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Original Article

Can We Discharge Dynamically Risk-Stratified Low-Risk (Excellent Response to Treatment) Thyroid Cancer Patients After 5 Years of Follow-Up?

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Abstract

Aims: The 2014 British Thyroid Association thyroid cancer guidelines recommend lifelong follow-up of thyroid cancer patients. This is probably unnecessary, can cause patient anxiety, is time consuming and places significant demand on National Health Service resources. It has been suggested that low-risk differentiated thyroid cancer (DTC) patients could be discharged to primary care once they are 5 years from diagnosis and treatment. The aim of this study was to investigate the potential safety of this practice.
Materials and methods: In total, 756 patients with dynamically risk-stratified (DRS) low-risk/excellent response to treatment DTC treated over 2001–2013 in the Leeds region were followed after diagnostic surgery and the recurrence rate calculated.
Results: The median follow-up time was nearly 10 years (5–17 years). Radiological recurrence occurred in 13/756 (1.7%) patients and was always preceded by raised thyroglobulin/ thyroglobulin antibody levels. In all 13 patients elevation of thyroglobulin occurred within 5 years of diagnosis. Two additional patients were found to have rising thyroglobulin at almost 9 and 10.5 years from diagnosis, although to date radiological recurrence has not been detected. Assuming these two patients developed recurrence with longer duration of follow-up, then 0.26% (2/756) of patients would not have their recurrence discovered within 5 years of diagnosis. To detect 100% of patients with a putative recurrence in our cohort would require 10.5 years of follow-up. Four patients had transiently raised thyroglobulin, which became undetectable within 2 years (in three patients), without any treatment and radiological recurrence was not discovered.
Conclusion: Discharge of DRS low-risk DTC patients to primary care after 5 years of secondary care follow-up is reasonable, accepting that late recurrence may occur in a very small minority of individuals (0.26%, ~1:400). A more cautious approach would be to continue monitoring for 10 years, although the frequency of assessments could be reduced with increasing duration of follow-up.

Key words: Discharge; follow-up; recurrence; thyroid carcinoma

Introduction

The incidence of thyroid carcinoma has increased consistently over the last four to five decades [1,2], with most of this increase accounted for by lower stage papillary cancers and incidental micropapillary cancers discovered during surgery for benign thyroid disease [3]. Survival of low-risk differentiated thyroid cancer (DTC) is similar to that of the general population [4,5].

Guidelines for the diagnosis, treatment and follow-up of thyroid cancer have evolved over time [6]. One of the most fundamental changes introduced in the 2014 British Thyroid Association (BTA) guidelines was dynamic risk stratification (DRS) of those patients treated with surgery and radioiodine remnant ablation (RRA) [7]. The 9–12 months after radioiodine risk stratification is based upon the combined outcome of imaging and stimulated thyroglobulin. At

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this time point, the combination of absence of residual disease on imaging with a stimulated thyroglobulin level <1.0 μg/l defines the patient as having an excellent response to treatment/low-risk disease with a low risk of recurrence. In these patients, optimal thyroid hormone replacement would aim to maintain thyroid stimulating hormone (TSH) levels in the lower half of the reference range, with the aim of avoiding the long-term sequelae of excess thyroid hormone replacement [7,8].

The ideal duration of follow-up of individuals categorised as having low-risk thyroid carcinoma, who account for most DTC patients, is as yet not entirely clear. The 2014 BTA guidelines advise lifelong follow-up [7]. It has been suggested that patients remaining free of disease for several years and not requiring TSH suppression could be discharged to primary care [7], but may need lifelong thyroglobulin testing, which can be challenging in primary care. To date there are no long-term outcome data for patients with low-risk disease defined by DRS to accurately quantify recurrence rates within this cohort and, therefore, the appropriate duration and intensity of follow-up and disease monitoring. We have therefore examined the time from diagnostic surgery to the first raised thyroglobulin level of our patients treated for DTC, and who have been categorised as having low-risk disease by DRS, with the aim of determining how long these patients require follow-up with thyroglobulin monitoring.

Materials and Methods

We undertook a retrospective analysis of DTC patients who received RRA at the Leeds Cancer Centre between 2001 and 2013. The Leeds Cancer Centre is a single tertiary centre with referrals from several hospitals in the North and West Yorkshire area, serving a catchment population of about 2.7 million. The cancer centre alternated thyroid cancer patient follow-up with the cancer units. All patients had been treated and followed prospectively from the time of diagnostic surgery under a pre-established management pathway [7,9]. Diagnostic surgery was defined as total thyroidectomy, hemithyroidectomy or lobectomy.

Inclusion criteria were a histological diagnosis of papillary (PTC), follicular (FTC) or Hurthle cell (HTC) thyroid carcinoma; a one or two stage total/near-total thyroidectomy; RRA administered within 6 months of thyroid surgery; DRS performed within 6–12 months following RRA; and subsequent follow-up with 3–12 monthly thyroid function tests, thyroglobulin and thyroglobulin antibody measurement. Exclusion criteria were: (i) patients with anaplastic or poorly differentiated thyroid carcinoma; (ii) patients with DTC who could not be followed-up for more than 5 years as they had moved out of the region ($n = 6$) or due to death from unrelated non-thyroidal illness ($n = 4$); (iii) patients defined as DRS intermediate or high risk of recurrence (except where reclassified as low risk as per response to treatment); (iv) those who underwent less extensive thyroidal surgery than a near-total thyroidectomy; and (v) those who did not receive RRA. Some patients classified as having postoperative American Thyroid Association (ATA) intermediate- or high-risk disease were risk stratified into the low-risk group after the 6–12-month assessment and were included in the study.

Dynamic Risk Stratification

DRS was carried out using recombinant TSH 0.9 mg intramuscularly on days 1 and 2, followed by measurement of stimulated thyroglobulin levels on day 5. Patients were categorised as having a low risk of recurrence (excellent response to treatment/low-risk disease) if at the time of DRS the stimulated thyroglobulin was <1.0 μg/l, thyroglobulin antibodies were undetectable and neck ultrasound and/or radioiodine uptake scan imaging showed no evidence of residual thyroid tissue. Most patients had radioiodine uptake scans rather than neck ultrasound at DRS. Patients who were DRS after 2012 had both radioiodine scans and neck ultrasound. Some patients in the early years of the study were prepared with thyroid hormone withdrawal rather than with recombinant TSH. Recurrence was taken as evidence for reappearance of the tumour, at any site, after a disease-free period where serum thyroglobulin levels were undetectable and concurrent thyroglobulin antibody levels not elevated. Biochemical recurrence was defined as rising thyroglobulin above 1.0 μg/l or elevated thyroglobulin antibody levels; radiological recurrence was defined as evidence of recurrent thyroid carcinoma seen on imaging. An immunometric conventional assay, the Immulite 1000, was used to measure thyroglobulin with a functional sensitivity of <0.9 μg/l. Highly sensitive thyroglobulin assays, with a functional sensitivity of <0.1 μg/l, were not available in the Leeds region during the study period (2001–2013).

Results

Demographics

In total, 756 patients treated with total thyroidectomy and radioiodine ablation were stratified in to the low risk of recurrence group following DRS. Of these patients, 544 were female, of median age 46 years (range 3–91 years). Most were histologically PTC ($n = 582$, 77%), with FTC and HTC accounting for 14% ($n = 106$) and 9% ($n = 68$) of patients, respectively. Only 5/756 patients initially DRS as having high-risk disease were reclassified into the low-risk group some months or years later. These 5/756 patients had a radioiodine scan and serial ultrasounds, computed tomography or magnetic resonance imaging until their serum thyroglobulin was undetectable. They were classified as being in the low-risk group when their serum thyroglobulin became undetectable and their scans failed to show any sign of thyroid cancer. They were included in the study.

The median length of follow-up dated from the time of diagnostic surgery was 9.9 years, with a minimum follow-up of 5 years and the longest duration of follow-up 17 years.

Radiological Recurrence

Radiological recurrence occurred in 13 (1.7%) patients. The mean age at recurrence was 62 years (range 46–89 years). Histologically, five (38%) had HTC, seven (54%) PTC and one (8%) FTC. Tumour staging is shown in Table 1.

Radiological recurrence occurred exclusively after biochemical recurrence. Of these patients, 11 (85%) showed progressively rising thyroglobulin levels, with negative thyroglobulin antibodies. The additional two (15%) patients had progressively rising thyroglobulin antibodies with a concurrently unrecordable thyroglobulin level. In these 13 patients, the longest interval from definitive surgery to the initial rise in thyroglobulin/thyroglobulin antibodies was 59 months. The shortest duration to biochemical recurrence was 19 months; the mean time was 37 months. The mean interval between biochemical recurrence and the first sign of radiological recurrence was 22 months, with a range of 1–58 months. The longest interval from diagnostic surgery to radiological recurrence was 98 months, the shortest time was 20 months and the mean time was 59 months.

The most common site of recurrence was the lungs in 6/13 (46%) patients followed by the regional nodes in 5/13 (38%). Two patients had thyroid bed recurrence and one had more than one site of disease. One patient had a solitary bone metastasis and another had multiple liver metastases (Table 1).

Six patients, following discovery of radiological recurrence, were given a therapy activity of radioiodine, but in all cases, the post-treatment radioiodine scan failed to show radioiodine uptake in the known metastases. Four patients had surgery, with three undergoing neck dissections and the fourth patient having a lung metastectomy. One had radiofrequency ablation of a solitary bone metastasis. Two patients are under active surveillance with serial scans without further treatment to date. One patient had radical radiotherapy to an inoperable thyroid bed recurrence and one had palliative neck radiotherapy to symptomatic inoperable neck nodes (she also had progressing lung metastases). The final patient was unfit for further active treatment when she was found to have multiple liver metastases. Three of the 13 patients with radiological recurrence have died of metastatic thyroid cancer (Table 1).

Three patients, all of whom underwent resection of the radiological recurrence, have had an undetectable thyroglobulin level that to date has persisted for 2, 9 and 11 years of follow-up. These patients have probably been cured after treatment for radiological recurrence.

Isolated Raised Thyroglobulin Levels

A further six patients showed an elevated thyroglobulin level during follow-up, but have not gone on to develop radiological recurrence. No thyroglobulin antibodies have been detectable in these six patients. Four of these six patients showed only transient elevation of thyroglobulin, with levels falling spontaneously to undetectable levels ($<$1.0 μg/l). Three of these four patients had detectable thyroglobulin (on more than one occasion) for less than 2 years duration. The remaining patient, who had an elevated thyroglobulin for nearly 9 years, and 6 years before it became undetectable, had been given empirical radioiodine therapy. His post-treatment radioiodine whole body scan failed to show abnormal uptake and his thyroglobulin continued to increase for a further 2 years after the radioiodine therapy. Therefore, it is hard to explain why his thyroglobulin gradually became unrecordable over the years. Many anatomical scans were carried out when his thyroglobulin was raised but no radiological recurrence was detected.

Two patients have persistently elevated thyroglobulin, but to date have only been followed for 31 and 40 months with negative serial scans. The thyroglobulin in these patients first became elevated at 9 years and 10.5 years after diagnostic surgery, respectively. All patients who developed elevated thyroglobulin or thyroglobulin antibodies have been managed with TSH suppression to $<$0.1 miu/l.

Discussion

The study shows that in a cohort of 756 DRS low-risk/excellent response to treatment DTC patients with a median follow-up of nearly 10 years, only 13 patients (1.7%) had evidence of biochemical and radiological recurrence. Importantly, all of these individuals developed an elevated thyroglobulin within 5 years of diagnostic surgery, although unfortunately only three of these 13 individuals were found to have ‘curable’ recurrence. We also describe a group of patients with transitory increases in thyroglobulin, which occurred in the absence of radiological evidence of recurrence. In three patients, the elevated thyroglobulin became undetectable within 24 months and the remaining patient had raised thyroglobulin for nearly 9 years before it became undetectable. Two patients without evidence of radiological recurrence were found to have an elevated thyroglobulin level almost 9 and 10.5 years after diagnostic surgery and it remains unclear as to whether these individuals will go on to develop a true recurrence, as follow-up after detection of measurable thyroglobulin is at present limited to 31 and 40 months, respectively. In the 13 patients with radiological recurrence, the mean time between thyroglobulin elevation and finding disease on scans was 22 months, although one patient waited 58 months to find their radiological recurrence. It is possible that the two patients with persistently elevated thyroglobulin could have a spontaneous decline in thyroglobulin over time.

Taking these data together, we suggest that patients with DRS low-risk thyroid cancer could be safely discharged after 5 years of follow-up. All 13 cases of radiological recurrence were found within this time frame, initially by detectable thyroglobulin levels, and would therefore necessitate more prolonged follow-up in the thyroid cancer services. However, assuming all other patients were discharged at 5 years and the two individuals who showed elevated thyroglobulin at 9 and 10.5 years did go on to develop a recurrence, 99.7% (741/743) of patients would have been safely discharged at 5 years. This figure would be 99.9% (741/742) if

Table 1
Details of tumour staging and timings of biochemical and radiological recurrence of the 13/756 low-risk thyroid cancer patients who showed evidence of recurrence.

Patient	TNM stage	Histological diagnosis	Time from diagnosis to raised thyroglobulin (months)	Time from elevated thyroglobulin to radiological recurrence (months)	Time from diagnosis to radiological recurrence (months)	Site of recurrence	Further treatment	Outcome
1	pT3N0*	PTC	48	23	71	Solitary bone metastasis	Radiofrequency ablation of metastasis	Thyroglobulin stable
2	pT2Nx	HTC	24	30	54	Lung metastases	Radioiodine therapy	Thyroglobulin increasing
3	pT3Nx	FTC	21	27	48	Lung metastases	Observation – surveillance	Thyroglobulin increasing
4	pT3NxR1*	HTC	19	1	20	Regional nodes, thyroid bed + lung metastases	Radioiodine therapy then palliative neck radiotherapy	Death
5	pT2Nx	PTC	40	58	98	Solitary lung metastasis	Radioiodine therapy then lung metastectomy	Thyroglobulin undetectable
6	pT3Nx	HTC	26	58	84	Lung metastases	Radioiodine therapy	Death
7	pT2Nx	PTC	26	1	27	Liver metastases	None. Unfit for treatment	Death
8	pT3NxR1*	HTC	51	7	58	Thyroid bed	Radical neck radiotherapy	Thyroglobulin stable
9	pT3N1b*	HTC	53	1	54	Regional nodes	Neck dissection then radioiodine therapy	Thyroglobulin undetectable
10	pT3N1bR1*	PTC	43	53	96	Regional nodes	Observation – surveillance	Thyroglobulin antibody level stable
11	pT3N1b	PTC	36	2	38	Regional nodes	Neck dissection	Thyroglobulin antibody level stable
12	pT3N1a	PTC	40	1	41	Regional nodes	Neck dissection	Thyroglobulin undetectable
13	pT4aN1b	PTC	59	18	77	Lung metastases	Radioiodine therapy	Thyroglobulin increasing

FTC, follicular thyroid cancer; PTC, papillary thyroid cancer; HTC, Hurthle cell thyroid cancer.
* Thyroid capsular invasion.

the policy was to discharge this patient group after 10 years or 100% (in this study) if patients were discharged after 10.5 years. It is possible that a small number of further patients would go on to develop raised thyroglobulin and subsequent radiological recurrence many years after initial treatment [10], although the incidence would probably be very low.

All patients were DRS according to the 2014 BTA guidelines. Retrospectively classifying patients into the postoperative ATA risk stratification system [11] is challenging and can lead to inaccuracies, especially because the traditionally documented TMN staging classification for thyroid cancer (used to retrospectively determine the ATA postoperative risk) has been revised twice over the study period. The ATA risk stratification system was devised in 2009 and this cohort of patients includes patients treated from 2001 onwards. The ATA system is reliant on the surgeon informing the multidisciplinary team when the tumour has been incompletely excised and when there is macroscopic invasion of structures in the neck. Also, in the past, the histopathologist did not always report vascular invasion. Whether extrathyroidal extension was minor or gross was not always recorded. The number and size of lymph nodes are dependent on how the specimen was cut. Without these critical pieces of information, ATA risk stratification will probably be inaccurate and potentially misleading. This study involved collecting the results from DRS, i.e. stimulated thyroglobulin and radioiodine or ultrasound scan reports, which may be more accurate and meaningful. Prospective postoperative ATA risk stratification would be useful in future studies, but the criteria used to stratify patients into each group can change with time.

A study with comparable findings was conducted by Durante *et al.* [12], whose aim was to look at time to recurrence and length of follow-up required. All of their patients had annual neck ultrasound scans and unstimulated thyroglobulin measurements. However, Durante *et al.*'s study only included PTC patients and not all of them had RRA or serum thyroglobulin levels measured. Nevertheless, their recurrence rate was 13/948 (1.4%), similar to the current study. Ten of these recurrences were discovered within 5 years and all 13 were within 8 years of treatment. These results suggest that low-risk postoperative ATA risk-stratified patients could be discharged within 8 years of treatment, but prospective studies are recommended.

It may be impractical to aim to detect 100% of the recurrences. To put this in the context of healthcare demand, if all of these patients underwent at least annual follow-up over the 10 years, this would total over 7500 clinic visits, with the consequent burden on healthcare resources, as well as the psychosocial impact of unnecessary intense monitoring on patients. The current position of lifelong follow-up with measurement of thyroglobulin leaves the patient without the prospect of ultimately being told they have been 'cured'. Recurrent hospital visits and the status of not being 'cured' leads to chronic anxiety and continued concern for the patient [13,14]. Much of this could be addressed by early implementation of a simple effective plan of follow-up after DRS with the patient that incorporated annual follow-up with measurement of thyroglobulin and thyroglobulin antibodies for 5 years, with an explanation that thereafter the risk of recurrence would be very low indeed (<0.3%). A more cautious approach would be to continue follow-up of all DRS low-risk patients for 10 years, by reviewing them annually for 5 years for thyroglobulin monitoring, then at a lower frequency of visits (18–24 monthly) thereafter. Following this period, they could be discharged to their primary care physician simply for monitoring of their thyroid hormone replacement, aiming to place the TSH in the lower half of the normal range, as per patients with primary hypothyroidism of other aetiologies [15]. Some primary care practices have difficulty performing and interpreting annual thyroglobulin levels and thus a regimen for simply monitoring thyroid function following discharge of the patients to primary care would be preferable. This study shows that routine thyroglobulin testing would not be necessary once the patient has been discharged to primary care after a period of monitoring within specialist services.

Our recommendations for discharge to primary care holds true only for those DRS low-risk/excellent response to treatment DTC patients [16] who continue to have thyroglobulin levels <1 μg/l and undetectable thyroglobulin antibody for 5 years after diagnostic surgery. By contrast, there are a number of groups of patients with DTC who will require longer, even lifelong follow-up. Patients with DRS intermediate- and high-risk disease and those with DRS low-risk disease who develop raised thyroglobulin or thyroglobulin antibody levels or evidence of persistent disease on imaging will require long-term follow-up in the multidisciplinary thyroid cancer clinic [7]. Patients who have received external beam radiotherapy to the neck require long-term monitoring for late adverse effects and those with concomitant hypoparathyroidism will need long-term endocrinology input and monitoring [7].

With the advent of highly sensitive thyroglobulin assays with the ability to accurately measure to as low as 0.1 μg/l, it may be possible in the future to identify individuals where the risk of recurrence is so low as to allow discharge at an earlier stage. To determine whether this can be achieved will, however, require a further audit once long-term data have been accumulated using the highly sensitive thyroglobulin assays.

Although our numbers of recurrences are reassuringly small, there are several observations that can be made as to the individuals that recurred and which can be interpreted further once data are present from other centres. Of particular note from our series is that 38% (5/13) of the recurrences were HTC and in our region only 9% of DTC patients have HTC, suggesting that these individuals may be at increased risk of recurrence despite what appears to be excellent initial disease control following treatment. HTC has traditionally been thought to be a more aggressive histological subtype of thyroid carcinoma compared with PTC and FTC, with higher recurrence rates [17], although more recent data suggest equivalent outcomes for this histological subtype [18]. From the TNM staging of our patients who recurred, all were T2, T3 or T4, providing further data to suggest that those with T1 disease have an excellent outcome [19]. There is a move to treat T1 stage DTC tumours with hemithyroidectomy alone and possibly perform follow-up with neck ultrasound together with thyroglobulin, the duration of which needs to be formally established [6,7].

All patients included in this study had DRS low-risk/excellent response to treatment DTC. According to the postoperative ATA risk stratification system in the 13 patients who recurred (Table 1), one had ATA high-risk disease, five had ATA low-risk and the remaining seven had ATA intermediate-risk disease, suggesting a prevalence rate of 62% (8/13) of ATA intermediate- and high-risk disease in the recurrence group. Taking these data together, we recommend to continue monitoring patients with HTC and/or ATA intermediate- and high-risk DTC at presentation until further information is available from more prospective studies [16].

Our study presents some limitations largely due to its retrospective nature – DRS as per the BTA 2014 guidelines was assigned many years after RRA in some cases. It was a single-centre study, all patients being subject to standardised clinical practice as per a pre-established treatment protocol. There was no variation in our follow-up schema and frequency of use of imaging during the study period, except for the introduction of routine neck ultrasound at DRS from 2012 onwards.

Conclusions

We have shown, in a large cohort of thyroid cancer patients defined as low risk by DRS, that recurrences are infrequent (1.7%) and when these do occur they are almost

exclusively observed within the first 5 years. In addition, we describe a transitory increase in thyroglobulin that resolved spontaneously within 24 months in a small number of individuals. These data suggest that patients with DRS low-risk DTC who maintain a thyroglobulin level <1.0 μg/l without thyroglobulin antibody interference for 5 years after diagnostic surgery could be safely discharged to primary care. Because 2/756 patients were found to have raised thyroglobulin 9 and 10.5 years from diagnosis (with no radiological recurrence as yet), a more cautious approach, at the present state of our knowledge, would be to continue follow-up for 10 years, particularly for selected cases of HTC and ATA intermediate and high risk at presentation; annually for the first 5 years and at a lower frequency (18–24 monthly) thereafter. This approach may require individualised adjustments, depending on the findings of these patients during their serial clinic follow-up to provide a personalised survivorship programme [16], with a possible role for molecular testing to predict risk of recurrence in the future [6]. More prospective studies aiming to define recurrence rates of DTC, and to identify times to which these recurrences occurred, are required to validate this approach and to design rational, cost-effective surveillance protocols.

Conflict of interest

G.E. Gerrard has received honoraria for speaker's bureau and advisory roles from Genzyme and Eisai Pharmaceuticals.

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