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## Value of Surveillance Ultrasound Following Hemithyroidectomy

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## **Abstract**

**Background** There is limited evidence or agreement on the benefit, duration and frequency of post-operative surveillance neck ultrasound (US) in patients with differentiated thyroid cancer (DTC) treated with hemithyroidectomy alone. Our primary aim was to assess the benefit of neck US in this situation, with a secondary aim to assess the detection of malignancy in the contralateral lobe in patients undergoing completion surgery. **Methods** Retrospective observational study involving patients who had DTC found at diagnostic hemithyroidectomy between 01/12/2013–31/12/2016. **Results** Of 105 patients, 74 underwent completion thyroidectomy. 35% of these had malignancy identified in the contralateral lobe, the majority unsuspected sonographically. Of 31 hemithyroidectomy patients, one had a U3 nodule at first US surveillance, ultimately incidental papillary microcarcinomas identified on completion thyroidectomy. No other disease recurrence/malignancy at median 3.8 years follow-up. **Conclusion** Findings indicate a limited role for US follow-up of patients with DTC treated with hemithyroidectomy alone.

## **Keywords**

Thyroid neoplasms, Thyroid Cancer - Papillary, Thyroidectomy, Ultrasonography.

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## Introduction

The incidence of differentiated thyroid cancer (DTC) has increased worldwide over the past four decades [1]. Despite this, mortality rates from thyroid cancer have remained stable [2], likely due to the relative increase in low-risk papillary microcarcinoma (PMC), defined as  $\leq 1$ cm, often discovered incidentally after surgery for benign pathology, and is widely reported in autopsy studies with prevalence ranging from 2-35.6 % [3].

TNM stage provides information on disease-specific survival (DSS) with T1/T2, N0, M0 thyroid cancers having an estimated DSS at 20 years of 99% [4]. Traditionally, total thyroidectomy was the procedure of choice for DTC followed by radioiodine remnant ablation (RRA), a treatment model often disproportionate to excellent patient prognosis. A more conservative approach with hemithyroidectomy alone in low-risk DTC is increasingly considered an appropriate treatment strategy [5,6], studies demonstrating good clinical outcomes in appropriately selected patients with structural recurrence rates ranging from 0 to 10.6% over 0.6 to 30.5 years [7-10].

The definition of low risk is continuously evolving but at present, includes cN0M0 tumours  $< 4$  cm and tumours without adverse features such as extrathyroidal extension (ETE), multifocality, angioinvasion or positive family history. A three-tier initial risk stratification system developed by the American Thyroid Association (ATA) and modified in 2015 [11] divides patients after initial therapy into low, intermediate and high risk of structural disease recurrence although this risk level, and complete TNM status, is only possible post-operatively. In patients with larger tumours or with intermediate/ high risk histological features following lobectomy, completion thyroidectomy is indicated, to facilitate RRA.

Dynamic risk assessment (DRA), recommended by British Thyroid Association (BTA), ATA and the European Society for Medical Oncology (ESMO) allows re-evaluation of the initial risk of structural disease recurrence Based on serum thyroglobulin (Tg) and anti-thyroglobulin antibody (TgAb) assays along with imaging, the patient's response to therapy is graded as excellent, indeterminate, biochemically incomplete or structurally incomplete [11-13]. While originally developed based on studies of patients who underwent total thyroidectomy and RRA, Momesso et al. in 2014 developed [14], and in 2016 validated [15], serum Tg values for excellent and biochemically incomplete response categories for both lobectomy and total thyroidectomy patients without RRA.

Despite wide use of DRA, there is limited consensus on the duration and frequency of surveillance neck ultrasound (US) in the hemithyroidectomy-only DTC group. ESMO guidelines, 2019, recommend a single neck US with serum Tg and TgAb assays at 6-18 months post-treatment. If there is no evidence of structural disease in a low-risk DTC patient at this first follow up, 12-24 monthly biochemical assessment is advised with repeat neck US only necessary if rising Tg and/or TgAb levels [13].

To determine the value of surveillance neck US, we evaluated findings and outcomes in patients with DTC found at hemithyroidectomy who were considered sufficiently low risk that there was no mandate for completion surgery. In addition, in order to determine the utility of US for the detection of small contralateral cancers, we assessed the histological outcome, in comparison with initial US findings, in the remnant thyroid in patients meeting criteria for up-front completion.

## **Materials and methods**

### **Study Design and Subjects**

Research ethics committee advice was sought using the online tool from the NHS health research authority and Medical Research council website [16] and was not required.

Included in this retrospective study were patients who had DTC identified between 1<sup>st</sup> December 2013 and 31<sup>st</sup> December 2016 following hemithyroidectomy or isthmusectomy, performed either as a diagnostic or therapeutic procedure with curative intent, with at least one follow-up US scan in hemithyroidectomy-only patients. A total of 105 patients met the inclusion criteria. Exclusion criteria were: patients out-with the healthboard whose samples were sent for tertiary opinion, patients with core biopsy only or initial total thyroidectomy, anaplastic carcinoma, medullary carcinoma and lymphoma histological types. One further patient was excluded as co-morbidities rather than low-risk status precluded completion thyroidectomy. All patients were discussed at the regional thyroid cancer MDT.

### **Imaging Techniques**

US examinations were performed across 6 hospital sites on several different ultrasound machines by one of 14 consultant radiologists with head and neck specialist interest or one of five sonographers with experience in thyroid US. Images were captured on picture archiving and communications system (PACS) and a formal written report linked to the Radiology Information System. Reports described nodules using BTA 'U' classification, from July 2014 onwards, or an opinion on whether a nodule was considered generally benign, indeterminate or suspicious with fine needle aspiration biopsy (FNAB) utilised as indicated.

## **Image and data analyses**

For all included patients, clinical notes and histology reports were reviewed. Post-operative surveillance neck ultrasound reports in the hemithyroidectomy-only group were examined and also initial US reports, when relevant, in the completion group.

Variables recorded were patient age and sex, type and date of surgical procedure, histological type and size of either the largest or the worst prognosis cancer, tumour multifocality, pathological TNM status (AJCC 7<sup>th</sup> edition was in use during the study period but 8<sup>th</sup> edition also recorded to increase future applicability of the study), presence of and degree of extrathyroidal extension (ETE), vascular invasion and positive nodal status. If the patient proceeded to up-front completion thyroidectomy, we recorded time to completion (days), histological results and pre-operative US findings regarding the contralateral lobe. If the patient did not proceed to initial completion, follow-up US appointments and results, further management, later histology findings, when relevant, and last clinic date were recorded. Main clinical outcomes were locoregional recurrence detected at US within 5-7 years in hemithyroidectomy-only patients and the incidence, nature and sonographic conspicuity of remnant malignancy in patients having up-front completion.

## **Statistical methods**

Continuous data was presented as means and standard deviations or median and interquartile range. Categorical data is recorded as whole numbers +/- percentages. Microsoft excel (2016 version) was used for these descriptive statistics.

## Results and analysis

The included 105 patients consisted of 25 males and 80 females. Initial surgery comprised hemithyroidectomy (101) or isthmusectomy (4).

Group A comprised 74/105 patients (70 %) who underwent up-front completion thyroidectomy with median time to completion 56 days (42, 77).

35 % of group A patients (26 of 74) were found to have at least one malignant nodule in the subsequently excised contralateral lobe. Apart from one patient who was found to have follicular cancer as well as 4 PMC foci in the thyroid remnant these were all PMC, mean diameter 2.9 mm (+/- 2.3 mm). Regarding the completion contralateral lobe on pre-operative US, 15/26 had sonographically benign nodules or normal appearances reported. A further 8 had sub-centimetre nodules reported which were either unclassified (6) or 'of doubtful significance' (2). In 2 the contralateral lobe was not mentioned in the report. The US report for the final patient was not accessible as the scan was performed privately.

Group B comprised 31/105 (30%) patients who underwent follow-up after hemithyroidectomy-only.

No patients in this group had pathological lymph nodes. 30 (97%) would have been considered ATA low-risk and 1 (3%) ATA intermediate risk. Please see Table 1 for details on demographics, tumour size, histological findings and TNM status of both groups. Group B had median clinical follow up of 3.8 years (2.6 ,6.3) and underwent surveillance neck US over a median duration of 3.7 years (0.9, 5.3). A total of 106 surveillance neck ultrasounds were carried out, each patient undergoing an average of 3.4 (+/- 2.2) neck US exams over the



follow up period. 22 patients have since been discharged, 1 patient died of unrelated causes and a further patient moved to a different healthboard.

During group B follow-up, in one patient a contralateral nodule graded U3 at first surveillance neck US 2 years post-operatively underwent FNAB with Thy3f cytology. Multifocal PMC was discovered on later completion, 2 foci measuring 7.9 and 1.2 mm, with no intermediate or high-risk features and no further treatment required. Another had a contralateral U2 graded nodule upgraded to U3 at their third annual US surveillance follow-up with Thy3a cytology on FNAB. At later completion thyroidectomy, this lesion was a benign adenoma. A third patient had a 3 mm 'unclassifiable nodule' in the remnant lobe on first surveillance neck US 3 months post-operatively with Thy1 cytology on FNAB 9 months later. Further surveillance neck US in this patient at 33-months demonstrated no change to the tiny nodule, ultimately labelled 'of limited significance'. A final patient has a static 1.3 mm remnant 'hypoechoic area' under ultrasound surveillance for over 3 years. Remaining patients had normal appearances or sonographically benign nodules with no cervical lymphadenopathy demonstrated on follow-up US and no clinical recurrences.

## **Discussion**

This study analysed 105 consecutive patients with DTC discovered at hemithyroidectomy.

The patient cohort was subdivided into two groups, those with up-front completion and those

undergoing hemithyroidectomy-only with US follow-up. Follow-up US findings and rate of disease recurrence was identified in the hemithyroidectomy group while the rate of remnant malignancy and its pre-operative US identification was assessed in those having up-front completion.

In 35% of the up-front completion thyroidectomy specimens, remnant malignancy was found. This was PMC in all but one of the 26 cases, multifocal in most. The vast majority of these patients had no concerning findings in the contralateral lobe on pre-operative US. This confirms previous reports that papillary microcarcinoma can be 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. [17].

Almost all (97%) patients in group B were ATA low-risk. In just under half of the patients, the histologically identified tumour was an incidental unifocal PMC. A low rate of structural disease recurrence of 3.2% (1 of 31) was found in the contralateral lobe in the hemithyroidectomy-only group. This was a multifocal PMC, with no adverse histological features. We found no cervical nodal recurrences. A relatively similar rate, 4.2%, of structural recurrence was found by Vaisman et al. in 72 lobectomy cases with median follow-up of 5 years [8]. Lee et al [18] in a recent 2022 study also found a similar low recurrence rate of 4.3% in 46 hemithyroidectomy cases with median follow-up of 3.5 years. These recurrence rates are similar to the 2-6% recurrence rate described in ATA guidelines for low-risk PTC

[11] although notably lower than the pooled recurrence rate of 9% that Chan et al [19] reports in their recent 2020 systematic review of post-hemithyroidectomy low-risk DTC patients.

Despite the recognised favourable outcomes, there has been an increase in the use of imaging in post-treatment DTC patients. Banerjee et al. [20] observed substantial growth in imaging in a cohort of 28,220 DTC patients studied from 1998 to 2011 including 5317 lobectomy patients. In this study an association between neck US usage and increased recurrence treatment with surgery and radioactive iodine therapy was found, but no effect on DSS. Furthermore, surveillance US in post-treatment patients is associated with a high false-positive rate as described by Yang et al. [21,22]. Although regarding post total thyroidectomy patients +/- RRA they found a false-positive rate of 67% and 57% in 171 ATA low-risk and 90 ATA intermediate-risk papillary thyroid cancer patients, respectively, who had an initial unremarkable post treatment US. There was a corresponding 1.2% and 10% structural recurrence rate.

A high relative cost in surveillance of a low-risk group is also a consideration. Wang et al. [23] found an imbalance of a factor of 7 in cost to detect recurrence between low- and high-risk papillary cancer following total thyroidectomy. Another consideration is patient's mental well-being. Ongoing unnecessary US surveillance may provoke ongoing patient anxiety regarding recurrence. A population-based cohort study of 353 Swedish patients with DTC [24] found that despite a low incidence of recurrence (7%), almost half of the 279 patients reported ongoing concerns about recurrence, 14 to 17 years after initial diagnosis, with a negative impact on their Health-Related Quality of Life (HRQoL).

Finally, it is also worth discussing the background prevalence of PMC. Interestingly, similar to the rate of remnant malignancy in group A which were almost all papillary microcarcinomas, a prevalence of 35.6% of occult small papillary cancers was found in a previous autopsy study, concluding that these small cancers may almost be a “normal” finding [25]. It is widely accepted that the expanding gap between incidence of and mortality from DTC, high rates of DTC in screening populations and at autopsy suggest overdiagnosis. One could argue that the 3.2% structural recurrence in group B, also PMC, is entirely reflective of the normal population rate of this disease.

Similar to ESMO recommendations, Lamartina et al. [26] conclude in their update on management of low-risk DTC by suggesting annual serum TSH, Tg and TgAb for 5 years and then every 2 years in low-risk DTC, with neck ultrasound only being performed in patients with abnormal biochemical or clinical findings. In regard to Tg/TgAb in lobectomy-only patients, Momesso et al. [14,15] previously defined excellent response as: Tg <30 ng/mL, negative TgAb with negative imaging and biochemically incomplete response as: Tg >30 ng/ml or rising and/or increasing antibodies, with negative imaging. Structural recurrence was detected in 33% of patients with a biochemically incomplete and in 0% patients with an excellent response.

While Ritter et al. and Park et al. [27,28] did not find a significant difference in Tg levels in papillary cancer lobectomy patients with disease recurrence compared to non-recurrence,

Vaisman et al found a significant association between Tg trend and recurrence with a NPV of 98% for rising Tg level [9].

In the current cohort, one hemithyroidectomy patient had a contralateral nodule found at US follow-up prompting completion surgery where low-risk PMC was found requiring no further treatment. Another patient had a sonographically and cytologically indeterminate nodule which led to further surgery for ultimately benign disease. A further two hemithyroidectomy patients had chronically stable tiny nodules in the contralateral lobe, neither requiring further surgery. Furthermore, apart from a single patient who was found to have follicular cancer in the contralateral excised lobe all of the contralateral malignancies found in the up-front completion specimens were PMCs, the vast majority of which were sonographically occult or non-concerning preoperatively. Allowing for a single patient in the current study being intermediate rather than low-risk, the results would indicate no significant value of indiscriminate US surveillance in hemithyroidectomy-only patients.

Limitations of our study include relatively small numbers. Post treatment US were performed by a variety of operators on a number of different US machines however this may widen the applicability of the findings. Tg and TgAb levels were not analysed however these assays did not have a routine role in follow-up of hemithyroidectomy patients in this 2014-2016 cohort. BRAF<sup>V600E</sup> mutation status was also not recorded, however this was not routinely tested during the study period and would not have altered risk level in the hemithyroidectomy-only group. From a cost-benefit point of view we did not record number of clinic visits, other scans

or blood tests generated as a result of ongoing clinical follow-up however this was beyond the scope of our objectives.

Future directions could include continued clinical and US assessment in the hemithyroidectomy-only patients to obtain a larger cohort and to determine the practical validity of biochemical follow-up.

### **Submission Summary**

- In recent years there has been a move to less aggressive treatment for thyroid cancer from traditional total thyroidectomy and radioactive iodine.
- Significant numbers of patients are being treated with hemi-thyroidectomy and surveillance.
- Ultrasound is an excellent tool for picking up recurrent disease in the thyroid bed.
- There is little evidence to advise on the need or frequency of ongoing ultrasound surveillance in patients post-hemithyroidectomy for malignancy and the findings in our paper would support this.

### **Conclusion(s)**

Our findings indicate a limited role for US follow-up of patients with DTC treated with hemithyroidectomy alone. Scanning would be preferably directed by a combination of initial sonographic findings and clinical examination with biochemical assessment a potential adjunct.

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## **Statement of Ethics**

Research ethics committee advice was sought and ultimately was not required.

## **Conflict of Interest Statement**

The authors have no conflicts of interest to declare.

## **Author Contributions**

All four authors met the ICMJE Criteria for Authorship [ICMJE | Recommendations | Defining the Role of Authors and Contributors](#)

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TABLE I  
 Baseline Patient Characteristics

<b>Charateristics</b>	<b>Group A</b>	<b>Group B</b>
	<b>N (%)</b>	
Number of patients	74/105 (70%)	31/105 (30%)
Age at diagnosis (years) (mean [standard deviation])	45.1 [+/- 16.3]	46.2 [+/-17.7]
Age range (years)	12 - 81	15-75
Histology		
Papillary	43 (58%)	28 (90%)
(Papillary microcarcinoma)	(18 of 43) (42%)	(19 of 28) (68%)
Follicular	25 (34%)	3 (10%)
Hurthle cell	5 (7%)	0 (0%)
Poorly differentiated thyroid cancer	1 (1%)	0 (0%)
Size of largest primary tumour (mm)		
Mean +/- SD	27.4 [+/- 19.8]	10.3 [+/-10.2]
Range	0.3 – 80	0.2 – 39
Multifocality		
Yes	20	1
No	54	30
AJCC TNM 7th ed pathological tumour stage (pT)		
T1a	14	16
T1b	5	7
T2	26	5
T3	29	3
T4	0	0
AJCC TNM 8th ed pathological tumour stage (pT)		
T1a	20	19
T1b	8	7
T2	27	5
T3	19 (T3a)	0
T4	0	0
Extrathyroidal extension (ETE)		
Yes	15 (10 minimal, 1 microscopic)	3 (minimal)
No	59	28
Vascular Invasion		
Yes	33	2 (1 PMC and 1 follicular)
No	41	29
If papillary cancer, was it incidental		
Yes	11 of 18	15 of 19
No	7 of 18	4 of 19