have not achieved an upgrade to assay with adequate sensitivity by Summer 2020, to explore sending Tg samples to another laboratory that could provide the adequate test sensitivity required*

## Tg and TgAB monitoring based on DRS

Dynamic Risk Stratification (DRS) using Tg and a neck ultrasound, nine to twelve months after Radioiodine Ablation (RAIA), is now widely used following publication of the British Thyroid Association's 2014 guidelines (Perros P, 2014). DRS has been proposed and validated for patients who have received total thyroidectomy and RAI ablations.

The American Thyroid Association's (ATA) 2015 guidelines (Haugen, et al., 2016) used the following response to therapy re-classification in differentiated thyroid cancer patients who are treated with total thyroidectomy and RAI remnant ablation.

Excellent response: no clinical, biochemical, or structural evidence of disease

(1-4% recurrence and <1% disease specific death)

Biochemical incomplete response: abnormally increased serum Tg or increasing anti-Tg antibody (TgAb) levels in the absence of localizable disease

(30% evolve to no evident disease (NED), 20% achieve NED after additional therapy and 20% develop structural disease; <1% disease specific death)

Structural incomplete response: persistent or newly identified loco-regional or distant metastases with or without abnormal Tg or TgAb

(50-80% continue to have persistent disease, disease specific death rate 11% in loco-regional disease and 50% with structural distant metastases)

Indeterminate response: nonspecific biochemical or structural findings, which cannot be confidently classified as either benign or malignant

(15-20% will have structural disease during follow-up, in the remainder non-specific changes are either stable or resolve, <1% disease specific death)

There is lack of validation in patients who have had a total thyroidectomy without RAI ablation and those who have had a lobectomy. There is however potential to impact positively on patient care, but this needs to be studied further. These have been modified to include dynamic risk stratification in patients with Differentiated Thyroid Cancer (DTC) who have not had remnant ablation (Park, et al., 2015) (Momesso DP V. F., 2016). Recent ESMO guidelines (Filetti, et al., 2019) have included a modified response to therapy definitions, in the absence of remnant ablation and lobectomy.

The modified DRS would aid the categorisation of patients into the response to therapy definitions, noted above and as defined in the table included (see Appendix E). This would allow for a more personalised approach to treatment and follow-up, similar to that laid out in the ESMO 2019 guidelines. We are currently awaiting consensus from the Birmingham group before finalising recommendations, as there is variable practice across Scotland.

## Thyroid function monitoring and TSH target based on DRS

Patients who have had a thyroidectomy need lifelong thyroxine. Historically, supra-physiological thyroxine doses were used to suppress any remnant thyroid cancer. This practice has changed in recent years, following the recognition of the adverse effects of Thyroid Stimulating Hormone (TSH) suppression - including atrial fibrillation and osteoporosis. The 2014 BTA guidelines (Perros P, 2014) and subsequent guidelines have used DRS to relax the TSH suppression in excellent responders. Patients with intermediate to high risk thyroid cancer at initial presentation may need continued TSH suppression but this should be discussed on an individual basis through personalised decision making.

Recommendations

*In patients with NIFTP and unifocal micro-PTC who have no high risk features, the TFTs are to be monitored every one to two years with the aim of maintaining TSH in the normal range.*

- *In patients who have had a lobectomy for PTC >1cm and FTC, the recommendation is to monitor TFTs every one to two years with a goal of maintaining TSH below two, but avoiding TSH suppression*
- *In patients treated with total thyroidectomy with or without RAI:*
  - *Initial low or intermediate risk: Annual TFTs and TSH less than 2, non-suppressed*
  - *Initial high risk: possible TSH suppression, personalised decision making*
- *In patients with intermediate response: Annual TFTs, TSH target 0.1 to 0.3mU/l await Birmingham)*
- *In patients with incomplete response: Annual TFTs and TSH target <0.1, personalised decision making re: revised target after a few years*

## Ultrasound monitoring based on DRS

Ultrasound (US) assessment at nine to twelve months following thyroidectomy and remnant ablation is an essential component of Dynamic Risk Stratification (DRS). US monitoring practice is variable across Scotland among patients who have not had remnant ablation and patients who have had a lobectomy. The recommendation in the ESMO 2019 guidelines (Filetti, et al., 2019) is reported in Appendix F.

**We await consensus from Birmingham before making final recommendations as some of the Scottish centres will need to make changes in practice**

## Discharge from secondary care based on DRS

There is variation in practice across the Scottish centres regarding discharge to primary care. This is evident in thyroid cancer patients after lobectomy and in patients who have been excellent responders to treatment. Discharge from secondary care to primary care would mainly be UK specific practice and is not tackled in recent ATA or ESMO guidelines but is being addressed in the UK Birmingham consensus. The possibility of a national endocrine register is being explored, with thyroid cancer being one of the diseases included at an early stage. This was strongly supported by members of the group as it would facilitate ongoing remote monitoring and the safe discharge of patients to primary care at appropriate disease stages.

**We await consensus from Birmingham before making final recommendations as some of the Scottish centres will need to make changes in practice.**

## Conclusions

The thyroid cancer project has proved to be an extremely useful forum in allowing us to better understand the delivery of thyroid cancer follow-up across Scotland. There have been major gains in agreeing similar strategies for Dynamic Risk Stratification (DRS) and laboratory measurements, across those NHS Health Boards providing this service. Practice currently varies across Scotland in terms of ultrasound monitoring and follow-up of lobectomy patients and there will be challenges in achieving the recommendations. However, there has been a positive spirit of collaboration among clinicians in our network to drive forward these important changes. Similar strategies around testing, follow-up and discharge would also be facilitated by a national endocrine register and are currently under discussion.

*Dr Prakash Abraham*

Chair, Scottish Thyroid Cancer Long Term Follow Up Group

# 6. PATIENT MATERIAL GROUP

## Group members

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|---|---|---|
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| **Lesley Sabey** | Head and Neck | NHS GG&C |
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| **Linda McCormick** | Head and Neck nurse | NHS D&G |
| **Fiona Kerr** | Head and Neck Nurse Specialist | NHS D&G |
| **Helen Taylor** | Patient Involvement Manager | SCAN |
| **Kate Farnell** | Patient Representative and Director of Butterfly Thyroid Cancer Trust | Newcastle |
| **Micol Salvetto** | Project Manager | SCAN |

## Introduction

This group was formed at a late stage in our National Thyroid Cancer Project, when the need for uniform patient material in Scotland became evident. Once significant steps towards harmonising Differentiated Thyroid Carcinoma (DTC) treatment protocols were made, we were tasked by the Long-Term Follow-Up Group to work on information materials for patients undergoing thyroid cancer treatment. The focus has been on modifying and adapting patient materials, rather than creating new ones.

This group identified a lack of patient support for thyroid cancer patients in the North of Scotland and has escalated this to the North Region Health and Care Collaboration (NCA) who are currently looking at ways to enhance provision.

## Patient information materials

The group identified two distinct opportunities where information should be provided to patients. Regardless of how thyroid cancer services are organised across Scotland, all patients undergo surgery and many also receive RAI ablation or therapy. Work is underway to produce information materials which can be handed out to patients at these two points in their journey. Where possible, patients should also be made aware of the two charities in the UK who support those living with thyroid cancer: the Butterfly Thyroid Cancer Trust and the British Thyroid Foundation. Information for patients with advanced/persistent thyroid cancer and under the care of an oncologist was deemed outside of the remit of this group.

### Information prior to surgery

Patients should be handed out a DVD produced by the Butterfly Thyroid Cancer Trust (BTCT), as recommended by the surgical group. These can be requested by emailing enquiries@butterfly.org.uk and they are free for services across the UK and patients alike. In addition to (ideally) or as an alternative to the BTCT materials, patients should ideally also be given a copy of the Understanding Follicular and Papillary Thyroid Cancer booklet published by Macmillan Cancer Support.

### Information prior to RAIA or therapy

The RAI and Nuclear Medicine Group agreed and recommends that patients should follow a simple Low-Iodine Diet (LID) in the week prior to RAI administration only. This is included in Appendix G.

Another form of patient information should be produced informing patients about contact restrictions during and post RAI administration and what to expect during treatment. This work is in progress as post-ablation restrictions guidelines are still pending from the Medical and Dental Guidance Notes. The four individual treatment centres in Scotland may wish to adapt the advice and national materials to address their local needs.

*Ms Irene Wotherspoon*

Coordinator, Scottish Thyroid Cancer Patient Material Group

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# Appendices

## Appendix A: Fine Needle Aspiration (FNA) sample guidance

The pathology subgroup are keen to support radiology colleagues in striving to minimise Thy1 rates and increase definitive diagnoses. The group appreciates that the Royal College of Radiologists (RCR) FNA target is to achieve a minimum 70% diagnostic rate but given the central role of FNA in diagnosis of thyroid lesions, feels that centres should be striving for Thy1 rates around 15-18%. Radiologists should monitor their individual Thy1 rates.

The group agrees that close collaboration between radiologists and pathologists should be encouraged, with laboratory staff providing practical guidance on sample preparation if requested.

### Sample preparation

The preferred sample type for thyroid diagnosis is direct spreads, ideally both air dried and fixed, along with the needle washing having been rinsed into buffered saline. Rinsing the sample into Cytolysis is an alternative that can be agreed locally with the pathologist. However, a well spread air-dried slide for giemsa staining is very helpful when assessing colloids and other features in thyroid cytology.

For direct spreads, prepare only **one air dried and one fixed slide** from each aspirate sample obtained. Rinse the rest of the material from the needle into the saline.

The sample from a second aspirate in the lesion should be prepared in the same way. Needle washings should be amalgamated. If it is evident that there is material on the first sample slides (colloid sheen or cell fragments seen grossly or on-site evaluation confirms cells) the second pass can be rinsed entirely into the needle washings fluid.

A maximum of two samples prepared as slides (a total of 2 air dried, 2 fixed slides) is recommended. More passes for needle washings may be taken, especially if a neoplasm is suspected. Needle washing material might be needed for immunohistochemistry/molecular, or if there was nothing left to rinse out after making the slides from initial passes.

### Technique for spreading slides

It is recommended that radiologists are given a demonstration of spreading technique by their cytopathologist/BMS or watch a demonstration video.

In advance of each aspiration: lay out three slides, label two slides in pencil with patient details and have a fixative and needle washing tube at the ready.

After sampling, expel a small drop, pinhead size –3mm diameter maximum, onto each of the two labelled slides, about 1cm below the labelled end. With very bloody or fluid samples, the drop may inevitably be larger.

Take the third spreader slide, touch it gently onto the drop to draw the material along the slide evenly away from the labelled end (see video link https://youtu.be/X1C2u4_jHxc). Leave this slide to air dry.

Spread the second slide in the same way and fix **immediately,** either in a pot of 3% acetic alcohol or, if not available, spraying the slides with Cytology Fixative.

*Squashing the material between two slides should not be done.

*Spreader slides should be discarded as there should be minimal material on these.

The attached flow chart summarises the slide labelling, spreading and fixation, process.

### FNA technique

It is not the role of the pathologist to advise on technique for taking the sample. However, with respect to thyroids which are particularly bloody, we recommend:

Using as fine a needle as possible (23-27G) to minimise bleeding. Please note that longer blue and orange needles can be sourced.

Using a small amount of material in the needle hub for each pass is sufficient. If blood starts to appear in the syringe, stop immediately.

### BMS assistance and/or Rapid On-Site Evaluation

The attendance of a BMS may be helpful in ensuring well spread and rapidly fixed samples, along with prompt delivery of samples to the laboratory.

If resources permit, Rapid On-Site Evaluation (ROSE) by a cytopathology trained BMS can be useful in determining adequacy. They can also advise on the best use of further material, particularly for lesions that have had a previous inconclusive aspiration. ROSE has been shown to improve adequacy rates. Depending on the training which the microscopist has received, ROSE can also provide preliminary diagnostic feedback to inform the ultrasound impression.

However, it is recognised that ROSE can be time consuming and an inefficient use of staff time. This is due to the fact that it requires staff to be on-site, extra resources and an appropriate environment. In many cases this may not be feasible. Alternatively, laboratory staff can offer practical advice and guidance, such as demonstrating sample preparation on request to radiologists concerned about their diagnostic yield.

## Fine Needle Aspirate Labelling Guide For Cytology Users

### Labelling of slides

Slides should be labelled using a **PENCIL ONLY, NOT PEN**

Please leave a gap at the top of the slide to accommodate the laboratory number

SLIDES SHOULD BE LABELLED **AD** FOR AIR DRIED SLIDES OR **WF** FOR SLIDES THAT ARE **IMMEDIATELY FIXED** WITH **ALCOHOL BASED FIXATIVE**




**Before packaging the slides and washings for sending to the Laboratory, please ensure the following:**

Slides are labelled with patients Forename, Surname and Date of Birth

Slides that have been covered in Cytological Fixative are labelled WF

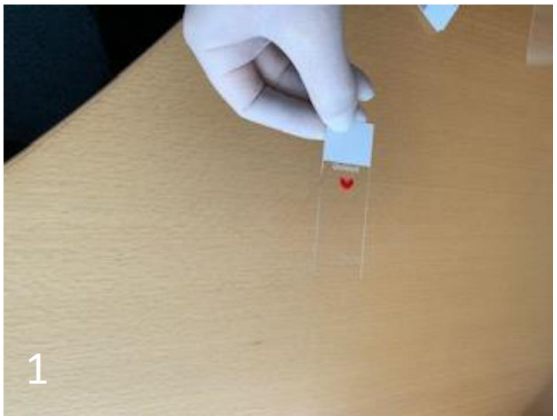
Slides left to dry that have not had fixative sprayed on them are labelled AD

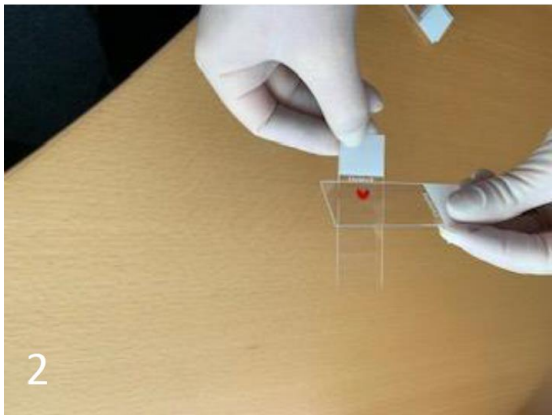
WF and AD slides are placed in SEPARATE slide mailers but sent in the same specimen bag, with needle washings

Slides fixed in a pot of acetic alcohol can be sent in the pot or fixed for minimum 10 mins then transferred to a slide box

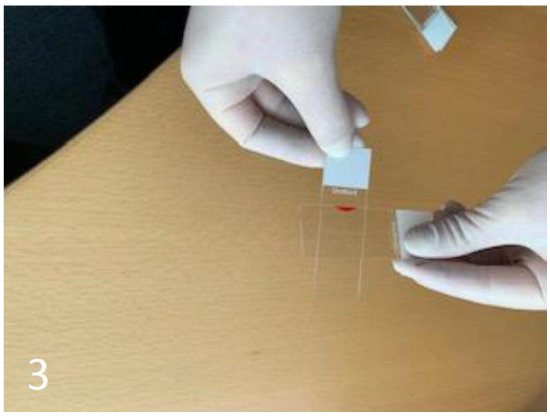
Washings MUST be labelled with patients Forename, Surname and Date of Birth

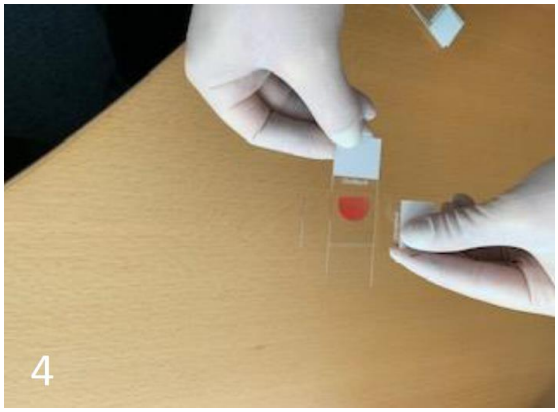
(N.B Needle washings- Rinse out needle out with saline and send in a clean universal container)

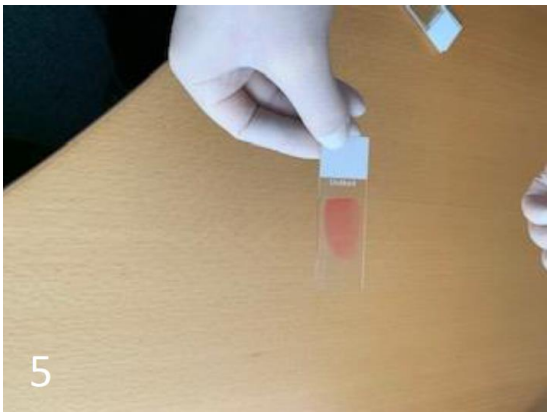



1. Expel a drop on to slide – near the label end but far enough down to be covered by liquid fixative if required
2. Place spreader against top of drop at 45 degrees
3. Allow the drop to spread out by capillary action
4. With the spreader flat and touching, lightly spread the material
5. The resulting spread will be bullet shaped




6. Slides for fixation must be placed in fixative or sprayed with fixative immediately

Please note: Thick blobs will not spread laterally as much as bloody or fluid ones

## Appendix B: Consistency note - additional notes/amendments to using the ICCR dataset agreed by the Pathology Subgroup

Reference: http://www.iccr-cancer.org/datasets/published-datasets/endocrine-organs/carcinoma-of-the-thyroid-tnm8

### General

Core dataset items are to be included in reports although the style of report is not prescribed.

The dataset items must be completed for the largest tumour but other tumours should be described and dataset items applied if appropriate (e.g. follicular carcinoma and papillary carcinoma in the same specimen; multifocal papillary carcinoma with differing histological types).

### Histologic Tumour Type

The definition of tall cell variant (TCV) is ≥ 30%. A minor component of TCV should be mentioned and the proportion estimated if possible.

Poorly differentiated carcinoma (PDTC): The WHO classification gives an algorithm for diagnosis. PDTC may be pure or be coexistent with PTC or another type. In most cases, the majority of the tumour will be PDTC but even a minority component should be described and the proportion estimated.

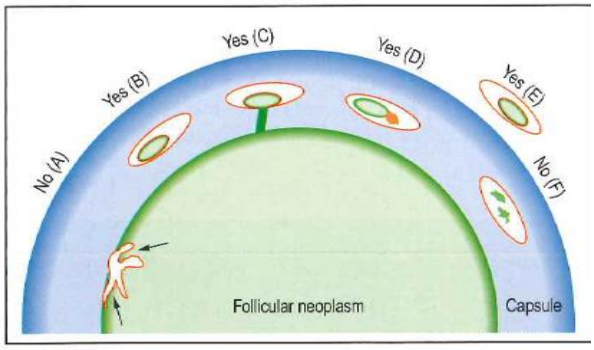
### Mitotic Activity

Mitoses ≥3 /2 mm2 (or 10hpf) must be documented but it is not necessary to mention the lack of mitotic activity.

### Tumour Grade

Not core and not necessary as stated in the histological type.

### Vascular Invasion (VI)



Both the RCPath guidelines and the ICCR dataset recommend the above diagrammatic definition proposed by Chan for encapsulated tumours. The RCPath guideline defines VI as "invasion of definite blood vessels (i.e. angioinvasion) within the tumour capsule or out with the tumour in adjacent thyroid tissue". Typically, these are "medium or large sized vessels and possess not only endothelium but also an elastic lamina." Interestingly, the RCPath dataset does not include VI as a data item for papillary carcinoma. Angioinvasion can occur in papillary carcinoma but is much less frequent than lymphatic invasion. According to Nikiforov's recent textbook, blood vessel invasion is seen more commonly in FVPTC than other variants.

The ICCR dataset recommends in its notes that Lymphovascular Space Invasion (LVI) should be reported but only links VI to adverse prognosis. Lymphatic invasion does not occur in follicular carcinomas.

For encapsulated angioinvasive follicular carcinomas, after thorough sampling of the capsule, the number of foci of VI should be documented (i.e. less than or equal to four, or greater than four). Encapsulated angioinvasive follicular carcinomas with minimal (≤ 4) vascular invasion are ATA low risk of recurrence. Follicular carcinomas, encapsulated or not, with extensive vascular invasion (>4 vessels) are ATA high risk.

It is important to distinguish, where possible, between intrathyroidal lymphatic spread and invasion of the tumour into blood vessels for papillary carcinoma, as this indicates an ATA intermediate risk.

A search for LVI (any vessel) is important when considering the diagnosis of NIFTP, as this is an exclusion criterion.

### Ancillary Tests

If molecular results are not available at the time of reporting they can be issued separately, so long as they are available to the MDT.

## Appendix C: Thyroid Urgent Suspected Cancer referral form sample

Northumbria Healthcare NHS Foundation Trust:

Thyroid Urgent Suspected Cancer Referral

Please tick the box of the hospital clinic you are referring to and fax this form to the relevant Urgent Referral Team within 24 hours.

☐ North Tyneside General Hospital
Fax:
Tel:

☐ Wansbeck General Hospital
Fax:
Tel:

☐ Hexham General Hospital
Fax:
Tel:

| | | |
|---|---|---|
| SURNAME | | NHS Number / Hospital Number |
| FIRST NAME | | |
| Gender M / F | D.O.B. | Patient aware the referral is urgent? Y / N |
| Address<br><br>Post Code | | First language<br>Interpreter required? Y / N<br>Transport required? Y / N |
| Daytime Telephone | | Home Telephone (if different) / Mobile No. |
| Referring GP | | Date of referral |
| Practice Address<br><br>Post Code | | Telephone<br>Fax |

**Symptoms & History**

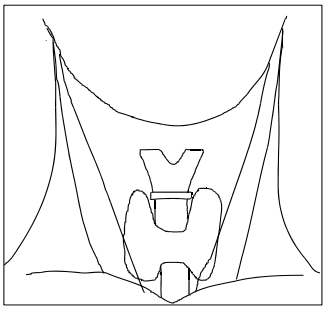
Refer urgently in a patient with thyroid nodule associated with any of the following…

- ☐ Solitary / dominant nodule increasing size
- ☐ Firm / immobile nodule
- ☐ Unexplained hoarseness or voice changes
- ☐ Cervical lymphadenopathy
- ☐ Other (please specify)
- ☐ History of neck irradiation
- ☐ Family history of endocrine tumour or MEN
- ☐ Previous diagnosis / family history of thyroid cancer
- ☐ Patient aged 65 years and older

**Refer immediately (acute admission)**

- ☐ A thyroid swelling rapidly increasing over days or weeks.
- ☐ With recent onset of tracheal compression including stridor due to thyroid swelling.

**Please indicate site of thyroid nodule and any lymphadenopathy below:**



Additional information **- Attach patient past medical history / medications - Continue on separate sheet if required.**

Resources for GPs are available at www.cancernorth.nhs.uk

## Appendix D: RAI algorithm to aid in patient management decision making

## Appendix E: Patient follow-up Summary table

(Pending consensus on thyroidectomy follow up)

| | Tg & TgAB Monitoring (TSH less than 2) | Ultrasound monitoring | TFTs monitoring TSH target | Discharge |
|---|---|---|---|---|
| **NIFTP & Unifocal MicroPTC No high risk features, e.g. vascular invasion, 'aggressive' histological subtype** | NO | NIFTP at 6-12 months<br>No, providing contralateral lobe has no concerning features | Monitor 1 to 2 yearly TSH in reference range | Yes – No follow-up |
| **Unifocal MicroPTC -uncertain about other lobe and/or high risk features** | No | Once at 6 to 12 months or Annually for 5 years | Monitor 1 to 2 yearly TSH in reference range | If no concerns in 5 to 10 years |
| **Lobectomy PTC >= 1cm** | No | Once at 6 to 12 months or Annually for 5 years | Monitor 1 to 2 yearly TSH less than 2, Non suppressed | If no concerns in 5 to 10 years |
| **Lobectomy FTC** | Consider monitoring TG trends for 5 years | Years 1,3 and 5 | Monitor 1 to 2 yearly TSH less than 2, Non suppressed | If no concerns in 5 to 10 years |
| **PTC - Total Thyroidectomy, No RAI** | Annually for 5 years Non-stimulated TG<0.2ng/mL with 'normal' neck USS classed as 'Excellent Response' | Within 12 months of surgery, as part of DRS<br>Thereafter based on TG trends | Annually<br>TSH suppressed first year, then less than 2, Non suppressed 'Excellent response – initial low/intermediate risk' 'Indeterminate response & Excellent – Initial high risk' - PDM, possible TSH suppression | If no concerns in 5 to 10 years<br>Register? |
| **Total Thyroidectomy, RAI 'Excellent response' in DRS** | Annually for 5 years<br>Nonstimulated | Based on TG trends | Annually<br>TSH suppressed first year, then lower half of reference range | If no concerns in 5 years<br>Register? |
| **Total Thyroidectomy, RAI Intermediate or incomplete response in DRS** | Annually<br>Nonstimulated TG >1ng/mL | Based on TG trends | Annually<br>TSH 0.1 to 0.3 (indeterminate) and <0.1 in incomplete.PDM after a few years | Intermittent<br>Nurse led and medical review based on TG trends |

## Appendix F: ESMO Response to treatment categories in DTC patients

**Table 4. Response to treatment categories in DTC patients[a]**

| Responses to treatment | Treatments | | |
|---|---|---|---|
| | TT+RRA | TT alone | Lobectomy |
| Excellent | Negative imaging<br>and<br>Undetectable TgAb<br>and<br>Tg <0.2 ng/ml or stimTg <1 ng/ml | Negative imaging<br>and<br>Undetectable TgAb<br>and<br>Tg <0.2 ng/ml | Negative imaging<br>and<br>Undetectable TgAb<br>and<br>Stable Tg levels |
| Biochemical incomplete | Negative imaging<br>and<br>Tg ≥1 ng/ml or stimTg ≥10 ng/ml or rising TgAb levels | Negative imaging<br>and<br>Tg >5 ng/ml or rising Tg values with similar TSH levels or rising TgAb levels | Negative imaging<br>and<br>Rising Tg values with similar TSH levels or rising TgAb levels |
| Structural incomplete | Imaging evidence of disease (regardless of Tg or TgAb levels) | Imaging evidence of disease (regardless of Tg or TgAb levels) | Imaging evidence of disease (regardless of Tg or TgAb levels) |
| Indeterminate | Nonspecific imaging findings<br>or<br>Faint uptake in thyroid bed on RAI scanning<br>or<br>Tg 0.2–1 ng/ml or stimTg 1–10 ng/ml or TgAb stable or declining in patient with no imaging evidence of disease | Nonspecific imaging findings<br>or<br>Tg 0.2–5 ng/ml or TgAb levels stable or declining in the absence of structural or functional disease | Nonspecific imaging findings |

[a]Modified from the 2015 ATA ongoing risk stratification (response to therapy) system [8].
ATA, American Thyroid Association; DTC, differentiated thyroid cancer; RAI, radioactive iodine; RRA, radioactive iodine remnant ablation; stimTg, TSH-stimulated serum thyroglobulin; Tg, thyroglobulin; TgAb, anti-serum thyroglobulin antibody; TSH, thyroid-stimulating hormone; TT, total thyroidectomy.

Source: ESMO 2019 Guidelines: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology: official Journal of the European Society for Medical Oncology. Annals of Oncology, Vol. 30, Issue 12, page. 1861

## Appendix G: Low-Iodine Diet (LID) brochure for Scottish patients

**RECOMMENDED DIET FOR ONE WEEK BEFORE RADIOACTIVE IODINE TREATMENT FOR THYROID CANCER**

Please do not feel anxious about the diet. Only the foods listed in the "Try not to Eat" column below need to be avoided.

| DO EAT | TRY NOT TO EAT |
|---|---|
|  |  |
| Fresh and frozen fruit and vegetables | Seafood and Fish |
| Fresh and frozen meats | Cow's / goat's milk, cheese, ice cream, yoghurt and butter |
| Rice, pasta and potatoes | Egg yolks |
| Soft drinks, fruit juices, beer, wine, tea and coffee | Some cough mixtures and health foods (such as seaweed, kelp, cod liver oil, vitamins and mineral supplements) contain iodine. If the label lists iodine, do not take the supplement while on this diet |
| Plain fats and oils (non-dairy) | Avoid food from restaurants, fast-food chains and takeaways and imported processed foods. In the USA and many European countries iodine is added to table salt and used in baking. |
| Olive oil spread | |
| Fresh (shop bought) and homemade bread | |

**Preparing your meals from ingredients and foods listed in the "Do Eat" column is the best way to avoid Iodine in your diet. Table salt and sea salt with no added iodine may be used. Please do not stop taking any of your regular medicines without speaking to your Thyroid team.**

*This Low Iodine Diet has been endorsed for use in Scotland by the health professionals involved in the national Thyroid Cancer Project*

NHS SCOTLAND