Case for staged thyroidectomy

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Abbreviations: PTC, papillary thyroid cancer; WDTC, well-differentiated thyroid cancer; RLN, recurrent laryngeal nerve; FNA, fine-needle aspiration; RAI, radioactive iodine; ETE, extrathyroidal extension.

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**Abstract**

Recent modifications in the management of well-differentiated thyroid cancer have resulted in significant alterations in clinical approach. Utilizing a series of preoperative and postoperative risk factors involving both the patient and the disease pathology, we offer the term “staged thyroidectomy” to help organize these risk factors for patients and the endocrine team to optimize management. This approach is intended to incorporate our latest nuanced understanding of certain endocrine pathology and may serve to optimize patient outcomes.

**KEYWORDS**

completion thyroidectomy, morbidity, partial thyroidectomy, total thyroidectomy

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1 | INTRODUCTION

The mainstay of thyroid cancer therapy is surgery, either a total or a partial thyroidectomy. The latter includes such terms as hemithyroidectomy and thyroid lobectomy with isthmusectomy. The choice between the unilateral and bilateral surgery is typically based on risk characteristics of both cancer and patient. Guidelines outlining these factors have been recently updated by the American Thyroid Association (ATA) and the National Comprehensive Cancer Network (NCCN).1,2 The only time that the ATA and NCCN advocate total thyroidectomy over thyroid lobectomy as first-line therapy for well-differentiated thyroid cancer (WDTC) are as follows: tumors >4 cm, extrathyroidal tumor extension, a family history of thyroid cancer, and previous neck irradiation. Previously, based on earlier iterations of these guidelines, total thyroidectomy was recommended for all but the lowest risk thyroid cancers. As such, total thyroidectomy was recommended as initial therapy in most cases of thyroid malignancy.

Total thyroidectomy implies performing a single operation with or without the use of intraoperative frozen section histologic analysis. The alternative strategy for patients with lower risk disease is to perform a partial thyroidectomy, following which a postoperative decision is made to perform a completion thyroidectomy of the contralateral lobe as a second-stage procedure based on specific indications.

The undeniable advantage of performing a lobectomy is to decrease operative morbidity. The risk of transient and permanent hypocalcemia is almost zero after lobectomy as is the risk of bilateral recurrent nerve paralysis.3 Typically, completion thyroidectomy is performed when the risk of clinically relevant cancer in the contralateral lobe is high,4 as well as to facilitate radioactive iodine (RAI) use, when this adjuvant treatment is indicated. The latter is used for radioablation of residual normal thyroid tissue and allows for detection of recurrent/persistent disease with 131I whole-body scanning. Ablation of all normal thyroid tissue enables accurate posttreatment biochemical monitoring of the level of serum thyroglobulin. Some argue that biochemical monitoring may still be of value for patients who have not undergone total thyroidectomy.5 In these cases, serum thyroglobulin has less sensitivity when compared with patients without thyroid remnant tissue.6 Many studies have shown that the risk of surgical complications after completion thyroidectomy is not higher than after initial total thyroidectomy.7-10

For papillary thyroid carcinoma (PTC), trends have changed with regard to how much thyroid tissue should be removed in the initial surgery. For example, Hirshoren et al found that upfront total thyroidectomy was performed in the majority of patients (61%) prior to the 2015 American Thyroid Association revised guidelines compared to only 31% following these recommendations.11 The decrease corresponded to a nearly 10-fold increase in the rate for partial thyroidectomy. However, there was no corresponding increase in completion thyroidectomy (8.3% vs 7.9%), and oncologic outcomes appeared to be unchanged.12

With this background, we believe that it has become appropriate to perform surgery in a staged approach for preoperatively low-risk PTC using an algorithm based on a series of risk parameters. We have chosen to use the
term “staged thyroidectomy” for this strategy. This incremental approach is distinct from the staged thyroidectomy recommended for patients whose intended procedure of total thyroidectomy is aborted because of unexpected complications during the surgery. Furthermore, our use of the term staged thyroidectomy should not be confused with the need to reoperate for recurrent disease following a total thyroidectomy.\textsuperscript{7,13-15}

2 | DECISION-MAKING PROCESS IN THE STAGED THYROIDECTOMY APPROACH

Patients presenting with WDTC are usually diagnosed based on the results of fine-needle aspiration (FNA). To further decide on the extent of thyroid surgery, two broad categories of risk parameters should be considered: pre-treatment of available characteristics (patient history, TNM staging, family history, FNA pathology, ATA risk group); and postpartial thyroidectomy findings. The latter scenario includes histopathology and surgical morbidity (Figure 1).

Each of these characteristics will be addressed as follows:

2.1 | Pretreatment parameters

2.1.1 | Patient characteristics

1. Clinical findings: Certain characteristics found during the evaluation may indicate that a total thyroidectomy is optimal. These include concurrent laryngeal paralysis, stridor, or a rapidly enlarging thyroid mass.

2. History of radiation exposure: Total thyroidectomy continues to be the operation of choice for patients who had the combination of a history of radiation exposure to the thyroid gland and a thyroid nodule/mass that is positive for PTC. Nikiforov has published an extensive review on the data from the Chernobyl accident\textsuperscript{16} from which important observations were made. These include the following: exposure to ionizing radiation increases the risk of PTC and the risk is dose dependent, younger children are more prone to develop cancer after exposure; cancer development can have a latency as short as 4 years; and the molecular basis for carcinogenesis is chromosomal rearrangements, such as RET/PTC.\textsuperscript{16} Thus, patients presenting with a thyroid nodule and a history of radiation exposure should have an FNA, and if positive should undergo an upfront total thyroidectomy based on a higher risk for contralateral disease.

3. Family history: Although there is a higher risk for malignancy when other family members have a record of a WDTC,\textsuperscript{17,18} the true entity of familial WDTC requires at least two additional first-degree family members to be affected.\textsuperscript{19} Included are syndromes that are associated with a higher incidence of differentiated thyroid cancer such as Cowden’s disease and Werner syndrome.\textsuperscript{20} However, there is no consensus on the aggressiveness of the cancer among these latter patients. Nonetheless, on an individual basis
after patient counseling, it is justified to recommend a total thyroidectomy primarily because the genetic substrate of the disease implies that the entire thyroid gland and all nodules within it are suspect.

4. Age: Although it is relevant that older age is associated with a more advanced T classification and stage group, it has not been shown to affect overall or cause-specific survival in low-risk patients who undergo a total compared to a partial thyroidectomy.21 Furthermore, older patients with intrathyroidal microPTC are considered to be good candidates for active surveillance protocols.22 High-risk older patients should be considered for an upfront total thyroidectomy.23 Thus, specific individual circumstances become very important such as the influence of comorbidity in the elderly and its risk for having a second surgery, and the presence of other high-risk factors.

2.1.2 Tumor characteristics

1. Size: This has now become an important determinant for deciding whether to perform a staged thyroidectomy. Based on the analysis of patients who undergo partial thyroidectomy for a PTC with a diameter less than 4 cm, with unifocal disease, no extrathyroidal extension (ETE), and no lymph node metastases, studies have shown that the overall survival rate is similar to those treated with a total thyroidectomy.21,24,25 Furthermore, a recent analysis of over 60,000 patients from the National Cancer Database has demonstrated that there is no survival benefit for patients with a well-differentiated PTC smaller than 4 cm who undergo a total thyroidectomy.26 In contrast, one recent survey indicated a preference to use the 2 cm cutoff rather than 4 cm for recommending total thyroidectomy,27 while another survey, albeit prior to the 2015 ATA guidelines, found that 61% of participants favored a total thyroidectomy for unifocal intrathyroidal microcarcinomas.28 Such reports underscore the variability in attitudes that may occur between data-driven guidelines vs practical surgical application and personal philosophy.

2. Bilateral disease: The known presence of PTC involving both thyroid lobes will dictate an upfront total thyroidectomy. However, if there is a lesion, either single or multiple, in the contralateral lobe in a patient with PTC, the decision to perform a total thyroidectomy may be tempered based on the degree of certainty of bilateral malignant lesions. For example, a contralateral single nodule that is benign on FNA without suspicious ultrasound characteristics does not necessarily dictate removal. Also, the size of the contralateral nodules may impact on the decision-making. Careful patient counseling is important, balancing the potential for complications associated with total thyroidectomy against the need for lifelong monitoring of contralateral nodules.

3. FNA: Although not commonly encountered, cytologic analysis may reveal features indicative of a PTC variant with more aggressive behavior. These include hobnail, tall cell, columnar, and solid variants. However, such variants are more often diagnosed on histopathology. Classically for these tumors that are considered as “intermediate risk” according to the ATA, the option of a total thyroidectomy is generally retained.29-31 In particular, the tall-cell variant of PTC is more likely to present with multifocal and bilateral disease, thus the indication becomes more compelling under such circumstances.32 The removal of all thyroid tissue is justified for most tall-cell and other aggressive variants based on a higher likelihood for ETE. This biologic aggressiveness results in lower rates for local and regional control as well as metastatic-free and disease-free survival.33 As a result, adjuvant RAI is routinely recommended in such cases, which again necessitates total thyroidectomy.

4. Lymph node involvement: When lymph nodes are suspected, an FNA for cytology as well as a biochemical measurement of thyroglobulin of the needle washout is recommended. The presence of positive lymph node disease will influence the need for a total thyroidectomy and a neck dissection.34 Patients with proven nodal metastases preoperatively are likely to have RAI recommended, and as a result total thyroidectomy is required. In particular, the paratracheal lymph nodes should be evaluated preoperatively and again intraoperatively. Appropriate frozen sections may be obtained. The cutoff number of involved lymph nodes of prognostic significance is five, while patients harboring more than five metastatic nodes are at a higher risk for recurrence.1 However, if there are multiple positive nodes at the time of initial surgery in the paratracheal area, one would definitely consider total thyroidectomy at the same time.35 Every patient undergoing lobectomy should be consented and appraised of the possibility for extending the procedure to a total thyroidectomy. The central neck is seen poorly by ultrasonography with sensitivity of 26%, that is, many small metastatic lymph nodes in the central compartment are not diagnosed.36 Lesnik et al showed that combined ultrasonography and computed tomography (CT) significantly expanded the scope of surgery in a quarter of patients with PTC, both in primary and revision surgeries when known lymph nodes are present. Physical examination for the presence of nodes has low yield even at the hands of experienced surgeons.36
5. Molecular testing: If preoperative molecular testing is done, the combination of BRAF and TERT promoter mutations can facilitate the decision to perform an upfront total thyroidectomy. Patients with coexisting BRAF and TERT mutations are at high risk for ETE and nodal metastases. Although there is a lack of studies on the rare cases of micro-PTC with a combination of BRAF and TERT mutations, due to the reported aggressiveness of these tumors, a completion thyroidectomy, and possibly RAI, should be discussed in a multidisciplinary tumor board setting.

6. Extrathyroidal extension (ETE): In case of suspected macroscopic ETE on preoperative evaluation, either clinical such as vocal cord paralysis, or on ultrasound, one should consider upfront total thyroidectomy, irrespective of tumor size. Ultrasound features raising concerns of high risk include nodule size, its composition, shape, margins, echogenicity, and the presence of echogenic foci. Contralateral findings as well as cervical lymphadenopathy are discussed earlier. Except for gross ETE and significant lymphadenopathy, the other features on ultrasound are not by themselves an indication for a total thyroidectomy. It should be noted that often in patients with poorly differentiated thyroid cancer, the role of completion thyroidectomy is debatable as these patients are typically not sensitive to RAI and the use of RAI in these patients remains controversial. These patients may require external beam radiation therapy and long-term follow-up with a positron emission tomography (PET) scan. They are generally elderly patients with poorly differentiated thyroid cancer where the prognosis is unlikely to relate to staged or completion thyroidectomy.

### 2.2 Postpartial thyroidectomy parameters

#### 2.2.1 Histopathology

There are several ATA intermediate-risk or high-risk histologic features that may require the patient to proceed to a completion thyroidectomy. These include the following:

1. The histologic diagnosis of an aggressive variant of PTC, such as hobnail, tall cell, columnar, and solid, is an indication for the complete removal of the thyroid gland or completion thyroidectomy.
2. The presence of multicentric malignant foci when diagnosed on the histopathologic examination of the resected specimen presents an increased risk factor for residual disease involving the contralateral lobe. For example, Ibrahim et al found that multiple foci in the initial specimen formed the only variable independently associated with bilateral disease. However, subsequent reports have shown that the contralateral lobe rarely contains high-risk disease if the ipsilateral lobe has multicentric disease. While the prognostic importance of multicentric PTC may be controversial, strong consideration should be given to performing a total thyroidectomy when the multicentric nodules are larger than 1 cm.

3. The presence of macroscopic extracapsular extension (ETE) when documented on histopathologic examination is justification for performing a completion thyroidectomy, although this is likely to have been recognized intraoperatively. Unlike posterior ETE that interfaces with the trachea, esophagus, or recurrent laryngeal nerve (RLN), anterior ETE that invades the strap muscles can be often recognized preoperatively and does not influence recurrence and survival in patients with WDTC. When ETE is suspected, CT scan may be a valuable tool to appreciate invasion to adjacent structures, preferably in combination with an ultrasound scan. While it may be possible to recognize some cases of ETE on preoperative ultrasound, some cases will only be diagnosed or confirmed on the pathology examination of the resected specimen. A finding of microscopic ETE in not an indication for total or completion thyroidectomy.

4. Angioinvasion is a characteristic that is diagnosed histologically, and usually its presence is unknown preoperatively. For patients who undergo partial thyroidectomy based on a preoperative diagnosis of a follicular or Hürthle cell neoplasm, and final pathology shows significant angioinvasion, completion thyroidectomy is recommended along with diagnostic and therapeutic RAI for the potential risk of distant metastasis. Higher risk patients require a completion thyroidectomy to facilitate RAI management. Generally, it is considered that four areas of vascular invasion form an acceptable cutoff for RAI vs no RAI.

5. As discussed earlier, there is some evidence that the combination of BRAF and TERT promoter mutation warrants a completion thyroidectomy of the contralateral lobe due to the aggressive nature of this subset of tumors.

6. The presence of positive lymph node disease when detected following a partial thyroidectomy warrants a completion thyroidectomy with an appropriate neck dissection in selected patients according to the size and number of metastatic lymph nodes, which determines the ATA-risk group. When positive perithyroidal lymph nodes are accidentally included in
the specimen, and later found to harbor small volume metastatic disease, observation is an acceptable option.35

In contrast to identifying high-risk parameters based on the histopathology, a small percentage of patients will be found to have benign histology even though the pre-operative FNA was suspicious or definitively positive. Both the Bethesda system for reporting thyroid cytology results53 and the Thyroid Imaging, Reporting and Data System (TIRADS)38 carry less than a 100% specificity outcome. Frozen section results also do not always correlate with the final pathology report.54

2.2.2 | The impact of surgical complications

1. The risk of postoperative hypocalcemia does influence the decision in selected patients to perform an upfront total thyroidectomy. While transitory hypocalcemia is uncommon after hemithyroidectomy, up to 68% of patients undergoing total thyroidectomy will experience this complication.55-58 Fortunately, most of these patients will regain their parathyroid hormone levels if related to a perfusion insult to the parathyroid glands during the dissection, or traction of the glands and ligation and excision of their blood vessels. However, some patients with hypocalcemia necessitate prolonged hospitalization with administration of intravenous calcium and vitamin D supplements. Many studies have been conducted trying to successfully predict and isolate those patients who are susceptible to develop hypocalcemia thus prolonging hospitalization. Among patients who have relevant comorbidities, a staged thyroidectomy should be considered in which the contralateral thyroid lobe is excised in a delayed procedure. This gives the parathyroid glands of the ipsilateral side time to recover, thus reducing the risk of postoperative hypocalcemia, as well as allowing time in this vulnerable group to fully consider the histopathological report and confirm the potential benefit of completion thyroidectomy. This was demonstrated in a retrospective study, where the rate of transient hypocalcemia in patients undergoing hemithyroidectomy followed by completion thyroidectomy was found to be lower than in patients undergoing upfront total thyroidectomy.58

2. RLN injury: An inherent risk of thyroid surgery is injury to the superior and RLNs. If vocal cord paralysis occurs following a partial thyroidectomy, careful consideration should be given to performing a completion thyroidectomy when indicated based on risk factors. If the paralysis persists, it is reasonable not to perform a completion thyroidectomy provided alternative treatment of the disease can be achieved using RAI therapy.59,60 Thus, the risk of bilateral vocal cord paralysis and its severe morbidity can be eliminated in many cases. Relative to this discussion is the importance of assessing the status of vocal cord mobility prior to thyroid surgery, particularly second stage surgery. Furthermore, the presence of nerve invasion in a patient presenting with PTC is indicative of disease that is biologically more aggressive tumor. Under such circumstances, a comprehensive compartmental dissection of the central compartment should be performed on the side of the nerve invasion. In the same patient, if total thyroidectomy is essential, extreme care is necessary to avoid the consequence of bilateral vocal cord paralysis. Such patients should ideally be referred to high volume centers. However, if a unilateral vocal cord paralysis occurs during a partial thyroidectomy, the contralateral nerve is not put at immediate risk. Consequently, the option remains for not performing a completion thyroidectomy until the risk-benefit ratio can be reassessed. RLN injury is often suspected during surgery with the aid of intraoperative RLN monitoring and posterior cricoarytenoid muscle palpation, in which case an intraoperative decision can be made to abort removing the contralateral thyroid lobe.59,61 Following the partial thyroidectomy with resultant RLN injury, the patient, the surgeon, and the endocrinologist will have a more concise and informed discussion on the risks vs the benefits of a completion thyroidectomy.59 A patient undergoing a partial thyroidectomy in which the ipsilateral RLN becomes injured has the option of foregoing additional surgery (completion thyroidectomy) to avoid the risk of needing a tracheostomy. Influencing this decision following a partial thyroidectomy is the possibility that the RLN can regain its function spontaneously, thus permitting a completion thyroidectomy.

While some studies demonstrated that the timing of a completion thyroidectomy does not affect the complication rate,62 others have shown that a delayed procedure has a lower complication rate.63 Regardless of the controversy of when to operate, completion thyroidectomy should be performed based on the relevant pathology, physical findings (RLN function), and parathyroid function.64

There has been some interest in ablation of the contralateral lobe using a larger dose of RAI in highly selected patients who definitely require completion
thyroidectomy. Potential candidates are either not suitable for completion thyroidectomy due to comorbidities or ipsilateral nerve paralysis, and the patient and the physicians do not want to take a chance of injuring the nerve on the opposite side. A dose of 30 mCi of RAI may ablate the opposite lobe although a larger dose may subsequently be required.60,65

3 | ECONOMIC AND PSYCHOSOCIAL CONSIDERATIONS

The main disadvantage of a staged procedure is the inconvenience and added risk of having a second operation. Using the present algorithm as outlined based on risk factors, a minority of patients (8%-30%) will require this.64,66 However, performing a second surgery in a staged thyroidectomy approach does reduce the risk of surgical complications, particularly for hypocalcemia. In a cost-effectiveness analysis done prior to the ATA 2015 guidelines, total thyroidectomy was found to be superior over hemithyroidectomy.67 However, recent cost-analysis studies were done for patients with low-risk PTC, based on the assumption that one half of the patients would require a completion thyroidectomy. Cost-effectiveness analyses found that thyroid lobectomy was more expensive than total thyroidectomy but had a higher quality-adjusted life year (QALY) score and thus more cost effective. The lobectomy cost was $2577 more per QALY than total thyroidectomy, which is well within the social acceptable range for improved quality of life based on cost.68,69 In another recent decision analysis model for low-risk PTC patients, hemithyroidectomy was found to be superior to total thyroidectomy based on quality-of-life parameters.70

The requirement for thyroid replacement therapy presents additional issues. Patients undergoing total thyroidectomy may have difficulties in adjusting to synthetic thyroid replacement. Health-related quality of life may be affected by the patient including untoward surgical complications. This has been demonstrated in a systematic review and meta-analysis that found surgical complications having a significant and long-term impact on such outcomes.72 Additional support for a staged thyroidectomy approach can be gathered through the lens of qualitative analysis. A recent report of the personal needs of patients with thyroid cancer both after diagnosis and before surgery found that the anxiety levels of patients can be relieved when disease- and treatment-related information is individualized taking into account the aspects of their daily life.73

In the process of a staged thyroidectomy, ample time should be made available for patient counseling during each decision-making interval, thus allowing treatment to be tailored based on both disease parameters and patient needs.

4 | DISCUSSION

The term “staged thyroidectomy” has been previously reported but not in the same context as described here. Randolph et al used this term to describe intraoperative situations in which the risk-benefit ratio for performing a total thyroidectomy became adverse following an unexpected complication such as RLN injury.74 Thus, the intended procedure can be aborted following the ipsilateral lobectomy leaving the contralateral lobe to be either removed later or ultimately deferred. In contrast to this “aborted” scenario for staged thyroidectomy, we propose expanding the use of the term for the “sequential” scenario as described. Thus, staged thyroidectomy refers to the process of sequential risk analysis, and the thyroid surgery when indicated is performed in an incremental fashion. Also, within the context of this latter strategy, sequentially staged thyroidectomy could be applied to benign thyroid surgery to minimize complications such as staging surgery for patients with massive bilateral thyroid goiters or the excision of chronically inflamed thyroid glands as seen in severe Hashimoto’s thyroiditis.

Treatment planning for patients requiring prolonged complex surgery or who have severe comorbidities should take into account the risk vs the benefit of performing a staged thyroidectomy procedure instead of an upfront total thyroidectomy.74

It should be noted that most patients who receive thyroidectomy for WDTC are treated by “low-volume” surgeons performing less than 25 cases per year and are less likely to have multidisciplinary team involvement. Furthermore, complications are greater within “low-volume” centers and justify the use of lobectomy as the optimal choice for most low-risk WDTC patients.75,76

It is important to note that the resources for determining the criteria for risk analysis may not be uniformly available worldwide. Under such circumstances, modifications are necessary to ensure optimal care. Also of relevance is the need to adjust treatment decision algorithms for low-resource countries including the predominant reliance of surgery without ancillary therapy and minimizing postoperative complications through less
extensive surgery. Nonetheless, the decision-making process outlined does present a uniform approach for treating WDTC in most developed countries and encourages a standardized plan for treatment.

5 | CONCLUSION

The rationale for performing thyroid cancer surgery in a stepwise protocol based on a series of important risk factors is outlined. We offer to expand the indications for “staged thyroidectomy” to include this “sequential” process in addition to the previously described “aborted” situation. We conclude that the staged thyroidectomy approach is advantageous for a large proportion of patients with PTC and a select group with suspected follicular carcinoma despite the potential requirement for a second surgery resulting in repeat hospitalization and recovery. A staged procedure allows for a full histological analysis to be provided to determine further treatment and reduces the risk for hypocalcemia and bilateral vocal cord paralysis. This sequential or incremental approach provides the opportunity to assess the risk-benefit ratio for additional surgery. While the disadvantage of potentially requiring a second operation appears to be outweighed by the benefits outlined, treatment decisions are often not without risks and should encompass the wisdom of consensus by a multidisciplinary team as well as the concerns of the patient.

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