Rates of unsuspected thyroid cancer in multinodular thyroid disease

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ABSTRACT

BACKGROUND: Previously the risk of concomitant thyroid cancer in multinodular goitre (MNG) has been reported as approximately 4%. Cancer risk in toxic MNG was often considered lower than for non-toxic MNG, due to a possible protective effect of TSH suppression. However, recent American data suggest an approximately 18% risk of occult malignancy in both toxic and non-toxic MNG.

AIMS: To assess malignancy risk in a New Zealand population undergoing thyroidectomy for MNG.

METHODS: Single-centre study of patients undergoing thyroidectomy for MNG from 1 December 2006 to 30 November 2016.

RESULTS: Six hundred and two patients underwent surgery for MNG (448 non-toxic and 154 toxic). Of these, 95/602 (16%) had thyroid cancer. After excluding patients operated for preoperative suspicion for cancer, 30/401 (8%) patients with non-toxic MNG and 15/151 (10%) with toxic MNG had unsuspected or occult thyroid cancer (p=0.358). Patients with toxic MNG were less likely to undergo preoperative fine needle aspiration than those with non-toxic MNG (34% vs 52%, respectively p=0.0001). Two-thirds of unsuspected thyroid cancers were incidental micropapillary carcinomas and unlikely to alter survival irrespective of therapy.

CONCLUSION: Malignancy rates in MNG are higher than historically reported, although most unsuspected cancers are unlikely to alter mortality even if diagnosis is delayed.

Multinodular goitre (MNG) is common particularly in iodine-deficient regions.[1] Animal studies demonstrate an increased proliferative rate of thyroid follicular cells in iodine deficiency, suggesting that low iodine intake may promote thyroid cancer.[2] It has been proposed that these rapidly proliferating cells are more vulnerable to mutagens and therefore deleterious genetic changes.[3] Rates of follicular thyroid cancer (FTC) and anaplastic thyroid cancer in particular have been reported to be higher in populations with endemic goitre, possibly due to chronic TSH stimulation, alone or in combination with other growth factors or goitrogens.[3] Papillary thyroid cancer (PTC), comprising at least 80% of all thyroid cancer, appears to be relatively less common in areas of iodine deficiency than those with high or moderate iodine intake.[3] Iodine levels have historically been low in New Zealand.[4] However, with adequate fortification of table salt, since 1938 and iodised salt in bread from 2009, iodine intake in New Zealand is now considered adequate.[5]

For patients with a typical MNG, clinicians typically quote the risk of thyroid cancer as being approximately 4%,[6] however recent data suggests this may be incorrect. A North American study of 2,551 patients undergoing thyroidectomy, after excluding patients with an FNA consistent with malignant or indeterminate disease, demonstrated a 15.6% rate of thyroid cancer: 6.1% in patients with Graves' disease, 17.5% in non-toxic nodular goitre, 18.3% in toxic nodular goitre and 4.5% in a solitary toxic nodule.[7,8] The mean cancer size was 1.1cm and most (89.9%) were of papillary subtype.[7] In contrast, a recent

Australian study showed a much lower rate of thyroid cancer with a comparable rate of PTC in patients with non-toxic MNG (5%) to those with thyrotoxicosis (Graves' disease or toxic MNG, 6.4% and 6.8%, respectively).[9] Similarly, a 2013 meta-analysis of five studies demonstrated a cancer incidence of 5.9% for patients with TMNG and 4.8% in those with a toxic adenoma.[10]

While New Zealand data on solitary cold nodules has been reported (17% cancer in a series of 100 consecutive surgically resected nodules)[11] and Graves' disease (6.8%),[12] we currently have no local information on thyroid cancer rates in patients with multinodular disease. For MNG it is unknown if the international experience is applicable to the New Zealand population due to differences in micronutrient intake, carcinogen and goitrogen exposure, and genetic background. In addition, if most of the unsuspected thyroid cancers identified are micropapillary carcinomas (papillary thyroid cancer <10mm) it may not alter patient outcome if these are not identified, as the risk of dying from disease is extremely low irrespective of therapy.[13–15]

The aim of this study was to determine the rate of incidental thyroid cancer in a New Zealand population undergoing thyroid surgery for multinodular goitre and to identify the proportion of cancers likely to be clinically significant.

Methods

A retrospective review of all patients undergoing thyroidectomy was conducted over a 10-year period from 1 December 2006 to 30 November 2016 at Waikato Hospital, Hamilton, New Zealand, including operations performed at the private hospitals in the Waikato region.

Patients were identified from hospital coding and surgical databases. The diagnosis of non-toxic multinodular goitre (NTMNG) was based on the diagnosis of a multinodular goitre with a normal TSH level in the six months prior to surgery and no previous history of treatment for thyrotoxicosis. A toxic multinodular goitre (TMNG) was based on the presence of a multinodular goitre with a suppressed TSH <0.3mU/L, or if anti-thyroid medication was required to maintain a normal TSH and no use of exogenous levothyroxine. Patients with Graves' disease were excluded.

Indications for surgery were determined from clinical notes. All preoperative ultrasound reports were reviewed for confirmation of diagnosis as well as for presence of features suspicious for malignancy. Results from preoperative cytology by fine needle aspiration (FNA) were reviewed for features of malignancy. Results of imaging, FNA and clinical letters were used to establish the clinical suspicion of malignancy leading to surgical treatment. All pathology reports were reviewed for final histological diagnosis. Standard pathology preparation and examination of thyroid specimens in our institution is 3–4mm slices.

Ethical approval for the project was granted by the Northern A Health and Disability Ethics Committee (16/NTA/127/AM01).

Statistical analysis was conducted using Statistica (data analysis software system, version 11. StatSoft Inc. 2012. Tulsa, OK 74104, USA) and involved descriptive statistics, followed by non-parametric comparisons. An alpha level of 0.05 was used for all statistical tests.

Results

A total of 602 patients underwent surgery for MNG during the time period studied. Of these, 448 were non-toxic and 154 toxic MNG. The median age of patients with a NTMNG was 49 years with 86% female, while the median age of patients undergoing surgery for a TMNG was 56 years and 93% were female. Demographic details are shown in Table 1.

Overall, 95/602 (16%) of patients undergoing surgery for multinodular disease had concomitant thyroid cancer.

Of the TMNG group, 18 patients (12%) were diagnosed with thyroid cancer (Tables 1 and 2). In three of these cases there was preoperative suspicion for the presence of malignancy (one FNA of undetermined significance, and two in which the preoperative FNA was suggestive of PTC). After excluding these three cases, 15/151 patients (10%) had unsuspected/occult thyroid cancer. Of these 15 cases, all were PTC (12 of which were micropapillary carcinomas, ie, ≤10mm). Two of the 15 patients with unsuspected cancer had metastatic disease identified postoperatively (in one case nodal recurrence two years after surgery and the

Table 1: Demographic characteristics of study sample.

	TMNG			NTMNG		
	Total group (N=154)	No cancer (N=136)	Cancer on histology (N=18)	Total group (N=448)	No cancer (N=371)	Cancer on histology (N=77)
Age: (years)						
Median (IQR)	56 (45–63)	56 (44–63)	55.5 (49–61)	49 (40–60)	49 (39–60)	50 (42–61)
Gender: N (%)						
Female Male	141 (92%) 13 (8%)	124 (91%) 12 (9%)	17 (94%) 1 (6%)	384 (86%) 64 (14%)	322 (87%) 49 (13%)	62 (81%) 15 (19%)
Ethnicity: N (%)						
NZE/Other European Māori Asian Pacific Peoples MEELA Not stated	83 (54%) 58 (38%) 6 (4) 1 (1%) 2 (1%) 4 (3%)	76 (56%) 50 (37%) 3 (2%) 1 (1%) 2 (1%) 4 (3%)	7 (39%) 8 (44%) 3 (17%) - - -	264 (59%) 146 (33%) 18 (4%) 4 (1%) 2 (1%) 6 (2%)	219 (59%) 128 (35%) 12 (3%) 4 (1%) 2 (1%) 6 (2%)	45 (58%) 18 (23%) 6 (8%) 3 (4%) 2 (3%) 3 (4%)

IQR = Interquartile Range; NZE = New Zealand European; MEELA – Middle Eastern, Latin American, African.

other intrathoracic disease seen on post-ablative imaging). Both patients had multifocal PTC (20mm maximal diameter at initial surgery) and had received adjuvant radioiodine therapy.

Of the 448 patients who underwent surgery for a NTMNG, 77 patients (17%) had thyroid cancer (Tables 1 and 2). In 47 cases there was preoperative clinical suspicion of cancer (based on clinical, radiological and/or cytology assessment). After excluding these 47 cases, 30/401 (7%) patients had unsuspected/occult thyroid cancer. Of these 30 cancers, 25 were PTC (19 micropapillary), four follicular (all MIFC), and one medullary thyroid cancer. In only one case was there nodal or metastatic spread (a 70mm PTC within a massive MNG).

Patients with TMNG were less likely than those with a NTMNG to undergo a preoperative FNA (34% vs 52%, p=0.0001).

During the same time period an additional 24 patients underwent hemithyroidectomy for a solitary toxic nodule. No cases had preoperative suspicion for malignancy. In only one case was an occult cancer identified (3mm PTC in the centre of the toxic nodule).

Table 2: Cancer size and subtype.

Cancer subtype	TMNG*		NTMNG*	
	Total group N=18	Unsuspected N=15	Total group N=77	Unsuspected N=30
PTC—total - Micropapillary <10mm	16 12	15 12	62	25 19
MIFC*	2	0	9	4
Hurtle cell	0	0	1	0
MTC	0	0	2	1
Poorly differentiated—insular/anaplastic	1	0	5	0

*One patient in each group had two cancer types.

Discussion

We have demonstrated an overall rate of thyroid cancer of 16% in patients undergoing surgery for multinodular thyroid disease. However, in 53% of these patients, cancer was suspected preoperatively. Interestingly only 3/18 patients with a TMNG were suspected to have cancer preoperatively compared to 47/77 of those with a NTMNG. In our cohort, all patients underwent ultrasound examination but not all patients who had biochemistry and ultrasound imaging consistent with TMNG underwent nuclear medical imaging. Therefore, in our patients a hypervascular nodule on ultrasound imaging in a patient with a TMNG may not have been recognised as a potentially malignant lesion and instead assumed to be a toxic nodule. In our institution in general we avoid FNA examination of toxic nodules as these often demonstrate atypical features such as a microfollicular pattern. Given the treatment of choice for a small thyroid cancer without any sonographic evidence of lymphadenopathy is identical to the treatment for TMNG (ie, total thyroidectomy) we believe this approach is reasonable and more cost effective than universal thyroid nuclear medicine scanning of all thyrotoxic patients. In the setting of a MNG only suspicious nodules should be targeted for FNA, and in the event of a total thyroidectomy occurring without any significant delay most intrathyroidal nodules <4cm do not require biopsy as it would not change surgical management (other than consideration of prophylactic central compartment neck dissection in the setting of papillary or medullary thyroid cancer). However, each patient should be evaluated on his or her own merits. Obvious exceptions include likely extrathyroidal extension, associated laryngeal nerve palsy and radiological evidence of cervical lymphadenopathy.

While recent reports suggest that a suppressed TSH does not exclude the development of thyroid cancer[9,10] clinicians appeared to have a lower degree of suspicion for cancer in patients with a TMNG. This is supported by the lower rate of FNA in this group, although the rate of unsuspected/occult thyroid cancer was not different in the TMNG group when compared to those with NTMNG (9.9% vs 7.5%, respectively). The overall cancer rate between the two groups was also not different (11.7% in TMNG vs 17.2% in the NTMNG cohort). While these cancer rates may be of concern to patients, it is reassuring that most (12/15) of the unsuspected cancers in a TMNG were micropapillary. While micropapillary thyroid carcinomas not uncommonly involve local lymph nodes and can be associated with distant metastases in rare cases, the risk of dying from disease is extremely low irrespective of therapy.[13–15] As such, it is likely that for most patients not identifying a micropapillary carcinoma would not result in any increased morbidity or mortality and may avoid both the anxiety that often comes with a diagnosis of cancer and the potential disadvantages of overtreatment. This differs from the recommendation by Smith et al, who suggest that the high cancer rates in patients with TMNG should impact the clinical decision in terms of choice of definitive therapy.[8] In that study of 164 patients with TMNG the largest unsuspected cancer was 1.5cm, although two patients did have local lymph node involvement.[8] In patients with a TMNG the usual alternative therapy to surgery is radioiodine (RAI) and it is possible that RAI, even at the low doses used for thyrotoxicosis, may be of therapeutic benefit and result in ablation of an incidental papillary microcarcinoma.

Our findings demonstrate a significantly lower rate of unsuspected cancer than that reported by Smith et al.[7,8] The reasons for this are unclear. One limitation of these retrospective studies is the lack of standardisation of pathological examination of the specimen. The rate of microcarcinomas in particular will be influenced by how carefully the specimen is examined. Smith did not report histology section thickness or whether all three pathologists performed the same slice thickness when sectioning the samples, but of note there was no difference in identified cancer rates between the three institutions within that study.[7] Our cancer rates are closer to that of two Australian studies.[9,16] It is possible that our populations are better matched in terms of risk factors (eg, both are currently deemed iodine adequate).[17] However, another possibility is that pathological examination of the thyroid

is similar across both countries with both New Zealand and Australian pathologists undergoing similar training and presumably following the Royal College of Pathologists of Australasia guidelines.[18] However, these guidelines are relatively recent and so there would have been less standardisation in the earlier years of the cohort. In addition, not all pathologists in our centre come through Australasian training and therefore some may not follow these guidelines. Furthermore, the entire thyroid gland is not examined microscopically with some blocks taken from routine or random parts of the gland while others are selected due to abnormal gross appearance or texture. As such it is likely that we may be underestimating the true incidence of unsuspected thyroid cancer. The hypothesis that the higher rate of cancer identified may be related to increased pathological sampling is supported by a study which demonstrated an increase in thyroid cancer diagnosis in retrosternal goitre over time from 3.6% to 7.5%, which was associated with increased pathological sampling of resected specimens.[16]

In summary, we have demonstrated that cancer in a multinodular goitre is common. However, it is likely that most of these occult thyroid cancers are not clinically significant and will not increase mortality. As such we would not necessarily recommend surgery over RAI for TMNG because of concerns regarding cancer risk in the absence of other indications for thyroidectomy.

Competing interests:
Nil.

Acknowledgements:
MK was supported by a Waikato District Health Board Summer studentship award, administered by the Waikato Clinical Campus, Faculty of Medical & Health Science, University of Auckland. No other funding.

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URL:
https://www.nzma.org.nz/journal/read-the-journal/all-issues/2010-2019/2018/vol-131-no-1468-19-january-2018/7466

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