

## Main Article

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# A study of variation in therapeutic approach to low-risk differentiated thyroid cancer in the UK

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## Abstract

**Background.** The British Thyroid Association and American Thyroid Association guideline definitions for low-risk differentiated thyroid cancers are susceptible to differing interpretations, resulting in different clinical management in the UK.

**Objective.** To explore the national effect of these guidelines on the management of low-risk differentiated thyroid cancers.

**Methods.** Anonymised questionnaires were sent to multidisciplinary teams performing thyroidectomies in the UK. Risk factors that multidisciplinary teams considered important when managing low-risk differentiated thyroid cancers were established.

**Results.** Most surgeons (71 out of 75; 94.7 per cent) confirmed they were core multidisciplinary team members. More than 80 per cent of respondents performed at least 30 hemi- and/or total thyroidectomies per annum. A majority of multidisciplinary teams (50 out of 75; 66.7 per cent) followed British Thyroid Association guidelines. Risk factors considered important when managing low-risk differentiated thyroid cancers included: type of tumour histology findings (87.8 per cent), tumour size of greater than 4 cm (86.5 per cent), tumour stage T<sub>3b</sub> (85.1 per cent) and central neck node involvement (85.1 per cent). Extent of thyroid surgery (e.g. hemi- or total thyroidectomy) was highly variable for low-risk differentiated thyroid cancers.

**Conclusion.** Management of low-risk differentiated thyroid cancers is highly variable, leading to a heterogeneous patient experience.

## Introduction

Over the last two decades, there has been an increase in the incidence of thyroid cancers, with the UK's incidence predicted to reach 11:100 000 by 2035.<sup>1,2</sup> This increase is mostly attributed to the overdiagnosis of low-risk differentiated thyroid cancers.<sup>3</sup> However, the majority of patients with low-risk differentiated thyroid cancers have an excellent prognosis, because the majority of these cancers tend to have an indolent course.<sup>4</sup> It is now well recognised that much of the observed increase in incidence of low-risk differentiated thyroid cancers is the result of increasing access to highly accurate ultrasonography and ultrasound-guided fine needle aspiration cytology (FNAC), as well as increasing scrutiny of cytology and surgical pathology samples.<sup>3,5</sup>

Risk, in the context of thyroid cancer, can be interpreted in various ways, and one individual's interpretation of low risk may be different from another's.<sup>6</sup> Thyroid cancer risk can be considered in terms of disease-specific mortality or risk of recurrence.<sup>7,8</sup> The Union for International Cancer Control/American Joint Committee on Cancer staging systems are designed to predict mortality.<sup>9</sup> However, disease-related death is uncommon and a more clinically relevant risk of recurrence system has been presented by the American Thyroid Association.<sup>8</sup> The majority of recurrences are within lymph nodes. These recurrences can often be successfully managed surgically without compromising the risk of disease-specific mortality. In addition to the risks mentioned above, there is another concept of risk associated with features of the thyroid tumour itself.<sup>8</sup> Certain tumour-related features, such as extra-thyroidal extension, multifocality, lymphovascular invasion and perineural invasion, may indirectly predict recurrence risk and affect disease-specific survival outcome.<sup>8</sup> However, although survival is of primary concern for patients with cancer, disease-specific death only occurs in approximately 1 per cent of patients with low-risk differentiated thyroid cancers, which makes recurrent risk more clinically relevant for the majority of patients.<sup>8</sup>

During the mid-twentieth century, great strides were made in understanding the biology of differentiated thyroid cancers.<sup>10</sup> Groups from Europe and the USA recognised that critical factors could predict outcome reliably in the majority of cases.<sup>11</sup> These risk-stratification systems have been refined over the years and adopted into international guideline documents, including the British Thyroid Association<sup>12</sup> and the American Thyroid Association<sup>8</sup> guidelines published in 2014 and 2015, respectively. The definitions

**Table 1.** Summary of definitions of low risk of recurrence according to BTA<sup>12</sup> and ATA<sup>8</sup> guidelines

<i>British Thyroid Association 2014 guidelines</i>
– No regional or distant metastases
– All macroscopic tumour resected
– No invasion of loco-regional tissues or structures
– Tumours with non-aggressive histology or angio-invasion
<i>American Thyroid Association 2015 guidelines</i>
Papillary thyroid cancer with all the following:
– No regional or distant metastases
– All macroscopic tumour has been resected
– No tumour invasion of loco-regional tissues or structures
– Tumour does not have aggressive histology
– If iodine-131 is given, no radioactive iodine avid metastatic foci outside thyroid bed on 1st post-treatment whole-body radioactive iodine scan
– No vascular invasion
– Clinical nodal (N) stage N <sub>0</sub> or ≤5 pathological N <sub>1</sub> metastases (<0.2 cm in largest diameter)
Intrathyroidal, encapsulated follicular variant of papillary thyroid cancer
Intrathyroidal, well-differentiated follicular variant thyroid cancer with capsular invasion & no or minimal (<4 foci) vascular invasion
Intrathyroidal, papillary microcarcinoma, unifocal or multifocal, including BRAF V600E mutation (if known)

BTA = British Thyroid Association; ATA = American Thyroid Association

from the two guidelines have been summarised in Table 1. These guidelines have published definitions for low-risk thyroid cancer. However, these definitions can be susceptible to differing interpretations, which in turn has the potential to significantly influence the management of low-risk differentiated thyroid cancers.

The availability of a variety of thyroid cancer management guidelines may influence clinicians' decision-making; consequently, this study aimed to explore the national effect of the latest British Thyroid Association and American Thyroid Association guidelines on the management of low-risk differentiated thyroid cancers from a surgeon's perspective in the UK.

## Materials and methods

An anonymised questionnaire was designed for national dissemination. The questionnaire was aimed at thyroid surgeons to ascertain the degree of variation of practice in relation to the management of low-risk differentiated thyroid cancers (Appendix 1, in the supplementary material, available on The Journal of Laryngology & Otology website). Surgeons performing thyroidectomies were identified through the British Association of Endocrine and Thyroid Surgeons national database of endocrine and thyroid procedures.<sup>13</sup>

The questionnaire was sent out via email, and through the British Association of Endocrine and Thyroid Surgeons, ENT-UK, National Cancer Research Institute and Thyroid Cancer Forum websites, with a covering letter to all the thyroid surgeons. This questionnaire enquired about which guidelines the surgeons or multidisciplinary teams (MDTs) followed, and the risk factors that the MDTs considered important when managing low-risk differentiated thyroid cancers. The questionnaire also presented index case scenarios to investigate

how different surgeons and MDTs managed low-risk differentiated thyroid cancer cases of varying complexity. The questionnaires were open for responses for one month to maximise responses. A reminder was also sent to participants at week two to maximise the response rate.

## Results

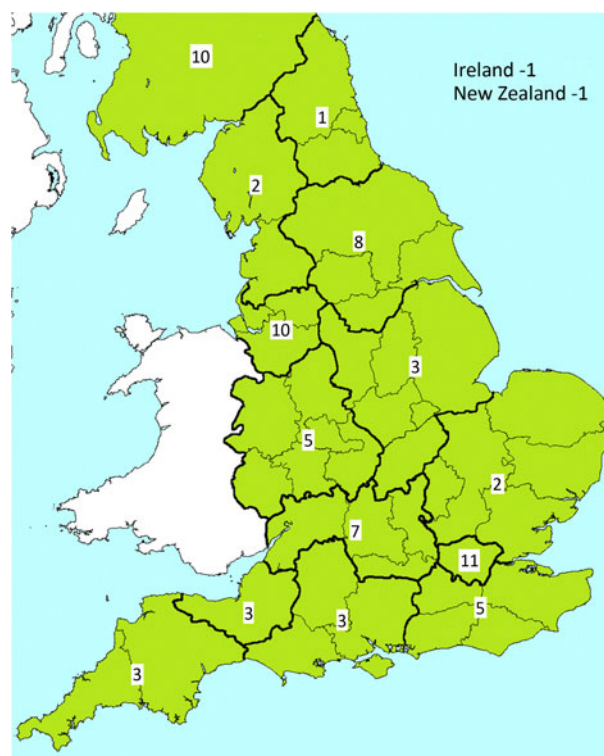
Twenty-eight per cent (75 out of 265) of the MDTs responded to the questionnaires sent to individual clinicians across the UK. The geographic distribution of responses is shown in Figure 1. No responses were recorded from Northern Ireland or Wales.

Of the 75 respondents, 71 surgeons (94.7 per cent) confirmed that they were core members of a thyroid MDT. The number of thyroid surgical procedures performed by the surgeons per annum in the UK is shown in Table 1 of Appendix 2. More than 80 per cent of respondents performed at least 30 hemi- and/or total thyroidectomies per annum.

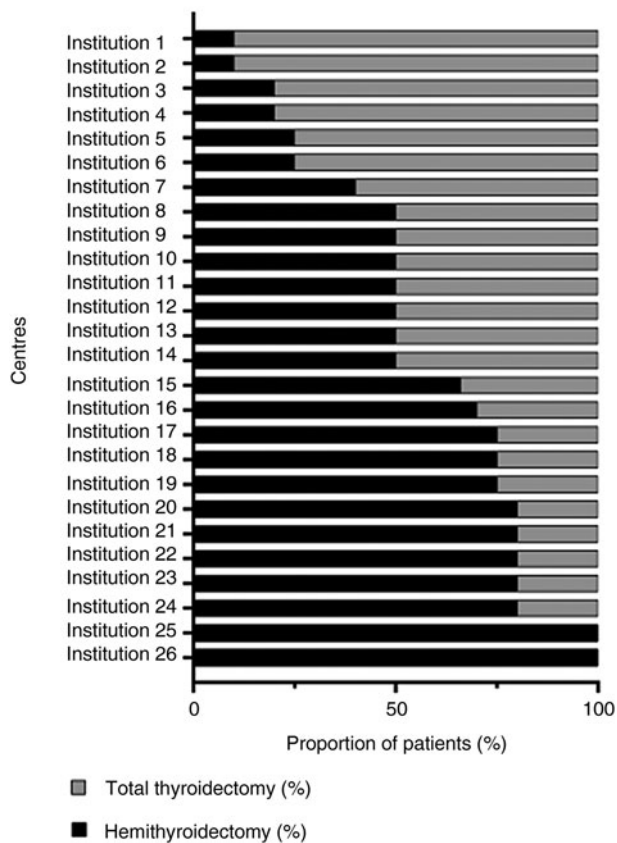
The majority of surgeons and MDTs ( $n = 50$ ; 66.7 per cent) followed the British Thyroid Association guideline alone, whilst 15 (20.3 per cent) surgeons and MDTs followed the British Thyroid Association and another guideline (Table 2 of Appendix 2).

When asked which risk factors for tumour recurrence were considered when constructing a management plan for patients with low-risk differentiated thyroid cancer, respondents stated the following were most important: type of tumour histology findings (87.8 per cent), tumour size of greater than 4 cm (86.5 per cent), tumour (T) stage T<sub>3b</sub> (tumour of any size with extra-thyroidal extension into strap muscles only) (85.1 per cent) and any central neck node involvement (85.1 per cent) (Table 3 of Appendix 2). The other risk factors taken into consideration are shown in Table 3 of Appendix 2.

Respondents were also asked about the number of hemithyroidectomies and total thyroidectomies performed for low-risk differentiated thyroid cancers in their unit. The



**Figure 1.** Number of surgeons or multidisciplinary team groups answering the questionnaire from different geographical regions in the UK.



**Figure 2.** Type of surgery (e.g. hemithyroidectomy or total thyroidectomy) offered for low-risk differentiated thyroid cancers by institution.

ratio of hemithyroidectomies to total thyroidectomies for different institutions is shown in Figure 2. The extent of thyroid surgery (e.g. hemi- or total thyroidectomy) recommended for low-risk differentiated thyroid cancers across the UK demonstrated considerable variation (Figure 2). Most institutions offered either hemi- or total thyroidectomy for low-risk differentiated thyroid cancers depending on the individual case. Two institutions offer hemithyroidectomy alone, whilst seven MDTs offered total thyroidectomy in most cases.

Clinical scenarios were provided in the questionnaire to understand how surgeons dealt with different presentations of low-risk differentiated thyroid cancers.

### Case one

A 38-year-old female with no past medical history presents with a thyroid swelling. An ultrasound scan confirmed an ultrasound 'U' classification of 'U5' (Malignant), and FNAC confirmed a Thy5 (malignant) classification, solitary, right-sided 2-cm lesion, with no other abnormalities in the thyroid or neck.

Forty-three (58.1 per cent) surgeons responded that they would offer a lobectomy, whereas 15 (20.3 per cent) surgeons would offer a total thyroidectomy. Six (8.1 per cent) surgeons responded that they would offer both options and undergo a shared decision-making process with the patient (Table 4 in Appendix 2, in the supplementary material, available on The Journal of Laryngology & Otology website). Responses on the management of case one are shown in Table 4 in Appendix 2.

### Case two

A 40-year-old male with no past medical history undergoes ultrasound and FNAC, which demonstrates a solitary, 3 cm,

sonographically indeterminate (ultrasound 'U' classification of 'U3') nodule, classified as Thy3a (indeterminate or follicular lesion of undetermined significance). He undergoes a diagnostic hemithyroidectomy, and a classical papillary thyroid cancer is diagnosed. A post-operative ultrasound scan of the neck shows no other nodules in the contralateral side or any involved nodes.

A total of 26 (35.1 per cent) surgeons opted for a completion thyroidectomy, 17 (23 per cent) offered active surveillance with serial clinical and ultrasound scan examinations, 16 (21.6 per cent) offered both options (i.e. completion thyroidectomy and active surveillance) for a shared decision-making process, and 14 (18.9 per cent) offered a completion thyroidectomy with either central neck dissection or radioactive iodine or both (Table 5 in Appendix 2).

### Case three

Case three entails the same pre-operative scenario as for case two, but the post-operative histology demonstrates a papillary thyroid cancer and four incidentally excised lymph nodes, two of which demonstrate microscopic positivity (< 3 mm).

The findings from the lymph nodes significantly altered management plans when compared with case two. Sixty-three respondents (85.1 per cent) reported that they would offer central neck dissection and/or radioactive iodine. Conversely, three (4.1 per cent) offered active surveillance of the tumour (Table 6 in Appendix 2).

### Case four

A 42-year-old female with no significant past medical history undergoes a hemithyroidectomy for a presumed colloid cyst for quality-of-life symptoms. Histopathology demonstrates three incidental foci of intrathyroidal papillary microcarcinoma, with the largest measuring 4 mm. The post-operative ultrasound scan does not demonstrate any further pathology in the neck.

Two-thirds of respondents (49 out of 75; 65.3 per cent) said they would continue with close surveillance, with the other third (24 out of 75; 32 per cent) offering a completion thyroidectomy (Table 7 in Appendix 2).

### Case five

Case five has the same pre-operative scenario and histology as case four, but the post-operative ultrasound scan demonstrates several contralateral thyroid nodules, measuring 2 cm maximally, with a U ultrasound classification of 'U2/3' (benign or indeterminate), and with a Thy2 (benign) classification on FNAC.

In contrast to case four, two-thirds (62.2 per cent) of surgeons responded that they would offer a completion thyroidectomy and the other third (35.1 per cent) were still happy to offer clinical surveillance (Table 8 in Appendix 2).

## Discussion

This study aimed to determine whether there was any variation in the interpretation by thyroid surgeons and MDTs of the term 'low-risk thyroid cancer' as defined by well-recognised international and national guidelines. The data presented are from a geographically wide range of MDTs, where more than 80 per cent of surgeons undertake 30 or more

thyroidectomy operations per annum. The results show clear variation in the treatment offered to patients by those MDTs. This suggests significant variation in both guideline interpretation and surgical practice by thyroid surgeons across the UK.

The current British Thyroid Association guidelines recommend that the management of all differentiated thyroid cancers be the responsibility of a specialist MDT (evidence level 4, recommendation level D).<sup>12</sup> Despite this standardised approach, our results suggest that there is still significant variation in practice for patients with low-risk differentiated thyroid cancer.

Previous studies have shown that higher surgical volume by surgeons favours better clinical outcomes, which benefits both patients and the healthcare economy.<sup>15–17</sup> For example, the European Society of Endocrine Surgeons considers a case load of fewer than 25 thyroidectomies per year as a low-volume surgeon.<sup>15</sup> Similarly, Adam *et al.* also reported that surgeons performing more than 25 total thyroidectomies per annum were associated with improved patient outcomes.<sup>16</sup> On the other hand, Aspinall *et al.* recommended more than 50 thyroidectomies per year to ensure good clinical outcomes.<sup>17</sup> From our survey, all responding surgeons performed at least 20 thyroidectomies (hemi- and total thyroidectomies) per annum, with 81.1 per cent performing 30 or more thyroidectomies per annum. This is encouraging because it suggests that few respondents would be considered low-volume surgeons by most measures.

Guidelines act as a framework for MDTs to make treatment recommendations. It was extremely encouraging to see that 97.2 per cent of surgeons followed at least one or a combination of two well-recognised guidelines. The most popular guideline followed was from the British Thyroid Association, which is to be expected because this survey was performed in the UK. Of the two remaining responders (3 per cent), one did not specify what guidelines they worked with and the other responded that their choice of guidance was 'ad hoc'. This last statement suggests that there may be increased heterogeneity in the management of thyroid cancers depending on the case.

The guidelines set out an array of factors to be considered when risk-stratifying a patient at the time of diagnosis. We asked surgeons what specific risk factors their MDTs took into consideration when assessing a patient's risk. The most frequently considered risk factors were type of tumour histology findings (87.8 per cent), tumour size of greater than 4 cm (86.5 per cent), extra-thyroidal extension (85.1 per cent) and any central neck node involvement (85.1 per cent). Interestingly, the age cut-off of 55 years old, as introduced by the eighth edition of the American Joint Committee on Cancer,<sup>12</sup> was considered less than the older age cut-off of 45 years, which may reflect the relatively recent change in age stratification. It also seems that any central neck node involvement is thought by many to be a significant risk factor. This is in contrast to the 50 per cent who would only consider central neck node involvement to be a risk factor once there was evidence of more than five nodes affected. These results show that even within a group of highly specialised clinicians and MDTs, there remains great variability in how risk is interpreted, which, again, will affect a patient's management.

One critical finding of this study is the variation reported in the primary surgical approach to low-risk differentiated thyroid cancer. Estimated rates of total versus hemithyroidectomy

range from 0 per cent to almost 100 per cent, representing an extremely heterogeneous approach in the UK. This variation in treatment recommendation is concerning, because patients find it difficult to understand why one group strongly favours a more aggressive approach whilst another group strongly favours a conservative approach. In order to further understand these trends, case scenarios were presented.

The case scenarios, all of which were theoretically low-risk, depending on the guidelines applied, produced interesting results. Case one enquired about the initial surgical management for a 2-cm, Thy5 (malignant) solitary thyroid nodule with no other pre-operative abnormality or risk. Despite both the British Thyroid Association and American Thyroid Association guidelines recommending lobectomy for such a case, only 58.1 per cent reported that they would offer a lobectomy, whilst 32.6 per cent offered a more aggressive approach of a thyroidectomy with or without another form of therapy (e.g. central neck dissection, radioactive iodine), whereas 8.1 per cent responded that they would allow a patient-based decision.

Cases two and three essentially demonstrated that the presence of microscopically positive lymph nodes of any number dramatically affected the management strategy of thyroid surgeons. Involvement of any number of lymph nodes drove a previously equally split decision among completion thyroidectomy, clinical surveillance and shared decision-making to a more aggressive strategy of completion thyroidectomy with or without another form of therapy (e.g. central neck dissection or radioactive iodine). This finding is despite the well-known fact that at least 50 per cent of clinically staged node-negative (N<sub>0</sub>) necks in papillary thyroid cancer harbour occult nodes, which are unrecognised on imaging and are not included in pathology if a neck dissection is not performed, although these nodes rarely progress to clinically meaningful disease.<sup>18</sup>

Cases four and five demonstrated that contralateral thyroid nodules, in the presence of papillary thyroid microcarcinoma, despite being radiologically benign/indeterminate (U ultrasound classification of U2/3) and cytologically benign (Thy2), encouraged surgeons towards a more aggressive form of management (i.e. completion thyroidectomy). Surgeons who initially were happy to continue clinical surveillance felt uncomfortable with conservative management despite the benign appearance of these contralateral nodules in an otherwise 'low-risk' patient. Presumably, these responses indicated a high level of suspicion of occult papillary thyroid microcarcinoma, despite the benign appearance of contralateral nodules. These responses are similar to findings from a qualitative study investigating clinicians' views on the management and terminology for papillary thyroid microcarcinomas.<sup>19</sup> Nickel *et al.* found that clinicians (surgeons and endocrinologists) were not comfortable supporting clinical surveillance of known multifocal papillary thyroid cancer, because of concern about metastases and the belief that their patients had a high preference for surgery.<sup>19</sup>

Overall, these responses demonstrate that there is considerable variability both in the basic approach to low-risk differentiated thyroid cancers and in how surgeons and MDTs approach individual thyroid cancer cases on a national level. This also has been reflected by Haymart *et al.* in the USA.<sup>20</sup> It appears that, despite the existence of guidelines from both international and national bodies, the recommendations within those guidelines can and are being interpreted variably across the UK.

The decision to offer total thyroidectomy for low-risk differentiated thyroid cancers may be driven by patient anxiety (e.g. uncertainty around recurrence risk and to facilitate follow up) despite an increased risk of complications. Total thyroidectomy has the potential advantage of allowing more accurate post-operative thyroglobulin monitoring, in comparison to thyroid lobectomy where the residual lobe hampers interpretation of fluctuating levels of thyroglobulin.<sup>21</sup> In contrast, thyroid lobectomy offers the advantage of lower rates of recurrent nerve injury and hypoparathyroidism, as well as the opportunity to avoid lifelong complications, irrespective of surgeon volume.<sup>22</sup> However, hemithyroidectomy may be associated with an increased recurrence risk, and the long-term safety, cost-effectiveness and follow up of this group remain uncertain. Recent evidence suggests little role for post-operative radioactive iodine in low-risk differentiated thyroid cancers, further questioning the need for total thyroidectomy.<sup>23</sup>

The variation in treatment that we report here is associated with a lack of high-level evidence in this field. Patients with low-risk differentiated thyroid cancers do well, irrespective of treatment approach. From a clinical perspective, this means that MDTs will rarely feel a wrong decision has been made in the management of this group. From a research perspective, low-risk differentiated thyroid cancers present a challenge. The low event rate of recurrences or complications makes level 1 evidence difficult to provide. The upcoming Hemi or Total ('HoT') trial is a multi-centre randomised, controlled trial that aims to investigate exactly this group of patients; it hopes to provide the highest quality evidence, to permit standardisation of practice in this field and reduce the variation experienced by patients across the UK.<sup>24</sup>

- Established guidelines have defined low-risk differentiated thyroid cancers, but interpretations among clinicians can differ
- Different guideline interpretations result in different clinical management of low-risk differentiated thyroid cancers in the UK
- Important risk factors when managing low-risk differentiated thyroid cancers included: type of tumour histology, tumour size greater than 4 cm, tumour stage T<sub>3b</sub> and central neck node involvement
- The extent of thyroid surgery for low-risk differentiated thyroid cancer is highly variable across the UK
- Highly variable management of low-risk differentiated thyroid cancers results in variation in patient experience; a standardised approach is crucial

### Strengths and limitations

The main strength of this study was that respondents were from most regions in the UK, reflecting the current national practice of low-risk differentiated thyroid cancers. This study has highlighted that, despite what seem like clear guidelines from well-recognised international bodies, there appears to be heterogeneous care across the UK. Selection bias was reduced by sending questionnaires to all surgeons and MDT groups identified from the anonymised British Association of Endocrine and Thyroid Surgeons database of endocrine and thyroid procedures.<sup>25</sup>

The main limitation of this study was the relatively small number of respondents. This was despite extensive advertisement of both questionnaires through various national bodies, and gentle reminders to surgeons and MDTs. Approximately 50 per cent of thyroid surgical procedures in the UK are captured by the British Association of Endocrine and Thyroid Surgeons database,<sup>25</sup> and the remaining half is captured by Hospital Episodes Statistics database for England.<sup>14</sup> The

surgeons performing total thyroidectomies from the Hospital Episodes Statistics database are predominantly low-volume surgeons when compared to British Association of Endocrine and Thyroid Surgeons.<sup>14</sup> For example, Hospital Episodes Statistics from 2017 to 2018 reported 388 surgeons performing total thyroidectomy, but only 37 surgeons (14.7 per cent) performed more than 20 total thyroidectomies per year.<sup>14</sup> However, in the 2021 British Association of Endocrine and Thyroid Surgeons report, approximately 200 surgeons recorded their 2017–2018 thyroid surgery data into the British Association of Endocrine and Thyroid Surgeons database,<sup>25</sup> suggesting that almost one-third of surgeons covering a wide geographic distribution responded to our questionnaire. The other limitation is that patients' perspectives and satisfaction in the management of low-risk differentiated thyroid cancers were not explored in this study.

### Conclusion

Diagnosis of thyroid cancer is continuing to increase with the development of more accurate imaging and increased scrutiny of pathological specimens. Most of these thyroid cancers are classified as low risk, which poses problems for clinicians when formulating a management plan. This study has demonstrated significant variation in practice in relation to low-risk differentiated thyroid cancers across the UK. This, in turn, leads to a heterogeneous patient experience, highlighting the need for a more standardised approach in this increasingly prevalent group of patients. Upcoming high-quality UK-based surgical research in this field aims to improve the available evidence upon which clinicians and patients can base future decisions, with the aim of reducing variation and improving the standards of care.

**Supplementary material.** The supplementary material for this article can be found at <https://doi.org/10.1017/S0022215123000841>.

**Competing interests.** None declared

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