The Role of Total Thyroidectomy in the Initial Treatment of Well-differentiated Follicular-cell-derived Thyroid Carcinomas

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Abstract

The incidence of thyroid cancer has been increasing over the past 30 years. The follicular-cell-derived thyroid carcinomas (DTC) – papillary thyroid cancer (PTC) and follicular thyroid cancer (FTC) – are most common (79 and 13%, respectively). Initial treatment of DTC involves resection of the primary tumour. Post-operative therapy consists of radioactive iodine ablation for most patients, followed by thyroid-stimulating hormone (TSH) suppression with thyroxine. An ongoing controversy in the surgical treatment of DTC is the extent of thyroid gland resection. Consensus guidelines recommend total or near-total thyroidectomy in high-risk DTC (PTC tumour >1–2cm, any tumour, node, metastasis [TNM] stage III and IV [extrathyroidal spread], any N1 [regional metastasis] or M1 [distant metastasis], any patient >45 years and <16 years of age, aggressive histological subtypes) rather than thyroid lobectomy as the initial procedure of choice, given its advantages of treating potential multicentric disease, facilitating maximal uptake of adjuvant radioactive iodine and facilitating post-treatment follow-up by monitoring serum thyroglobulin levels and neck ultrasonography. Low-risk patients are currently treated by thyroid lobectomy or total (or near-total) thyroidectomy; in fact, conflicting views persist for low-risk patients who have differentiated thyroid cancer. The main arguments for lobectomy in low-risk PTC patients are that there is no clear evidence that total thyroidectomy may affect the survival of patients with low-risk PTC, and that total thyroidectomy increases the risk of recurrent laryngeal nerve injury and hypoparathyroidism even in the hands of an experienced endocrine surgeon.

Keywords

Thyroid papillary cancer, thyroid follicular cancer, therapy, thyroidectomy, radioiodine

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Thyroid cancer is estimated to be the seventh most common cause of any new malignancy in women in the US. In 2007, 25,480 cases and 3.8% of new cases were diagnosed in women, while thyroid cancer represented just over 1% of new cases in men (8,070 cases), incidence rank 14th.[1–4] The annual incidence of thyroid cancer has been growing, from 7,800 cases in 1974 to 33,550 cases in 2007, with an incremental increase from 22,000 to 33,550 new cases/year between 2003 and 2007. During the same period, the percentage of cancer deaths per year, relative to the number of new cases, has decreased from 15 to 5%.[1–4] However, a larger proportion (and a large absolute number, given the high prevalence) of thyroid cancer patients will suffer usually loco-regional recurrence, and a subset of patients will have progressive disease, causing high morbidity but not necessarily death. Autopsy studies identify microscopic or occult papillary thyroid cancer (PTC) in 5–36% of cases.[5] The discrepancy between the relatively small number of clinically relevant thyroid cancers and the large number of incidental thyroid cancers suggests that much is not yet known about the molecular biology of thyroid cancer.

Well-differentiated Follicular-cell-derived Thyroid Carcinomas

Follicular-cell-derived thyroid carcinomas (DTCs: PTC and follicular thyroid cancer [FTC]) are most common. Using a large database, it was found[6] that 79% of cases of DTC are papillary, 13% follicular, 3% Hurthle cell, 3% medullary and 2% anaplastic. PTC presents most commonly between 30 and 50 years of age, with a female:male ratio of 2–3:1. The risk of PTC is increased in subjects exposed to radiation.[7]

Familial DTC accounts for approximately 3% of PTC, and it is more aggressive than sporadic cases. Autosomal dominant inheritance, with partial penetrance, is the mode of inheritance. Familial thyroid cancer is associated with familial adenosis polyposis, Gardner's syndrome, Cowden's disease and multiple endocrine neoplasia (MEN) type I.

Molecular Changes in Papillary Thyroid Cancer or Follicular Thyroid Cancer

In adult sporadic papillary carcinomas, RET/PTC rearrangements are found in 30–40% of cases, RAS mutations in about 10% and BRAF mutations in around 40% of cases.[8] In radiation-induced papillary carcinomas, and those in children, RET/PTC rearrangements have been seen in 50–80% of cases and BRAF mutations in 10% of cases.[8,9] BRAF mutations have been associated with more aggressive and less differentiated papillary tumours.[8]

Risk Stratification for Follicular-cell-derived Thyroid Carcinomas

Multifactorial risk stratification schemes have been developed, such as AGES (age, grade, extent and size),[10] AMES (age, metastases [distant] extent, size),[11] MACIS (metastasis, patient age, completeness of resection, local invasion and tumour size)[12] and TNM (tumour,

Table 1: Indications for Total or Near-total Thyroidectomy for High-risk Patients with Follicular-cell-derived Thyroid Carcinomas

Papillary Thyroid Cancer
Tumours >1–2cm
Age <16 and >45 years
Familial papillary thyroid cancer
Prior irradiation
Bilateral nodular disease
Extrathyroidal spread
Lymph-node metastasis
Distant metastasis
Aggressive histological subtypes (oxyphilic, tall-cell, diffuse sclerosing and columnar variants)
Follicular Thyroid Cancer
Invasive follicular thyroid cancer
Minimally invasive follicular thyroid cancer >2–4cm
Aggressive histological subtypes (Hurthle cell carcinoma and insular variants)
Other aggressive features (as above)

Table 2: Arguments in Favour of Total Thyroidectomy or Lobectomy plus Isthmectomy for Low-risk Patients with Papillary Thyroid Cancer

	Total Thyroidectomy	Lobectomy
Survival		No clear evidence that total thyroidectomy may affect survival
Recurrence	Most of the studies showed the prevalence of local recurrence in patients with PTC treated with lobectomy	
Neck metastasis	PTC may be associated with neck metastasis in 80–90% of cases	
Distant metastasis		No clear evidence that lobectomy is associated with higher prevalence of distant metastases
Risk of complications		Higher morbidity of total thyroidectomy
Follow-up	Superior surveillance with thyroglobulin measurements or diagnostic ^{131}I whole-body scan and neck ultrasonography	
Prediction of prognosis	Deaths and recurrences cannot be predicted pre-operatively by various classification systems	

PTC = papillary thyroid cancer.

nodes, metastasis).[13] Patients determined to be low-risk by various classification systems report 10–20-year mortality rates and recurrence rates of 2–5 and 10%, respectively, whereas high-risk patients have mortality and recurrence rates of 40–50% and 45%, respectively.[14] Low-risk patients (for recurrence and mortality) are: T1 or T2, N0, M0 (TNM);[13] <45 years and >16 years of age; with PTC, without aggressive histological variant (i.e. tall-cell variant); without family history of DTC; without bilateral disease; or FTC with minimal capsule invasion. Seventy-five per cent of patients are in the low-risk group. High-risk patients may be defined as having any TNM stage III and IV (extrathyroidal spread), any N1 (regional metastasis) or M1 (distant metastasis) and any patient >45 years and <16 years of age.

Total or Near-total Thyroidectomy for High-risk Patients with Follicular-cell-derived Thyroid Carcinomas

Surgery is the primary treatment for differentiated thyroid cancer. Two general surgical approaches have been advocated among experts: unilateral thyroid lobectomy (including the isthmus) and total or near-total thyroidectomy. A consensus has been reached for certain subgroups of patients. For example, total thyroidectomy is indicated for patients with tumours >4cm, extrathyroidal spread, regional or distant metastasis, high histological grade and age <16 and >45 years (see *Table 1*). Mortality rates in association with recurrences in high-risk patients approach 40–50%. Total thyroidectomy results in less recurrence and mortality over thyroid lobectomy in high-risk patients who have DTC.

Aggressive histological subtypes of PTC include oxyphilic, tall-cell, diffuse sclerosing and columnar variants, and of PTC Hurthle cell carcinoma and insular variants. Hurthle cell carcinoma is associated with the highest incidence of distant metastases among DTC, and responds poorly to radioiodine treatment. Total thyroidectomy with evaluation of the central node compartment is the treatment for histologically aggressive subtypes of DTC. It should be strongly considered even in otherwise low-risk patients.[15]

The BTA 2007 guidelines[16] confirm that most cancers >1cm should have a total or near-total thyroidectomy: the decision should be taken by assessing the risk of recurrence. Total or near-total thyroidectomy is recommended if the cancer is multifocal, if it extends beyond the thyroid capsule, when there is nodal disease/distant metastases, in patients with a history of previous neck irradiation and in cases of familial disease. The ETA 2006 consensus[17] recommends thyroidectomy for isolated 1–2cm tumours after patient discussion of the risks and benefits of a second operation, particularly if there are any high-risk features as listed above. The ATA 2006 guidelines[18] state that a thyroidectomy should be performed if the tumour is >1–1.5cm.

Extent of Resection for Low-risk Patients with Follicular-cell-derived Thyroid Carcinomas

Low-risk patients are currently treated by thyroid lobectomy or total or near-total thyroidectomy; in fact, conflicting views persist for low-risk patients who have differentiated thyroid cancer. The main arguments for lobectomy in low-risk PTC patients (see *Table 2*) are that there is no clear evidence that total thyroidectomy affects the survival of patients with low-risk PTC, and that total thyroidectomy increases the risk of complications of recurrent laryngeal nerve injury and hypoparathyroidism.

Survival, Recurrence and Metastasis

There is no clear evidence that total thyroidectomy affects the survival of patients with low-risk PTC. The long-term survival rate in the low-risk group exceeds 98%. Both DeGroot and Grant and their colleagues have documented fewer recurrences and deaths,[19,20] even in low-risk patients, with bilateral thyroidectomy. However, Bilimoria et al. (US National Cancer Data Base, 52 173 PTC, 1985–1998) showed that total thyroidectomy resulted in superior disease-free and overall survival in patients with PTC >1cm, but not in patients with PTC <1cm.[21] Other studies, by Shaha and colleagues[22,23] and Sanders and Cady,[24] also found no significant difference in recurrence rates or mortality rates for low-risk patients.

However, most of the studies showed that the prevalence of local recurrence in patients with PTC treated with lobectomy is higher than in those treated with total thyroidectomy. In fact, total or near-total thyroidectomy in patients with low-risk PTC is associated with an improved disease-free survival.[25,26] The rate of local recurrence and nodal metastasis after lobectomy was 14 and 19%, respectively, compared with 2 and 6%, respectively, after total or near-total thyroidectomy.[25] In another study a 5–10% risk of recurrence in the opposite lobe in patients treated with a lobectomy alone was observed.[27] Recurrence develops in the contralateral lobe in about 5% of patients, and many retrospective studies[25,28] with long-term follow-up demonstrate decreased recurrence (although not decreased mortality) in patients who have total thyroidectomy and radioactive iodine (RAI) ablation compared with lobectomy for low-risk patients.

Recurrence in the contralateral lobe is mainly due to the muticentricity of PTC. It has been demonstrated that tumours in multicentric PTC carry different RET/PTC oncogene rearrangements, suggesting that these tumours seem to arise *de novo*, synchronously or metachronously, from thyroid tissue prone to developing carcinoma.[29] The rate of occult cancer in the contralateral lobe ranges from 38[30] to 80% of patients[31,32] with clinically unilateral PTC. However, the high prevalence of microscopic foci in the opposite lobe does not correlate with the clinical recurrence rate, which is about 5%.

Multicentric PTC may be associated with neck metastasis in 80–90% of cases in which the neck is carefully dissected.[15] Massin and colleagues[33] showed that the risk of pulmonary metastasis is reduced in patients treated with total thyroidectomy; in fact, pulmonary metastases occurred in 11 of 831 patients (1.3%) who were treated with total thyroidectomy plus iodine-131 and in 91 of 831 (11%) who had thyroid lobectomies. However, other studies have not confirmed a higher incidence of distant metastases in patients treated with lobectomy.

Risk of Complications

Another argument for thyroid lobectomy for low-risk patients who have PTC centres around the higher morbidity of total thyroidectomy. A prospective cohort study of 5,583 cases of thyroid carcinoma suggests that complication rates are lower with lobectomy than with total thyroidectomy, with complication rates of 1.3 and 10%, respectively.[34]

However, numerous groups have reported comparable rates of recurrent laryngeal nerve injury and post-operative bleeding for total thyroidectomy, near-total thyroidectomy and thyroid lobectomy.[20,35–39] Nevertheless, temporary and permanent hypoparathyroidism and bilateral nerve injury are complications related only to total or near-total thyroidectomy and not to thyroid lobectomy.

It has been suggested that complication rates are higher for inexperienced thyroid surgeons. Surgeons who performed fewer than 10 procedures per year had a four-fold higher complication rate than more active thyroid surgeons.[40]

Minimally Invasive Endoscopic Technique

The minimally invasive endoscopic technique (MIVAT) can be applied only to a minority of cases of PTC, the so-called 'low-risk' carcinoma according to AGES and AMES criteria. Recently, it has been shown that MIVAT has a similar degree of completeness and rate of complications to conventional thyroidectomy, and that MIVAT is a valid option to treat low- and intermediate-risk PTC patients.[41–43]

Table 3: Arguments in Favour of Total Thyroidectomy or Lobectomy plus Isthmectomy in Paediatric Follicular-cell-derived Thyroid Carcinomas

	Total Thyroidectomy	Lobectomy
Tumour size	A 1cm tumour in an 18-year-old adult would correspond to a 4mm tumour in a 10-year-old child	
Recurrence	High prevalence of local recurrence in patients with PTC treated with lobectomy	
Neck metastasis	Regional lymph node involvement in 60–80%	
Distant metastasis	Pulmonary metastases, present in approximately 10%	
Survival		Excellent long-term prognosis
Risk of complications		Higher morbidity of total thyroidectomy
Follow-up	Superior surveillance with thyroglobulin measurements and neck ultrasonography	

PTC = papillary thyroid cancer.

Follow-up

The arguments for total thyroidectomy for PTC in low-risk patients include unequivocal superior surveillance with thyroglobulin measurements or diagnostic ^{131}I whole-body scan (^{131}I-WBS). Both of these tests are difficult to interpret in the presence of large amounts of residual thyroid tissue. Mazzaferri et al.[44] noted that 21% of 784 patients who had no clinical evidence of tumour on baseline serum thyroglobulin (Tg) levels (<1mg/l) during thyroid-hormone-suppressive therapy had a rise in serum Tg to >2mg/l in response to recombinant human thyroid-stimulating hormone (rTSH). When this occurred, 36% of the patients were found to have metastases, identified in 91% by an rTSH–stimulated Tg>2mg/l. Diagnostic ^{131}I-WBS after either rTSH or thyroid hormone withdrawal identified only 19% of cases of metastasis.

The actual follow-up of patients with DTC is performed by TSH-stimulated Tg and neck ultrasonography. Tg mesaurement is obviously not precise in the presence of a residual lobe, and neck ultrasonography is difficult to interpret in the presence of large amounts of residual thyroid tissue too.[45-47]

It is also evident that the effectiveness of ^{131}I therapy in patients with metastatic DTC after lobectomy is not adequate, and side effects may be observed (such as post-^{131}I-therapy thyroiditis).[15]

Prediction of Prognosis

Deaths and recurrences cannot be predicted pre-operatively by various classification systems; however, they occur and are observed even in patients with low-risk thyroid cancer. Elements of certain prognostic classification systems are only available post-operatively and can be limited in their ability to direct initial surgical treatment. Total thyroidectomy alleviates patient anxiety with respect to recurrence and the need for additional surgery. Kebebew and colleagues[48] used a decision-analysis model to compare total thyroidectomy and thyroid lobectomy: patients (61.5%) viewed thyroid cancer recurrence as less desirable than a thyroidectomy complication. The time and expense of repeated operations in recurrence must be considered as well.

Guidelines

All of the guidelines say that a lobectomy is sufficient for cancers <1cm without any high-risk factors. All three guidelines state that pre-operative ultrasound is valuable in planning surgery and should examine the contralateral lobe and neck nodes.[16-18]

Thyroid Lobectomy for Low-risk Follicular Thyroid Cancer

The most important factor to consider is the invasiveness of the FTC noted intraoperatively by the surgeon and the findings of the pathologist. In one study, well-differentiated FTC with minimal capsular invasion, no vascular invasion, patient age <45 years and tumours <4cm were associated with 100% survival with thyroid lobectomy.[49]

Unlike their American and European counterparts, the BTA 2007 guidelines include a section on minimally invasive follicular thyroid cancer (miFTC). The British guidelines say that if there is no vascular invasion and the tumour is <2cm, lobectomy is sufficient surgery, and adds that the patient should be female and <45 years of age. However, if the miFTC is 2–4cm (without vascular invasion), there is insufficient evidence for guidance and no clear recommendation can be given. Total or near-total thyroidectomy is advised if a similar lesion is >4cm. However, thyroid pathologists warn that it can be difficult to assess vascular invasion.

Paediatric Differentiated Thyroid Cancer

Paediatric DTC is twice as common in girls, and most cases are PTC (85–90%). Paediatric cancer is more common in children exposed to radiation, generally before 10 years of age,[50] for therapeutic external gamma radiation for head and neck disease (5–10% of PTCs),[51] atomic explosions or nuclear facility releases. The Chernobyl nuclear accident in 1986 led to a dramatic increase in the incidence of PTC in fallout regions, with a higher rate of extrathyroidal spread and distant metastasis at the time of diagnosis.[39,52]

Up to 70% of sporadic and radiation-induced PTCs in children carry RET/PTC mutations, compared with fewer than 40% in adults.[53] Paediatric DTC has a higher incidence of distant metastases (10–15%) versus adults (2%);[54] pulmonary metastases present in approximately 10%, and regional lymph node involvement in 60–80%. Multifocal disease is a predictor of recurrence (but not mortality) after surgical treatment of DTC in paediatric cases.[55] Paradoxically, although children who have DTC may present with more advanced disease, they generally have an excellent long-term prognosis, with survival rates of more than 90%. Furthermore, in children, when one adjusts tumour size to thyroid volume, a 1cm tumour in an 18-year-old adult would correspond to a 4mm tumour in a 10-year-old child or a 2mm tumour in a five-year-old child (see *Table 3*).[56]

Because of the above-mentioned reasons, uniformity of opinion does not exist for the extent of thyroidectomy with paediatric DTC. Newman and colleagues[57] reported that the recurrence rate after total or subtotal thyroidectomy was identical to the results of lobectomy. La Quaglia and colleagues[58] reported that the risk of a major complication in children under six years of age was more than 60%. Others have reported more local recurrences with lobectomy compared with total thyroidectomy.[59] Jarzab and colleagues[60] showed a 97% disease-free rate in a group of children treated with ^{131}I after five years compared with a 40% relapse rate without ^{131}I. DTC recurs in 25% of paediatric patients, sometimes months or years after initial treatment. Long-term monitoring is important, and neck ultrasonography and TSH-stimulated Tg are usually performed after total or near-total thyroidectmy, with high accuracy.[47] ■

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