Review Article

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The surgical approach to managing differentiated thyroid cancer

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In recent decades, our understanding of thyroid cancer has improved significantly with the recognition that differentiated thyroid cancer (DTC) has good survival and oncological outcomes. Along with the recent rise in the detection of otherwise subclinical tumours due to improved diagnostics, there has been much debate on how aggressive one should be when performing thyroid and lymph node surgery. The use of risk stratification to categorize patients into low, intermediate and high risk has led to a more tailored approach to treating differentiated thyroid cancer. This ensures patients are not subject to preventable morbidity from overtreatment while maintaining good outcomes. We discuss the approach to primary thyroid and lymph node surgery by reviewing the current literature.

Key words Differentiated thyroid cancer - lobectomy - lymph node dissection - radioactive iodine therapy - total thyroidectomy

Introduction

Differentiated thyroid cancer (DTC) is the most common endocrine malignancy and account for 90-95 per cent of all thyroid cancers[1]. Its subtypes include papillary thyroid carcinoma (PTC), follicular thyroid carcinoma and Hürthle cell carcinoma. Over the last few decades, the incidence of thyroid cancer has been increasing worldwide[2]. According to the Surveillance, Epidemiology and End Results program (SEER)[3], the incidence in the USA has tripled from 4.8 to 14.9/100,000 between 1974 and 2012. This increase has been attributed to the detection of previously subclinical tumours because of improved diagnostics and surveillance[4]. However, epidemiological studies have shown that the rate of advanced tumours also rose during this period with papillary microcarcinomas accounting for only 50 per cent of this rise[5].

Despite the rapid rise in incidence, mortality has remained static at 0.5/100,000 with a reported overall 5-year survival of 98 per cent[3]. The excellent outcomes mean that prospective trials relating to survival have not been feasible. Retrospective single institution series and reports from large national databases provide much of the evidence which underpins international management guidelines[6-9].

The mainstay of treatment for thyroid cancer is surgery. In the early 20th century, surgeons tended to be aggressive in their approach with a total thyroidectomy and bilateral radical neck dissection. However, this was associated with significant morbidity for the patient. As our understanding of thyroid cancer has evolved, the recognition that DTC has good outcomes has led to a less aggressive surgical approach. Simultaneously, our surgical techniques have improved but despite

this, the risk of permanent recurrent laryngeal nerve palsy is at least 1.8 per cent and around 6 per cent of patients require long-term calcium supplementation following total thyroidectomy[10]. Although these are not life-threatening complications, but these have an impact on quality of life. This is particularly relevant for young patients with small tumours who have excellent oncological outcomes. The lack of high quality evidence coupled with uncertainty about both oncological and surgical outcomes have led to much debate about the most appropriate surgical approach to this relatively indolent disease.

Several studies have identified risk factors that are predictors of poor overall survival[6,11-13]. These include age greater than 45 yr, male gender, familial disease, size greater than 4 cm, multifocal disease, bilateral disease, extrathyroidal extension (ETE), and distant metastases. The use of risk stratification schemes helps classify patients into low, intermediate, and high risk groups so that treatment can be tailored to the individual. This prevents low risk patients being subject to preventable morbidity from aggressive overtreatment, and ensures high risk patients are treated appropriately.

This paper reviews the current literature on the surgical approach to the management of DTC. We discuss the controversies around the extent of thyroid surgery and the role of therapeutic and prophylactic neck dissection.

Primary thyroid surgery

Ideally, all patients with a thyroid malignancy should be discussed at a multidisciplinary meeting prior to surgery. The primary aim of surgery is to resect disease, minimize the chance of recurrence and achieve this with minimal morbidity. Selecting the appropriate procedure is critical as not only does surgery provide initial therapy, but also optimises the patient for adjuvant radioactive iodine (RAI) therapy when required.

Controversy exists about the need for total thyroidectomy versus thyroid lobectomy in managing DTC. The first study to significantly shape the international approach to this question was published in 1977 when Mazzaferri *et al*[7] analysed the outcome of 576 patients managed by the US Airforce. The authors concluded that patients who had total thyroidectomy and those managed with RAI had improved outcomes. These findings had a profound impact on the surgical approach to DTC in the USA and beyond and were supported by others. Loh *et al*[8] showed that among 492 patients with DTC, those who did not undergo total thyroidectomy had a 2.5-fold risk of recurrence and 2.2-fold risk of death. In addition, those who were not treated with RAI had a 2.1-fold risk of recurrence[8]. Bilimoria *et al*[9] published an analysis of 52,173 patients with PTC from the US National Cancer Database. The 10 year recurrence rate was 7.7 per cent following total thyroidectomy compared to 9.8 per cent in lobectomy. However, for patients with microcarcinoma no difference in outcome was observed between lobectomy or total thyroidectomy. This paper was published in 2007 and the American Thyroid Association updated their guidelines in 2009 and recommended total thyroidectomy for all tumours >1cm in size[14].

However, not all groups agreed with this aggressive approach to all patients with DTC. At Memorial Sloan Kettering Cancer Center, New York, USA, 889 patients with T1T2N0 DTC underwent total thyroidectomy (59%) or thyroid lobectomy (41%). There was no difference in local or regional recurrence and on multivariate analysis, male gender and age over 45 yr were independent predictors of poorer overall survival[6]. In a study of 176 patients with DTC ≤2cm, clinical outcomes did not improve with total thyroidectomy and RAI in patients with no risk factors[15]. These findings were supported by Japanese reports where, unlike Western countries, RAI is not generally available and thyroid lobectomy has been the mainstay of surgery for PTC[16]. In a recent retrospective study, 967 patients with low risk PTC underwent total thyroidectomy and 791 patients underwent less than total thyroidectomy (lobectomy or subtotal thyroidectomy). The 10-year cause-specific survival was 99 per cent in both groups and disease-free survival was 91 and 87 per cent, respectively[17]. Matsuzu *et al*[18] reported on 1088 cases of PTC treated with thyroid lobectomy with median follow up of 17.6 years. There were no reported deaths in low risk patients[18].

As no prospective evidence exists on which to base a definitive recommendation, considerable controversy continues to exist. To address this, risk stratification must be considered. In high risk patients (older patients with large volume primary disease or distant metastases) total thyroidectomy is the procedure of choice. Not only does this remove the primary tumour, but also the contralateral lobe in order to facilitate adjuvant RAI. The potential for morbidity in this group is balanced by the potential for a poor outcome (recurrence and even death). In contrast, for low risk patients (young patients with low volume

disease limited to the thyroid) the balance between risk and benefit is quite different. This patient group is at extremely low risk of either recurrence or death and this must be considered when selecting appropriate therapy. Although patients will do well following total thyroidectomy, there are a number of disadvantages. Rates of vocal cord injury, permanent hypocalcaemia and tracheostomy are higher in total thyroidectomy than in thyroid lobectomy. This has now been shown to be true both in experienced and in-experienced hands[19]. In addition, patients who undergo total thyroidectomy require lifelong thyroxine therapy. In contrast, thyroid lobectomy has far less potential for morbidity and potentially allows patients to be managed without exogenous thyroid hormone replacement. However, the contralateral lobe presents a number of challenges. It prevents the use of RAI; due to thyroglobulin (Tg) production from the residual lobe, Tg use as a tumour marker is less clinically useful; also the residual lobe requires monitoring and around 10 per cent of patients will go on to require completion thyroidectomy during follow up[6].

The choice between total thyroidectomy and lobectomy has not only been driven by risk stratification but also by the perceived role of RAI in managing patients with DTC. The recognition that RAI was associated with improved outcomes in all patients with tumours >1.5 cm led to a steady increase in the percentage of patients managed with RAI in the USA over the second half of the 20th century[14]. However, its role in low to intermediate risk cases has been questioned[20,21]. It now appears safe to manage low risk patients without RAI which has removed the indication to resect the contralateral lobe in many cases further supporting lobectomy alone in well selected patients. Coupled with the recognition that RAI therapy is not side effect free, and can even be linked with increased rates of second primary malignances[22], these observations have led the major international guidelines away from total thyroidectomy as a blanket recommendation for all[12,13].

Papillary microcarcinoma account for 30 per cent of DTC and is rising in incidence faster than all other groups of DTC. The long-term survival is excellent at almost 100 per cent with mortality rate of 0.34 per cent and risk of distant metastases of 0.4 per cent[23]. Although the risk of loco-regional recurrence is 2.5 per cent, recurrences occur in the neck nodes rather than the thyroid bed and in most cases are treatable without adverse impact on survival[12].

Recently, Donatini *et al*[24] reported a series of 880 patients over a 24 years period which included patients with papillary thyroid microcarcinomas. In the group who underwent total thyroidectomy, there were no loco-regional or distant recurrences but complication rate, both temporary and permanent, were higher. In the lobectomy group, 7.3 per cent developed recurrence in the contralateral lobe in a mean follow up time of 11.2 years. There were no reported mortalities and the authors concluded that due to the low aggressive nature of papillary thyroid microcarcinomas, a lobectomy with follow up was the best approach while minimizing morbidity and improving quality of life[24].

At the Mayo Clinic, 900 patients with papillary thyroid microcarcinomas were treated over six decades with a mean follow up time of 17.2 years[25]. Of the 892 who underwent complete tumour resection at the initial operation, none developed distant metastases at 20 years follow up. Higher recurrence rates were seen in patients with multifocal or node-positive disease but more extensive surgery in terms of total thyroidectomy and RAI did not reduce recurrence rates compared to lobectomy[25].

Some groups now recommend observation rather than surgery for patients with microcarcinomas. Results from observational trials show that disease progression occurs in only a few patients and those that do can be safely identified and treated appropriately[26,27]. Oda *et al*[28] have recently suggested that surgical intervention in the low risk group may actually be disadvantageous.

The conflicting data presented in the literature are now recognised by the major international guidelines[12,13]. For microcarcinoma, thyroid lobectomy is adequate therapy. For cases with adverse risk features (large tumour size or the presence of metastases) total thyroidectomy is recommended to facilitate RAI. However, for intermediate cases >1 cm but <4 cm without evidence of metastases, the role of RAI is controversial and as such an individualized approach should be adopted balancing the individualised risks of treatment against the perceived benefits (Fig. 1).

Lymph node surgery

Metastases to cervical lymph nodes are not uncommon in DTC, particularly in PTC. In fact, 20-50 per cent of patients will have nodal metastases and up to 90 per cent will have micrometastases (<2mm)[13] when elective neck dissection is practiced and the surgical specimen is carefully scrutinized. Despite this,

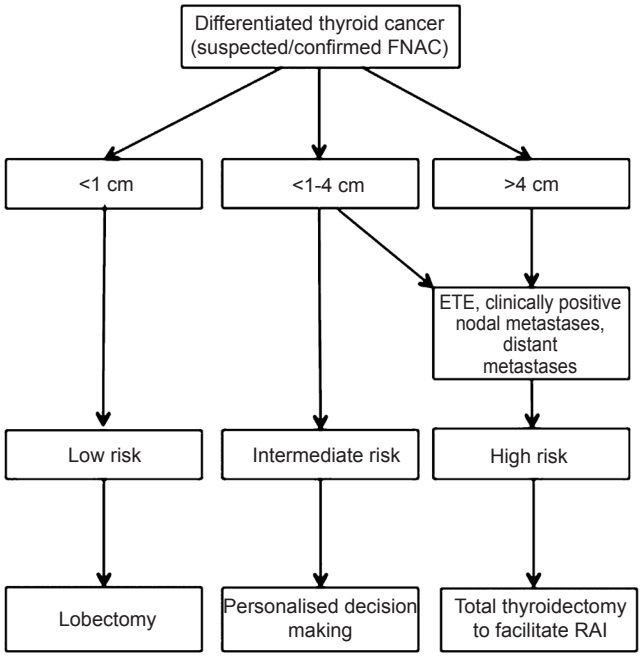

Fig.1. Selecting surgical approach to the thyroid gland. FNAC, fine needle aspiration cytology; ETE, extrathyroidal extension.

microscopic nodal metastases have little influence on survival but are associated with slightly higher rates of recurrence. Lymph node surgery in thyroid cancer has evolved significantly. In early years, prior to the recognition of the importance of histology as a predictor of outcome, some considered radical neck dissection the treatment of choice for all patients[14]. However, this led to significant morbidity. The recognition that DTC was associated with excellent outcomes called in to question the need for such an aggressive surgical approach.

Contemporary assessment of the neck includes high resolution ultrasound (US). The introduction of this investigation over the past 30 yr has resulted in a significant change in practice. Previously occult nodal metastases can now be identified pre-operatively allowing clinicians to accurately plan the extent of surgery prior to intra-operative examination of the neck. The ultrasound has a reported sensitivity of 83.5 per cent and specificity of 97.7 per cent and hence is a reliable way of assessing metastatic lymph nodes and guiding the extent of neck dissection[29], particularly in the lateral neck.

The first echelon nodes occur in the central compartment which is difficult to visualize on US and when there is suspicion of disease, patients should have computed tomography (CT) in order to assess the mediastinal lymph nodes[30]. The second echelon nodes occur in the lateral neck nodes although some groups report that these are as frequently involved as the central compartment[31,32].

Following assessment, one can consider the neck as either clinically positive or negative. In patients with a clinically positive neck (cN+) there is a consensus that surgical removal of the metastatic disease is indicated. Although previously a "berry picking" technique was employed by some to remove only clinically positive metastases, this approach was abandoned due to high rates of recurrence[14]. At present, a therapeutic compartment orientated neck dissection is recommended in patients with positive neck disease[13]. For cN+ disease in the central neck (cN1a) this requires dissection of levels VI and VII. For cN+ disease involving the lateral neck (cN1b) this requires dissection of levels II-V (possibly sparing regions cranial to the accessory nerve). For the vast majority of patients there is no extra nodal extension, and the neck dissection can therefore, spare the sternomastoid muscle, the jugular vein and the accessory nerve. This minimizes the morbidity of surgery without compromising outcome.

For those patients considered free of clinical evidence of nodal metastasis (cN0), the role of prophylactic neck dissection is controversial. The situation is complex as prophylactic surgery results in rates of occult disease approaching 40 per cent[33]. However, these occult nodal metastases rarely progress to clinically meaningful disease. This is in contrast to most malignant processes where regional metastases are associated with significantly worse outcome.

It is generally agreed that prophylactic lateral neck dissection does not carry sufficient benefit to warrant the significant morbidity of the procedure. As such no major international guidelines support prophylactic lateral neck dissection[12,13]. The central neck is more complex. Again rates of occult metastasis are high when prophylactic surgery is performed. However, a few patients progress to a clinical recurrence if surgery is not performed[34,35]. In addition, the morbidity of adding prophylactic central neck dissection to total thyroidectomy is significant. Increased rates of hypocalcaemia and nerve injury are reported even in experienced hands[36]. Although in the most expert hands the morbidity associated with central neck surgery is minimal, this is not the case for the average surgeon treating patients with DTC.

Some authors believe that the staging information gained by prophylactic central neck dissection is important in guiding adjuvant therapy[33]. Although a prospective randomized trial of sufficient power is not feasible, a possible improvement has been shown in recurrence rates following prophylactic central neck dissection[37]. Unlike in the lateral neck, the central neck must be opened in order to perform thyroidectomy. Revision central neck surgery, when required, is associated with higher risk than primary procedures, which is another attraction of performing the surgery at the time of thyroidectomy.

The clinician must consider whether the risk of prophylactic neck surgery for all is lower than the risk of observation and surgical salvage for a few patients who do present later with central neck recurrence. When making that decision it is critical to remember that these patients have excellent outcomes (survival >95% at 10 years) and, therefore, there is no impact on survival and the impact on recurrence rates is modest at best. It is also critical that the clinicians have an appreciation of the risks of surgery in their own departments. Most guidelines[12,13] now attempt to make that balance by recommending prophylactic central neck dissection in those at highest risk of harbouring occult disease (cT3/4 or cN1b disease) (Fig. 2).

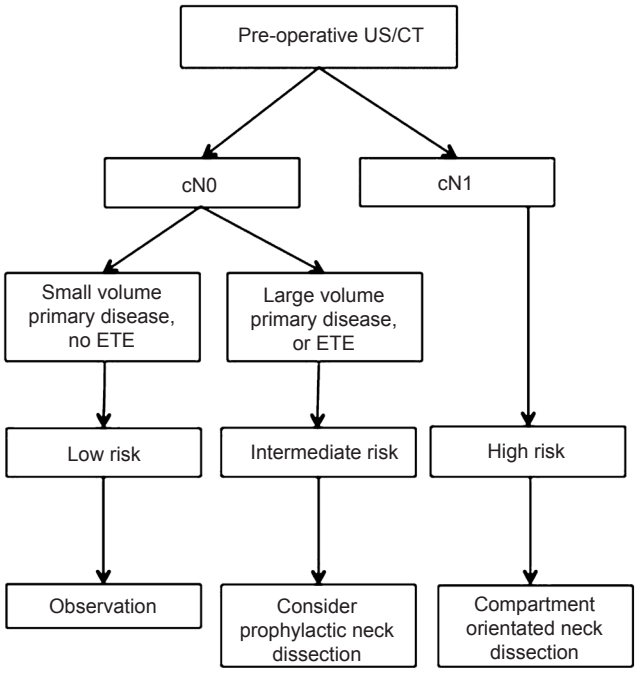

Fig. 2. Selecting surgical approach to the neck. The neck must be assessed pre-operatively with ultrasound scan. If there is disease in the lateral neck, imaging of the central compartment with a CT scan should be performed. In patients with no clinical evidence of nodal disease (cN0), those with small volume disease of ETE (cT3/4) a prophylactic central neck dissection should be considered. In clinically positive neck disease (cN1), a compartment oriented neck dissection is recommended. In disease of the lateral neck, this requires dissection of levels II-V. In disease of the central neck, this requires dissection of levels VI and VII. US, ultrasound; CT, computed tomography; ETE, extrathyroidal extension.

Conclusions

The surgical management of DTC has evolved towards a less aggressive approach as our understanding of thyroid cancer has advanced. The oncologic and survival outcomes are excellent in DTC and a personalized decision making approach using risk stratification should be considered for every patient. Those with small volume disease with no additional risk factors should be fully informed during the consent process of their suitability for a thyroid lobectomy over total thyroidectomy. The extent of thyroid surgery should be based not only on disease related factors but also on patient choice. Lymph node surgery should be compartment orientated and the extent of therapeutic neck dissection should be guided by radiological findings. Prophylactic neck dissection remains an area of debate but given the lack of effect on long-term survival, personalized decision making should again be applied to each individual. As prospective randomized trials are unlikely to be performed, the clinicians managing DTC must understand the biology of the disease and weigh that against the risk of treatment related injury in planning a surgical approach to patients with DTC.

***Conflicts of Interest*:** None.

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