The Extent of Thyroidectomy in Differentiated Thyroid Cancers- Revisited with Evidence

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ABSTRACT

Differentiated thyroid cancer has become increasingly prevalent in clinical practice. Papillary and follicular thyroid carcinoma are mainly included in this category. They are generally slow growing, and their prognosis is usually excellent. Contemporary management of differentiated thyroid cancer requires a multidisciplinary approach. The initial treatment is surgery. The current guideline focuses on risk stratification of patients with papillary thyroid cancer to guide the treatment strategy. Hence, the choice of initial operative treatment relies much on the tumor size. Thyroid lobectomy is preferred for small tumors less than one cm in size, unifocal, intrathyroidal papillary thyroid carcinoma without aggressive risk features. Total thyroidectomy is offered to patients for extrathyroidal extension, multifocal disease, aggressive risk features, size more than 4 cm, lymph node metastasis, distant metastasis, family history of thyroid cancer or genetic syndromes or childhood radiation.

Keywords: Thyroid Cancer, Thyroidectomy, Indeterminate Nodule, Molecular Testing, Lobectomy

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INTRODUCTION

Differentiated thyroid carcinoma includes papillary and follicular thyroid carcinoma, derived from follicular cells of epithelial origin. There has been a recent increase in the incidence of differentiated thyroid carcinoma globally owing to increase in incidental detection rate. Surgery is considered to be the primary modality of management. The extent of surgery varies from lobectomy to total thyroidectomy, depending on multiple risk factors. This paper intends to summarize the evidence concerning the extent of thyroidectomy in differentiated thyroid carcinoma. Here, we have scrutinized all the available literature with reference to tumor dimension, type of surgery and prognosis.

Selection of Thyroidectomy: The management of thyroid cancer involves a multidisciplinary team decision. The treatment should be individualized and based on multiple factors like the image finding of a thyroid nodule, presence of lymph node, distant metastasis, family history of thyroid cancer, hereditary syndrome, history of radiation in childhood, baseline thyroid level, contralateral thyroid nodule, patient preference and follow up availability. Previous American Thyroid Association (ATA) guidelines suggested total thyroidectomy for all differentiated thyroid cancer more than one cm in size with or without nodal or distant metastases.[1] This recommendation was based on Bilimoria et al. retrospective study, which suggested that the total thyroidectomy would improve survival,[2] decrease recurrence rate,[3-5] allow for radioiodine remnant ablation and help in the detection of residual/recurrent disease during follow up. Clinical outcomes are comparable in appropriately selected patients.[6-10] Routine use of radioiodine ablation(RAI) in low and intermediate risk was the important criterion for total thyroidectomy initially, which has been critically analyzed by many studies recently and

favours selective use of RAI after assessing the risk factors.[11-13] Presently the follow-up strategy strictly relies on an ultrasonogram (USG) of the neck and serial thyroglobulin assessment periodically; hence, choosing total thyroidectomy in lieu of an RAI scan and treatment is questionable.

Active surveillance versus Thyroidectomy: Active surveillance involves closely monitoring thyroid cancer over time instead of treating it with immediate surgery. Ito et al. observed that most micropapillary thyroid carcinoma grows very slowly; this subset may be monitored by the tumor growth rate. Surgery is indicated when the tumor progression signs are present. Based on this observation, active surveillance was recommended for papillary thyroid microcarcinoma without any risk factor.[14]

Various studies have supported the role of active surveillance in papillary thyroid carcinoma less than one cm, without clinically detected nodal and distant metastasis, no aggressive histology, without having the possibility of invading trachea or recurrent laryngeal nerve or with absent signs and symptoms of recurrent laryngeal nerve and trachea involvement.[14-17]

Lobectomy: Current ATA guidelines suggest lobectomy alone for unifocal tumors less than four cm without extrathyroidal extension and without lymph nodes and distant metastases in the absence of head and neck irradiation and family thyroid carcinoma history.[18] Vaisman et al. suggested that properly selected differentiated thyroid cancer patients with more than one cm size can be treated with lobectomy with excellent clinical outcomes.[19]

Evidence supporting Lobectomy: Nixon et al., in their 882-patient series of pT1-T2 well-differentiated thyroid cancer, found no difference in local or regional recurrence between lobectomy and total thyroidectomy. Multivariate analysis in his study showed that age over 45 years and male gender were independent predictors for poorer OS, whereas T stage and type of surgery were not.[10]

Adam et al. reported a series of 61,775 patients and said that after multivariable adjustment, overall survival was similar in patients undergoing total thyroidectomy versus lobectomy for tumors 1-4 cm. Older age, male sex, black race, lower income, tumour size, and presence of nodal or distant metastases were independently associated with compromised survival. These findings question whether tumor size should be an absolute indication for total thyroidectomy.[20] Matsuzu et al. concluded in their long-term follow-up study of 1088 cases that lobectomy is a valid alternative to total thyroidectomy for papillary thyroid carcinoma with 4 cm or less in size without clinically detected node and distant metastasis in patients less than 45 years.[6] The National Comprehensive Cancer Network (NCCN) guidelines recommend that thyroid. lobectomy can be an initial surgery for patients with DTC ≤4cm without prior history of radiation exposure, distant metastasis, cervical LN metastasis or ETE upon preoperative or intraoperative evaluation.[21]

There needs to be more high-quality data on this topic across the literature. Pinto et al. reported overall comparative survival for low-risk PTC patients who underwent lobectomy compared to total thyroidectomy. The locoregional recurrence (LRR) rate following lobectomy was less than 6% and salvaged with the completion thyroidectomy and concluded initial operative approach did not have a negative impact on overall survival. Long-term follow-up studies on oncologic and patient-centred outcomes are essential.[22]

The main reason lobectomy seems preferable to total thyroidectomy is that total thyroidectomy is more frequently associated with postoperative complications, including hypoparathyroidism and recurrent laryngeal nerve damage. Nevertheless, these complications have a low incidence in expert hands[23] Permanent hypoparathyroidism has been reported to range from 0 to 5.3%.[24] Jeannon et al. described a 9.8% of laryngeal nerve palsy incidence during the postoperative time, which decreases up to 2.3% during the follow-up in all patients because of the recovery of nerve function.[25]

Total thyroidectomy: The present ATA guideline strongly recommends total thyroidectomy for size more than 4 cm or gross extrathyroidal extension (clinical T4) or clinically detected metastatic disease to nodes (clinical N1) or distant metastases (clinical M1).[18]

Evidence supporting total thyroidectomy: Mazzaferri et al. reported 576 patients data in 1977 and observed that cancer-related death and recurrence were significant who underwent less than thyroidectomy.[26] They further expanded the number to 1355 patients and presented the result in 1944 patients stating that

improved outcome is related to more aggressive surgery.[27] Hay et al. analysed 1685 patients with low risk according to MACIS (metastasis, age, completeness of surgery, invasion and size). They reported no difference in the cause-specific mortality but significantly higher locoregional recurrences who underwent lobectomy. In their series, patients with intrathyroidal tumor and node-negative who underwent lobectomy had significant loco-regional recurrence.[29] A detailed analysis of 1000 patients' pathological data was presented by Kluijfhout.[31] He demonstrated that, of the patients who underwent total thyroidectomy for 1-4 cm tumor size as per ATA risk, 287 would have a lobectomy. But histopathology showed 43% would have required completion thyroidectomy with respect to aggressive pathology (3%), vascular invasion (12%), positive central neck node (17%), extrathyroidal extension (17%) and ipsilateral multifocality (25%). In 1-2 cm tumors, 36% would have needed completion thyroidectomy. 48 % would have required a total thyroidectomy based on pathology even after precluding bilateral nodules preoperatively. Hence, he suggested lobectomy should be considered only after excluding all possibilities.

Proponents of total thyroidectomy state that papillary thyroid carcinoma has a high risk of multifocal and multicentric disease with high chances of occult involvement of the contralateral lobe. Pacini et al. reported 44% of patients with one or more tumor foci in the pathology of completion thyroidectomy patients. They concluded that bilaterality is not associated with low and high-risk stratification and suggested doing total thyroidectomy in all papillary thyroid carcinoma diagnosed preoperatively.[30] Pitt et al. demonstrated that multifocal disease in the ipsilateral lobe has a high chance of tumor foci in the contralateral lobe, and contralateral lobe involvement is unrelated to primary tumor size.[31] Koo et al. also reported occult contralateral lobe involvement in unilateral papillary thyroid carcinoma in 16 % of cases. They proposed that multifocality in unilateral tumor and the presence of nodules in the contralateral lobe by preop evaluation can predict the occult contralateral lobe involvement.[32]

Molecular testing in indeterminate thyroid nodules: Extent of surgery in Atypia of undetermined significance or follicular lesion of undetermined significance (Bethesda Category III) or Follicular neoplasm or suspicious for follicular neoplasm (Bethesda Category IV) depends on clinical and radiological features. Molecular testing may be used to boost the malignant risk assessment for assessing the surgery. A 'Rule in' test is the one with high specificity and high positive predictive value (PPV). A 'positive' test has the high possibility that the disease is present. 7-gene specific mutation panel has been validated as an effective "rule-in" cytomolecular test for thyroid malignancy based on the high specificity and Positive Predictive Value (PPV) but it has not been considered an effective "rule-out" test because of low sensitivity. Nikiforov et al. reported 57% sensitivity and 97% specificity for Bethesda IV nodules. A positive test result (the PPV) increased the cancer risk to 88% for Bethesda III nodules and 87% for Bethesda IV nodules, whereas the absence of a mutation or fusion was associated with a cancer risk of 6% (NPV, 94%) and 14% (NPV, 86%) respectively.[33]

A 'Rule out' test is one with high sensitivity and high Negative Predictive Value (NPV). It will rule out the presence of the disease. A 'negative' test will reassure the patient that the cancer is not present. As per NCCN guidelines a "good" test should rule out cancer in 95% of cases. A gene expression classifier (GEC) was developed as a rule out test with the objective of having high sensitivity and negative predictive value to further classify cytological indeterminate thyroid nodules into either benign or suspicious categories. Alexander et al. found the negative predictive value of GEC result were 95%, 94%, and 85% for Bethesda III (atypia of undetermined significance/follicular lesion of undetermined significance), IV (follicular neoplasm/suspicious for follicular neoplasm), or V (suspicious for malignancy) respectively and with rates of malignancy among the 3 categories of 24%, 25%, and 62%, respectively.[34]

It is important to keep in mind that the validation studies for all molecular methods involve very small numbers of malignant nodules[35] and they are quite expensive. Their precise role in routine clinical practice continues to be a contentious issue. Majority of the studies in this context are retrospective, and impact of these mutations is not independent of other prognostic factors making the interpretation difficult. The feasibility in the Indian context is doubtful when the cost of such testing is considered.

Completion thyroidectomy: As per recent ATA guidelines, completion thyroidectomy is indicated for whom a total thyroidectomy would have been recommended had the diagnosis been available before the initial surgery. It may be necessary when the diagnosis is made following lobectomy for an indeterminate or non-diagnostic biopsy. Sometimes it is done to furnish complete resection of multicentric disease and to facilitate efficient RAI therapy.[18]

The completion thyroidectomy is not always indicated in low-risk intrathyroidal papillary or low-risk follicular thyroid carcinoma.[18] Murthy et al. conducted a retrospective study of patients who underwent total thyroidectomy for differentiated thyroid cancer (DTC) with tumors measuring 1 to 4 cm with no known preoperative adverse features and found that 59.1% of patients may require a completion thyroidectomy if unilateral lobectomy is done in tumors measuring 1 to 4 cm based on current ATA guidelines.[36] The surgical risk for completion thyroidectomy is similar to one-stage total thyroidectomy.[37]

CONCLUSION

Understanding differentiated thyroid carcinoma's biology and adapting treatment strategies based on risk factors is important. An attempt should be made to provide early definitive management in high-risk patients while avoiding overtreatment and its obligatory side effects in low-risk patients. The ATA guideline provides a personalized risk-based approach to manage differentiated thyroid cancer. Eventually, it requires discussion with the patient regarding all available options with their benefit and harm. The approach of using molecular markers to decide on he extent of thyroidectomy may not be feasible in India, due to the financial constraints.

END NOTE

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