

# Differentiated Thyroid Cancer: How Do Current Practice Guidelines Affect Management?

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## Keywords

Differentiated thyroid cancer · Papillary cancer · Follicular cancer · Guidelines · Risk stratification · British Thyroid Association

## Abstract

**Background:** International best-practice guidelines recommend completion thyroidectomy and radioiodine remnant ablation (RRA) for patients with differentiated thyroid cancer (DTC) >4 cm or with specific risk factors. Patients with DTC <1 cm without risk factors are recommended for lobectomy alone. Indications for aggressive surgery and RRA are less clearly defined for tumours measuring 1–4 cm. A personalised approach to decision-making is recommended. **Objectives:** This study assesses therapeutic approaches to DTC as compared to the current British Thyroid Association (BTA) clinical practice guidelines. We ascertained the effect of equivocal guidance in the 1–4 cm tumour cohort on contemporary practice patterns. **Methods:** Data were obtained from a prospectively maintained thyroid cancer database of patients treated for DTC in a tertiary referral centre at the University Hospital Galway. Consecutive patients attending a

dedicated thyroid cancer clinic between August 2014 and August 2017 were included. Clinicopathological characteristics and management strategies were assessed. **Results:** Ninety-four percent ( $n = 168/178$ ) of patients were surgically managed in adherence with guidelines. A minority ( $n = 10$ ) received surgery not aligned with guidelines. Ninety-seven percent ( $n = 172/178$ ) of RRA treatment decisions were in accordance with guidelines. The BTA guidelines recommended a personalised decision-making approach for 18.0% ( $n = 32$ ) and 44.9% ( $n = 80$ ) of surgery and RRA treatment decisions, respectively. The more aggressive, treatment-driven approach was typically favoured by the multidisciplinary team, with 97% ( $n = 31/32$ ) undergoing completion thyroidectomy and 100% ( $n = 80$ ) proceeding to RRA. **Conclusions:** Management of DTC at our institution closely adheres to contemporary clinical practice guidelines. The finding of more aggressive management in those requiring a personalised decision-making approach highlights the requirement for improved risk stratification in this cohort to rationalise management strategies.

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## Introduction

Thyroid cancer (TC) is the most common endocrine malignancy, accounting for 1% of all cancers, with an incidence of 162 cases per year in Ireland [1]. The National Cancer Registry Ireland reports increasing incidence of TC from 60 per year during the mid 1990s to 160 per year during the late 2000s [1]. Similar trends are reported worldwide, including the United Kingdom, the United States, and South Korea [2–4]. This observed increased incidence primarily comprises differentiated TC (DTC), without a concomitant increase in mortality, suggesting potential overdiagnosis of indolent pathology [4–7]. In Ireland, the 5-year TC survival rate has improved from 71% (1994–1998) to 91.8% (2010–2014), while the 5-year DTC-specific survival is 98% [1]. Data from 51,061 DTC patients from the US Surveillance, Epidemiology, and End Results database report an overall 5-year survival of 96.5% [8]. The mainstay of TC treatment involves surgical resection with or without adjuvant radioiodine remnant ablation (RRA); it follows that overdiagnosis of DTC results in potentially avoidable morbidity arising from surgical or RRA therapies.

The key recommendations of the British Thyroid Association (BTA) 2014 guidelines for the management of thyroid cancer include diagnostic lobectomy for those with Thy3 or Thy4 fine-needle aspiration cytology (FNAC). Total thyroidectomy (TT) is advised for patients with Thy5 FNAC or with confirmed DTC following diagnostic lobectomy where tumour size exceeds 4 cm or measures any size with risk factors including multifocal, bilateral, extrathyroidal, or familial disease, and those with clinically or radiologically involved nodes or distant metastases. Lobectomy alone is deemed sufficient for patients with unifocal papillary thyroid microcarcinoma (microPTC, <1 cm) without risk factors; these include multifocality, larger size (6–10 mm), extrathyroidal extension, poor differentiation, and desmoplastic fibrosis or an infiltrative growth pattern. There is a paucity of peer-reviewed randomised or prospective studies to support an advantage of TT over lobectomy in patients with unifocal tumours measuring 1–4 cm without risk factors. In these cases, the BTA guidelines recommend a personalised decision-making approach, which advocates a shared doctor-patient decision-making process in conjunction with multidisciplinary team input, with due consideration for recurrence risk, patient comorbidities, and personal circumstances and values [9].

The BTA recommends RRA for all patients with DTC >4 cm or any size with gross extrathyroidal extension or

distant metastases. Patients with tumours  $\leq 1$  cm without risk factors do not benefit from RRA. Personalised decision-making is advised for those with tumours measuring 1–4 cm without risk factors [9].

We aimed to describe the patterns of DTC presentation and treatment strategies and to assess the degree of adherence to clinical practice guidelines (BTA 2014) in patients treated for DTC at our institution. We further examined those patients where a personalised decision-making approach was recommended and how this subset was managed in the context of equivocal guidelines.

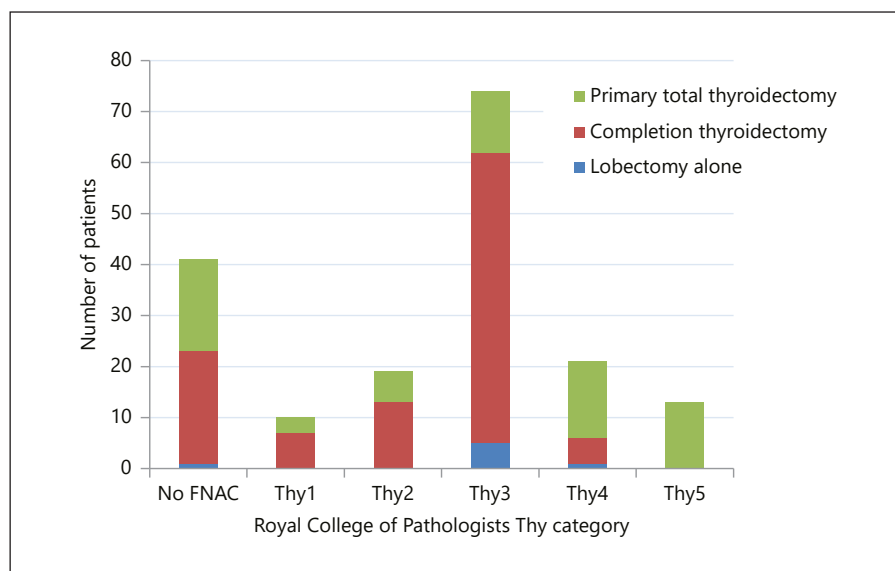
## Materials and Methods

Data were prospectively recorded from consecutive patients attending a specialist TC clinic in a tertiary referral centre (University Hospital Galway) over 3 years (August 2014–2017). Data collection was undertaken at the time of blood and sputum sample collection for inclusion in the University Hospital Galway TC Bio-Bank. Patient demographics, tumour histology, and staging parameters were recorded, in addition to surgical and RRA management strategies. All patients were discussed in an endocrine surgery multidisciplinary team. TC staging and FNAC were designated as per the AJCC Cancer Staging Manual (7th edition) and the UK Royal College of Pathologists thyroid cytology guidelines, respectively [10, 11]. The BTA guidelines for the management of thyroid cancer were accepted as best-practice guidelines [9]. Data recording and statistical analysis were performed using Microsoft Excel and IBM SPSS v22. Pearson's  $\chi^2$  test was used to compare categorical variables, while one-way ANOVA with Tukey post hoc analyses was utilised for comparing three or more categorical, independent samples.

## Results

Data were collected from 178 consecutive patients. Of these, 130 patients (73%) were female. The median age at diagnosis was 43.5 years (range 15–83 years). One hundred and fifty-two patients (85%) had papillary TC while 26 (15%) had follicular TC. The median tumour size was 26 mm (range 1–110 mm). Multifocal disease was present in 36% of patients ( $n = 64$ ). Lymphovascular invasion and extracapsular extension were evident in 33% ( $n = 58$ ) and 31% ( $n = 55$ ) of tumours, respectively. Forty-eight percent ( $n = 86$ ) had lymph nodes excised, with a mean harvest of  $7.6 \pm 8.5$  nodes. Thirty-four patients had confirmed lymph node metastases, representing 40% of those with nodes excised and 19% of all patients. The average number of positive nodes retrieved was  $4.7 \pm 4.4$ .

FNAC results were available for 77% of patients ( $n = 118$ ) (Fig. 1). All 13 patients with Thy5 FNAC underwent



**Fig. 1.** Surgical management per Royal College of Pathologists Thy category.

**Table 1.** Clinicopathological parameters based on surgical outcome

	Primary TT	Lobectomy alone	Lobectomy followed by completion thyroidectomy
Number of patients	67 (38%)	6 (3%)	105 (60%)
Female	51 (76%)	2 (33%)	77 (73%)
Age, years	46±16	50±23	46±16
Preoperative FNAC Thy1	3 (5%)	0 (0%)	7 (7%)
Preoperative FNAC Thy2	6 (9%)	0 (0%)	13 (12%)
Preoperative FNAC Thy3	12 (18%)	5 (83%)	57 (54%)
Preoperative FNAC Thy4	15 (22%)	1 (17%)	5 (5%)
Preoperative FNAC Thy5	13 (19%)	0 (0%)	0 (0%)
No preoperative FNAC	18 (27%)	0 (0%)	23 (22%)
Papillary (final histology)	61 (91%)	5 (83%)	86 (82%)
Follicular (final histology)	6 (9%)	1 (17%)	19 (18%)
Size, mm	22 (2–110)	5.25 (2–65)	30 (1–110)
Multifocal	26 (39%)	0 (0%)	38 (36%)
Nodal disease	25 (37%)	0 (0%)	9 (9%)
Lymphovascular invasion	29 (43%)	1 (17%)	28 (27%)
Extracapsular extension	23 (34%)	1 (17%)	31 (30%)

Values are presented as *n* (%), mean ± SD, or median (range). FNAC, fine-needle aspiration cytology; TT, total thyroidectomy.

primary TT. Primary TT was also performed for 3, 6, 12, and 15 patients with Thy1–4 FNACs, respectively. Of these 36 patients, 24 had features identified on preoperative imaging indicating TT (size >4 cm, lymphadenopathy, extracapsular or bilateral disease). TT was performed for benign indications (e.g., multinodular goitre, Graves' disease) in 9 patients, while 3 patients had no definitive indication for upfront TT.

### Surgery

Thirty-eight percent of patients (*n* = 67) underwent primary TT. Sixty-two percent (*n* = 111) had thyroid lobectomy, with 95% of those (*n* = 105/111) proceeding to completion thyroidectomy (Table 1). Six patients (3%) had lobectomy alone; these were more likely to be male (68%, *n* = 4/6) compared to those who proceeded to completion thyroidectomy (27%, *n* = 28/105) (*p* = 0.031). Tumour size >4 cm, multifocality, and extracapsular exten-

**Table 2.** Surgical management compliance with the BTA 2014 guidelines

	Patients	Compliant with BTA guidelines
All patients	178 (100%)	168 (94%)
<1 cm	27 (15%)	18 (67%)
1–4 cm	113 (63%)	113 (100%)
>4 cm	38 (21%)	37 (97%)
Multifocal	64 (36%)	64 (100%)
Lymphovascular invasion	58 (33%)	57 (98%)
Extracapsular extension	55 (31%)	54 (98%)
Age >45 years	86 (48%)	79 (92%)

Values are presented as *n* (%). BTA, British Thyroid Association.

**Table 3.** Clinicopathological details for patients where the BTA recommended a personalised decision-making approach (*n* = 178)

	PDM recommended for surgical management ( <i>n</i> = 32)	PDM recommended for RRA management ( <i>n</i> = 80)
Had thyroidectomy/RRA	31 (97%)	66 (83%)
Female	25 (78%)	66 (83%)
Age, years	37±10	43±15
Papillary cancer	28 (88%)	70 (88%)
Follicular cancer	4 (13%)	10 (12%)
Size, mm	21 (2–40)	22 (10–40)
<1 cm	8 (25%)	1 (1%)
1–4 cm	24 (75%)	79 (99%)
>4 cm	0 (0%)	0 (0%)
Multifocal disease	4 (all microPTC)	30 (38%)

Values are presented as *n* (%), mean ± SD, or median (range). BTA, British Thyroid Association; microPTC, papillary thyroid microcarcinoma; PDM, personalised decision-making; RRA, radioiodine remnant ablation.

sion were associated with an increased rate of completion thyroidectomy compared to lobectomy alone ( $p = 0.044$ ,  $p = 0.027$ , and  $p = 0.044$ , respectively). No significant association was observed between histological subtype or age and surgical procedure.

Ninety-four percent of patients ( $n = 168/178$ ) were surgically managed in strict adherence with the BTA guidelines (Table 2). Of those not aligned with the guidelines ( $n = 10$ ), 1 had a tumour >4 cm at lobectomy, but declined completion thyroidectomy. Nine patients had tumours <1 cm without risk factors, of whom 4 had primary TT for multinodular goitre causing mass effect. Five patients had interval completion thyroidectomy following lobectomy where not indicated by guidelines, and 2 due to personal preference on a background of thyroid tumour family history; another patient had interval ra-

diological lymphadenopathy and a recent history of metachronous laryngeal cancer. The remaining 2 patients proceeded to completion thyroidectomy based on preference alone, with age >45 years being their only relative risk factor for recurrence. The rate of surgical management in agreement with the guidelines was not significantly affected by sex ( $p = 0.824$ ), age >45 years ( $p = 0.158$ ), or histological subtype ( $p = 0.671$ ).

Personalised decision-making was recommended following thyroid lobectomy in 32 patients (Table 3); 24 patients had intermediate size tumours (1–4 cm) without risk factors, 4 had microPTC measuring 6–10 mm, while 4 with microPTC <6 mm exhibited multifocal disease. A more aggressive, treatment-driven approach was typically favoured by patients and the multidisciplinary team, with 97% ( $n = 31/32$ ) proceeding to completion thyroid-

ectomy; 1 patient with a unifocal 15-mm papillary TC without risk factors opted for lobectomy alone.

#### *Radioiodine Remnant Ablation*

Eighty-two percent of patients ( $n = 146/178$ ) underwent adjuvant RRA. RRA was more likely to be utilised in patients with node positivity ( $p = 0.002$ ), lymphovascular invasion ( $p < 0.001$ ), or extracapsular disease ( $p = 0.001$ ). RRA utilisation was not affected by sex ( $p = 0.547$ ), age  $>45$  years ( $p = 0.203$ ), histological subtype type ( $p = 0.139$ ), or multifocality ( $p = 0.067$ ).

In relation to the BTA guidelines, 43% of patients ( $n = 77$ ) had definitive indications for RRA, while 12% ( $n = 21$ ) had definitive recommendations against RRA. A personalised decision-making approach was recommended for 45% of patients ( $n = 80$ ), with 66 of those (83%) progressing to RRA (Table 3). Ninety-seven percent ( $n = 172/178$ ) of RRA treatment decisions satisfied the 2014 BTA guidelines; 1 patient recommended for RRA due to extrathyroidal extension declined, while the remaining 6 patients received RRA outside of the BTA recommendations. None of these 6 patients had definitive RRA indications; however, 2 had weaker risk factors for recurrence, one with unilateral multifocal microPTC, the other being  $>45$  years old. Agreement with the BTA recommendations was not significantly affected by sex ( $p = 0.721$ ), age  $>45$  years ( $p = 0.115$ ), or histological subtype ( $p = 0.884$ ). Patients with tumours measuring  $<1$  cm were more likely to undergo RRA management differing from the BTA recommendations (i.e., proceeding to RRA) when compared to patients in the 1–4 cm or  $>4$  cm subgroups ( $p < 0.001$ ).

## **Discussion**

This study assessed the DTC management patterns in an Irish tertiary referral centre, with a focus on patients with intermediate-size, low-risk tumours, where a paucity of evidence prevents guidelines from supporting a definitive therapeutic approach. DTC treatment strategies were largely in agreement with best-practice recommendations, with concordance demonstrated in 94% of surgical and 97% of RRA therapeutic decisions. Where discordance with guidelines was demonstrated, there was a tendency towards overtreatment, with 9 out of 10 surgical and 5 out of 6 RRA treatment decisions resulting in a more aggressive treatment (TT and RRA) where lobectomy and no RRA was recommended. Early studies examining the appropriate surgical management of DTC initially suggested a one size fits all approach with TT,

resulting in lower recurrence rates and improved survival for all patients with DTC  $>1$  cm [12, 13]. More recently, recognition of relevant prognosticators has improved risk stratification such that low-risk patients with tumours  $>1$  cm may be treated with more selective and individualised approaches while maintaining improved outcomes [14–17]. This is evidenced by incremental guideline amendments towards more conservative approaches; the 2009 American Thyroid Association (ATA) and the 2006 European Thyroid Cancer Consensus guidelines both previously recommended TT for DTC  $>1$  cm, while the more recent 2014 BTA and 2015 ATA guidelines now suggest lobectomy alone as an option for those with tumours 1–4 cm without risk factors. Emerging evidence also advocates active surveillance for microPTC, with interval growth over 5 years observed in  $<15\%$  of patients [18, 19]. Improved identification and classification of indolent subtypes further improves risk stratification; the encapsulated follicular variant of papillary TC has recently been re-designated as non-invasive follicular thyroid neoplasm with papillary-like nuclear features, effectively reclassifying it as non-cancerous [20].

Almost half of our cohort was subject to the equivocal BTA guidelines, whereby a personalised decision-making approach was suggested. These patients typically had intermediate-sized tumours without specific recurrence risk factors. Despite large retrospective cohort studies, the infrequency of mortality and disease recurrence events seen in this cohort poses a challenge for the development of definitive evidence-based guidelines. In the absence of specific recommendations, the personalised decision-making approach encourages consideration of factors such as patient preference, age, comorbidity, performance status, ability to engage with contralateral lobe follow-up, and the potential impact of surgical complications. Clinician preference, surgeon complication rates, and tumour parameters tending towards guideline cut-offs (e.g., size approaching 1 or 4 cm) should also be considered. Almost all patients in our cohort who were recommended for a personalised decision-making approach proceeded to the more aggressive options of completion surgery and RRA. The absence of sufficient evidence to support a definitive treatment course in these patients despite multiple large retrospective studies suggests that any benefit gained by this strategy is likely to be small [21]. Furthermore, the improved efficacy of treatments for recurrent DTC is such that the lower risk of recurrence for patients in the personalised decision-making cohort may be acceptable, given the benefit of avoiding a second surgery and exposure to RRA. Benefits gained by the more aggressive options may

be outweighed by both physical and psychological morbidity. The impact of extended patient waiting times, from initial diagnostic imaging and FNAC to thyroid lobectomy, subsequent completion surgery, and onward to RRA, is extensive, resulting in substantial psychological morbidity [22]. Surgical complications are also considerable and include transient (8%) and permanent (2%) hyperparathyroidism, permanent (1%), transient (2%), and diplegic (0.4%) palsies of the recurrent laryngeal nerve, superior thyroid nerve injury (4%), and dysphagia (1%) [23]. There are also financial implications; thyroid lobectomy costs EUR 5,277 per patient in Europe, including presurgical workup, follow-up, and management of complications over 12 months [24], in addition to the lifelong cost of thyroxine replacement, follow-up, and monitoring associated with TT. In New South Wales, Australia, the increased volume of DTC treatments from 2002 to 2012, for a population of 7.5 million, has cost an additional AUD 18,600,000 in surgery-related healthcare expenditure [25].

RRA is also associated with significant side effects. Twenty percent of patients experience nausea, taste and smell impairment, or sialadenitis. More significant complications include impairment of haematopoiesis and gonadal function and increased risk for second primary malignancies, both solid and haematological. A dose of 100 mCi (3.7 GBq) of radioiodine has been estimated to result in an extra 56 malignancies per 10,000 patients over 10 years [24], while Rubino et al. [26] observed up to 30% dose-dependent increased risk for second primary malignancies following RRA.

While DTC has a relatively good prognosis compared to other malignancies, there remains a recurrence risk of 5–30%, and approximately 10% of patients die of this cancer [8, 27–29]. Improved risk stratification is warranted to identify patients at risk of mortality and recurrence. Multiple risk factor assessment tools exist for estimating DTC mortality. Prognostication systems include the AJCC/UICC TNM system (Tumour Nodes Metastases), AMES (Age, Metastases, Extent, Size), MACIS (Metastases, Age, Completeness of resection, Extrathyroidal, Size), EORTC (European Organisation for Research and Treatment of Cancer methodology), and AGES (Age, Grade, Extent, Size) [30, 31]. These prognostication systems, using traditional demographic and staging parameters and focusing predominantly on mortality rather than recurrence risk, have largely failed to guide management in a large subset of patients, as demonstrated by the equivocal BTA 2014 guidelines for low-risk intermediate-size DTC.

Advances in molecular medicine have improved the understanding of DTC carcinogenesis and risk indica-

tors. Molecular markers including gene expression profiles, somatic gene alterations, and circulating biomarkers provide improved indices for diagnosis and prognostication [32]. Alterations in the MAPK and PI3K-AKT major signalling pathways have recently been elucidated as primary pathogenetic events in DTC carcinogenesis [33]. The 2015 ATA guidelines now advocate consideration of BRAF<sup>V600E</sup> proto-oncogene mutation status, if known, in their modified risk stratification system, although testing is not routinely advocated. The guidelines also acknowledge other gene mutations and rearrangements such as BRAF, TERT, TP53, RAS, or PAX8/PPAR $\gamma$ , although these are not recommended for routine testing [34]. Rather than assessing for individual high-impact mutations, commercially available risk assessment tools analyse panels of mutations, each with smaller odds ratios for recurrence and mortality, but with promising overall accuracy. These include the Afirma Gene Expression Classifier and the ThyroSeq Next-Generation Sequencing panel. These adjuncts have demonstrated encouraging results in the risk stratification of patients with indeterminate FNAC where diagnostic lobectomy is frequently required [35, 36]. In correctly identifying DTC from FNAC samples, ThyroSeq v2.1 reports a sensitivity of 91% (95% CI 79–100) and a specificity of 92% (95% CI 86–98) [36]. This application of molecular risk stratification may help reduce the number of diagnostic thyroid lobectomies undertaken; over one-third of the patients in our cohort had initial Thy3 FNAC results, with three-quarters of these requiring completion thyroidectomy. However, while multiple studies have evaluated the utility of molecular testing in patients with indeterminate thyroid nodules, there is a paucity of research examining the use of such markers in surgical and RRA management decisions after thyroid lobectomy for DTC [32, 37].

## Conclusions

DTC management in our cohort exhibited high levels of adherence to internationally recognised best-practice guidelines. Where surgical and RRA therapeutic decisions did not satisfy the guidelines, more aggressive management approaches were usually adopted.

A large proportion of patients are subject to a personalised decision-making approach, owing to a lack of conclusive high-level evidence to guide management. A tendency towards more aggressive surgical and RRA intervention was observed in this group.

These findings highlight the requirement for improved risk stratification to rationalise management strategies and avoid overtreatment of patients who fall into indeterminate-risk treatment groups.

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## Statement of Ethics

All patients provided informed written consent, which was ethically approved by the University Hospital Galway research ethics committee.

## Disclosure Statement

The authors declare no conflicts of interest.

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