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REVIEW ARTICLE

Nuances in the Surgical Management of Thyroid Cancer

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Abstract
The incidence of thyroid cancer is rapidly rising, primarily due to the increased use of imaging studies and incidentalomas. In the USA, the incidence has quadrupled. The last decades have seen remarkable advances in diagnosis and surgery for thyroid cancer. We will discuss the surgical advances in this manuscript. The American Thyroid Association and many other organizations around the world have been quite instrumental in developing the guidelines for the management of thyroid cancer, which have streamlined the treatment approaches. There have also been advances made in the management of medullary and anaplastic thyroid cancer, which will be a different subject not included in this manuscript. The major surgical advances include the following: impact of molecular markers, risk group stratifications, de-escalation in surgery, nerve monitoring, and endoscopic surgery. We will discuss some of these surgical nuances in this review article.

Keywords Well-differentiated thyroid cancer · Surgical advances · Treatment of thyroid cancer · Risk groups in thyroid cancer · Molecular markers · Endoscopic thyroidectomy

Introduction

The incidence of thyroid cancer is rapidly rising all over the world, especially in developed countries such as the USA. There is also a remarkable rise in Southeast Asia, particularly in South Korea where ultrasound is routinely used for cancer screening and diagnosis. Due to public health recommendations against the routine use of ultrasound screening of the neck, the incidence of thyroid cancer appears to have stabilized in the USA over the last few years; however, the incidence has nonetheless almost quadrupled over the last quarter of a century. Today, we see approximately 44,280 new patients with thyroid cancer in the USA, while the incidence has risen by almost 15 times in South Korea [1, 2]. Interestingly, most new cancers that we see are primarily microcarcinomas below 1–2 cm and the outcome in this group is excellent. The mortality rate of thyroid cancer, which ranges between 1500 and 2200 deaths per year in the USA, has essentially remained unchanged and most of the deaths are attributed to aggressive or high-risk thyroid cancers.

It is critical to distinguish low-risk and high-risk thyroid cancer following the American Thyroid Association (ATA) risk stratification system, which classifies thyroid cancer as low, intermediate, or high risk, also sometimes referred to as the good, bad, and ugly [3]. The survival rate in the low-risk group exceeds 99%, while mortality in high-risk thyroid cancer is approximately 30% and one needs to be more aggressive in this group of patients where the treatment choices and multidisciplinary approaches have a direct impact on the long-term outcome. The debate continues related to the extent of thyroidectomy, prophylactic central compartment dissection, and use of radioactive iodine (RAI) for low-risk thyroid cancer patients. However, we need to focus our attention and resources on the evaluation and management of high-risk thyroid cancer rather than low-risk where the treatment choices have very little impact on the long-term outcome. This probably is related to the identification of the small thyroid cancers that would have remained undetected during the patient's life. Although it remains somewhat unclear what would happen to these tumors over a long period of time, our experience from the active surveillance study has shown that these small tumors may remain dormant for the rest of the patient's life and it is not uncommon

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to find microscopic thyroid cancer in autopsy studies. While the overall incidence of microscopic thyroid cancer in the USA is approximately 6%, in certain parts of the world, it is as high as 30–35%, especially in Finland and the Philippines. Whether there is truly an increasing incidence of thyroid cancer, especially in advanced stages, remains somewhat debatable. Notably, the number of thyroidectomies performed in South Korea increased remarkably from 2000 to 2014; however, in 2014, the physician coalition group recommended discontinuing the use of routine ultrasound examination, which previously had been used as a regular diagnostic study for the identification of thyroid cancer. With a drop in routine ultrasound of the thyroid, the incidence of thyroidectomies decreased almost 50% in South Korea, suggesting that these microcarcinomas may otherwise remain undetected during the patient's life.

Diagnostic Evaluation

The best diagnostic study is an ultrasound of the thyroid. Certain ultrasound features, such as hypoechoic, hypervascularity, taller than wider, microcalcification, and irregular margins, are important radiological features suggestive of a likely malignant thyroid nodule [4]. The ultrasound should be performed and interpreted by an expert to estimate the risk of malignancy or suspicious features described. Various systems, including the Thyroid Imaging Reporting and Data System (TI-RADS), have been developed to streamline ultrasound reporting. One of the most commonly utilized TI-RADS is described by the American College of Radiology, which uses a point-based approach. Although this system is somewhat complex and may not be used by every radiologist, it appears that this system is now routinely employed in the USA [5]. It is important to realize that the ultrasound should be performed in both the thyroid and the neck. The neck should be evaluated both for central compartment and lateral compartment lymph nodes. The central compartment lymph node evaluation may be somewhat difficult in the presence of the thyroid gland; however, the lateral compartment evaluation is extremely critical to make sure there are no suspicious lymph nodes, and if any are found, appropriate preoperative evaluation with a fine needle aspiration biopsy, cytology, and possible thyroglobulin assay in the aspirate is important. In certain patients with larger tumors that are clinically difficult to evaluate or who have symptoms such as hoarseness of voice that may indicate locally aggressive thyroid cancer, it is important to use computed tomography (CT) scans with contrast for further evaluation. There was considerable difficulty in accepting CT scans due to fears surrounding the use of contrast dye, which may delay RAI ablation a few weeks after the surgery; however, it should be remembered that the information gained from the CT scan is vitally important for the surgeon to optimize the surgical procedure [4]. More importantly, CT scans allow for appropriate identification and evaluation of gross extrathyroidal extension, which is probably the most important prognostic factor in the management of thyroid cancer. The third version of the ATA guidelines definitively endorsed the use of CT scans in select patients for better preoperative evaluation of primary thyroid tumor and also the neck nodes. The CT scan also defines occult areas of lymph node involvement such as high level II, retropharyngeal, parapharyngeal, and superior mediastinal lymph nodes in (level VI and level VII).

Fine Needle Aspiration Biopsy

Over the last few decades, fine needle aspiration biopsy has become the mainstay for evaluation of a thyroid nodule. Core biopsy is rarely performed now unless the patient is suspected to have either lymphoma or anaplastic thyroid carcinoma where the histopathological evaluation is more critical rather than cytology alone. The cytology reporting system has been streamlined since the introduction of the Bethesda system. This has been practiced in the UK for many years prior assigned as the THY reporting system; however, the Bethesda system, which is divided into six categories, has been universally accepted now. Approximately 25–30% of the results are Bethesda III and IV, which are indeterminate, where the risk of malignancy varies based on the Bethesda III and IV category and the radiological findings. These patients are probably best evaluated with ultrasound and recently with the introduction of molecular testing. A variety of molecular testing technologies have been developed, including the Afirma system by Veracyte and Thyroseq system by CBLPath and the University of Pittsburgh [6]. The molecular analysis will describe the overall risk of malignancy and, in select cases, the prognostic implications such as BRAF or TERT mutation where the risk of malignancy is high and some of these tumors may be more aggressive. However, these tests are not available globally and are prohibitively expensive to be used widely around the world.

NIFTP

Our understanding of the histopathological evaluation of the thyroid nodules has recently improved remarkably with better definition of minor and major extrathyroidal extension and encapsulated variant of papillary lesions. Nikiforov et al. termed this non-invasive follicular tumor with papillary-like nuclear features (NIFTP), suggesting the precancerous nature of these lesions with a long-term excellent outcome and lack of metastasis [7]. This clearly has once

again changed the risk of malignancy noted in the Bethesda classification system.

Intraoperative Evaluation of Thyroid Nodules

The thyroid surgeon's responsibility is to evaluate the exact extent of the primary disease and complete evaluation of the paratracheal and central compartment lymph nodes. Extrathyroidal extension needs to be classified as either minor or major, and patients with major extrathyroidal extension will require appropriate surgery with resection of all gross tumor (R0) to achieve the best surgical results. This will include resection of the involved structures, such as recurrent laryngeal nerve, trachea, or esophagus based on the extent of involvement [8]. If the tumor is only adherent to the trachea, the shave resection can be easily performed; however, if the tumor is invading the tracheal wall or the tracheal lumen, the surgeon must be prepared for appropriate sleeve resection and primary anastomosis of up to 4–5 rings of the trachea. If the trachea is involved in more than 5–6 rings, the management becomes extremely difficult and complex.

There has been substantial debate over the last decade as to the role of prophylactic central compartment dissection. Initially, after the first publication of the ATA guidelines, there was considerable enthusiasm for routine central compartment dissection and finding almost 40–50% positive lymph nodes; however, we need to realize this is a normality in well-differentiated thyroid cancer with very little prognostic implication. In the subsequent ATA guidelines, the recommendation was changed to selective use of central compartment dissection in patients with aggressive thyroid cancers, gross extrathyroidal extension, or large primary tumor size. We have noticed a higher incidence of central compartment nodal metastasis if the patient has a positive Delphian node and this area may be critically evaluated in the beginning of the surgical procedure, with frozen section. It should be noted that there is a high incidence of surgical complications related to temporary or permanent recurrent laryngeal nerve injury and temporary or permanent hypoparathyroidism in patients undergoing routine central compartment dissection, and this has been essentially abandoned as a routine surgical procedure.

Extent of Surgery for the Primary Tumor

The debate regarding lobectomy versus total thyroidectomy continues to generate considerable controversy and animosity worldwide. This has been fueled in the past with routine use of RAI and requirement of total thyroidectomy as a routine surgical procedure. However, with the identification and surgery for microcarcinomas and low-risk thyroid cancer, the consensus has changed, and lobectomy is considered to be a satisfactory surgical procedure.

Risk group stratification began with the initial publication of EORTC, and subsequently, many different systems were developed, including AGES, MACIS, AMES, and GAMES. Memorial Sloan Kettering Cancer Center developed a three-tiered system that includes low-, intermediate-, and high-risk groups, with mortality as an endpoint [9]. The ATA guidelines similarly grouped patients into low-, intermediate-, and high-risk groups based on the pathological features but refer to risk of recurrence as an endpoint. The basic prognostic factors include age of the patient, grade of the tumor, extrathyroidal extension, size of the tumor, and distant metastases. Age cut-off of 45 was used up to the 7th edition of the staging system; however, in the 8th edition, the age cut-off was increased to 55. Patients below the age of 55 are either stage I or II while patients above the age of 55 are divided into four-stage groupings [4, 10]. This is the only human tumor where age is included in the staging system, with only two stages (I and II) below the age of 55. This just describes the biology of thyroid cancer and the overall best long-term outcome. Recently, in the 2015 ATA guidelines, the ATA endorsed lobectomy as a definitive treatment in low-risk thyroid cancers up to 4 cm; however, preoperative evaluation and intraoperative identification of adverse features are very critical. The lymph node cut-off was used as five positive lymph nodes with less than 2 mm metastatic deposit as a good prognostic feature. The 8th edition of the staging system adheres to the biology of thyroid cancer, prognostic factors, and risk group stratification, based on which the treatment philosophy can be developed. The new staging system down-staged approximately 30% of the patients from stage III and IV to stage I and II [11]. It is important to appreciate that the complications of thyroid surgery may be worse than the disease itself and we should adhere to the standard approach to thyroid cancer: "let the treatment not be worse than the disease" or "let the punishment fit the crime." The synoptic reporting system of thyroid pathology is very critical to better understanding the prognostic factors in thyroid cancer. Once again, an appropriate distinction should be made between minor and major extrathyroidal extension with capsular and vascular invasion.

The number of foci of vascular invasion should be well described in the final pathology report for clinicians to make appropriate decisions regarding the use of adjuvant RAI. There appears to be considerable decline in the routine use of RAI, as it has not shown major impact in low-risk thyroid cancer and also adds complications related to salivary gland dysfunction, lacrimal problems, and concerns about increasing incidence of second primary tumors. Since RAI is not used routinely, the philosophy of

completion thyroidectomy has changed remarkably in the past few years and completion thyroidectomy is used only in select patients with gross extrathyroidal extension, multiple positive nodes, or aggressive histology with major vascular invasion, where patients may benefit from RAI. The patients are best followed postoperatively with routine use of thyroglobulin and ultrasound findings. One needs to be very careful in evaluating and treating patients presenting with locally aggressive thyroid cancer and gross extrathyroidal extension. The overall outcome is directly related to the resection of all gross tumor. The final pathology report will also direct the future management based on the number of positive nodes, the extranodal extension, gross extrathyroidal extension, and the pathological features of the primary tumor, including major capsular and vascular invasion and the histology. Patients presenting with poorly differentiated thyroid cancer are clearly at higher risk of local recurrence and may require adjuvant therapy, including external radiation therapy in select cases where the risk of recurrence is high and may be highly detrimental for best control.

Management of Recurrent Thyroid Carcinoma

Recurrent thyroid carcinoma may involve the primary site such as thyroid bed, nodal disease either in the central compartment or lateral neck, or distant metastasis. Elaborating on the management of distant metastasis, including the current role of targeted therapies, is beyond the scope of this surgical article. However, management of local recurrence and nodal recurrence is a direct implication of the initial extent of the disease and need for further adequate surgery, which will include resection of the recurrent tumor in the thyroid bed and appropriate nodal clearance of the central compartment or lateral node recurrence depending upon the location of the disease. Active surveillance may be considered in some of the smaller recurrences that are not plastered against the trachea or in the region of the recurrent laryngeal nerve. The risk and complications of the surgery of recurrent thyroid cancer are much higher, especially in relation to the parathyroid dysfunction and nerve injury. Utmost care must be taken for avoiding bilateral recurrent laryngeal nerve injury especially if the patient presents initially or in the follow-up with unilateral vocal cord palsy. If the recurrent tumor appears to be smaller than 1 cm, it may be most appropriate to monitor this, as finding these subcentimeter tumors may be difficult during surgery, with scarring and fibrosis with higher risk of injury to the nerve or inability to find the recurrent disease, which may be the most humbling experience for the operating surgeon.

Active Surveillance

Understanding and recognizing the high incidence of micropapillary carcinomas, which are truly low-risk thyroid cancers incidentally noted on other imaging studies or routine clinical examination, Miyauchi from Kobe, Japan, suggested active surveillance as a management option of continuous monitoring [12]. The reported series exceeds 1200 patients with excellent long-term results, with only less than 10% of the patients migrating to surgical intervention either because of increase in the size of the primary tumor, suspicious lymph nodes, or the demand for surgery from the patient. The experience from Memorial Sloan Kettering Cancer Center reported by Tuttle et al. mirrors the reports from Miyauchi et al., with only 5% of the patients requiring surgery during the follow-up [12, 13]. Unfortunately, this has not been picked up in the rest of the world yet; however, there are other institutions in the USA looking at this critically and suggesting active surveillance to patients with tumors less than 1 cm and no aggressive features. The majority of the patients will continue to live with these tumors with no active progression of the disease. This approach has been well practiced in prostate cancer, but it still has not become popular in thyroid cancer. Even though 1 cm has been used as a cut-off for observation by Miyauchi et al., we have gone "out-of-the-box" and used up to 1.5 and 2.0 cm in select patients, especially with co-morbidities, older age, or other confounding issues. Age has not been a limitation for active surveillance. However, one needs to recognize the biology of thyroid cancer especially in young patients where the tumor may increase in size and almost 50% of these patients in the second and third decade may require surgery in their lifetime. Older age is definitely not a contraindication for active surveillance. Actually, we have a large number of patients with tumors up to 2 cm being observed, especially older patients and those with other co-morbidities or previous active malignant issues. We also like to call this "deferred intervention."

Technology in Thyroid Surgery

Technology has always played an important role in the surgical procedures including major advances with laparoscopic cholecystectomy and other surgical procedures. Various technological advances are applied through the use of nerve monitoring; energy devices such as harmonic and LigaSure have made a major impact in thyroid surgery. Robotic applications have also played an important role in the extra cervical approaches to thyroid surgery especially

in certain parts of the world, where women are very concerned about the scar on the neck.

The intraoperative recurrent laryngeal nerve monitoring

The major complications of thyroid surgery revolve around the nerve injury and temporary or permanent hypoparathyroidism. The technological advances have helped monitoring of the recurrent laryngeal nerve during thyroid surgery. Various instrumentations are available through different companies and there continues to be a debate between the use of nerve monitor and incidence of nerve injuries. Even though these studies are difficult, and every surgical procedure is different, suffice it to say that the nerve monitoring is definitely helpful in re-operative thyroid surgery and in select primary surgeries. The gold standard is the identification of the recurrent laryngeal nerve and preserving the continuity of the recurrent laryngeal nerve. The nerve monitor does help to trace the entire nerve and, more importantly, the anterior branch of the nerve, which is an important motor branch. It is also helpful to determine the issue of contralateral lobectomy if the signal is lost. The international guidelines recommend aborting the surgical procedure on the other side to minimize the risk of bilateral nerve injury and airway-related issues. The entire philosophy of thyroid surgery revolves around the avoidance of bilateral nerve injury (temporary or permanent) and airway-related issues such as prolonged intubation or tracheostomy. The newer energy devices such as harmonic scalpel and ligature have been quite helpful. Once again, even though it may be difficult to prove their advantage, most of the surgeons who use these energy devices feel very comfortable using them in almost 90–95% of the procedure except near the recurrent laryngeal nerve for the fear of transmitting heat to the nerve.

However, it should be noted that these devices are routinely used in extra cervical endoscopic approaches with no higher risk of nerve injury. There continues to be debate regarding continuous vs intermittent nerve monitoring. Some researchers are quite comfortable with the routine exposure and continuous monitoring of the vagus nerve, while other surgeons feel uncomfortable to expose the vagus in every case.

Extra Cervical Endoscopic Approaches

Some patients are very reluctant to accept a scar on the neck; certain cultures may be particularly adverse—especially in young women—to accept a scar in the cosmetic location of the neck [14]. There was considerable interest in Southeast Asia for an endoscopic robotic approach, and a large number of procedures were performed with the bilateral axillary breast/areola approach (BABA) for thyroidectomy. Even though the reported complication rate in the literature is small, one would be concerned about the learning curve in these surgical procedures. There was considerable enthusiasm to visit the centers of excellence for robotic thyroid surgery and then practice this procedure in the surgeons' home institutions, but it may be extremely difficult to perfect these techniques having visited another center and then starting to apply it in your own center. The average number of cases in the learning curve varies between 40 and 50, and unless one has performed a fellowship, it may be very difficult to become an expert in these endoscopic surgical procedures. There are a few centers in the USA that are using endoscopic procedures including transaxillary robotic approaches and, more recently, transoral surgical procedures. Transoral thyroidectomy was started by Anuwong in Thailand and has become more popular recently with minimal complications and less frequent inferior alveolar nerve issues [15]. What remains unclear is whether one could evaluate the extrathyroidal extension with the endoscopic approach and if the lymph nodes can be properly evaluated or not. There has been some enthusiasm for using the post-auricular approach for thyroidectomy, essentially akin to the facelift approach. The future of these techniques remains unclear, as well as whether patients will be able to afford the high cost of these surgical procedures, especially when not paid by the insurance companies at least at this time.

A variety of ablative techniques have been used, both in benign and small malignant tumors, such as radio frequency ablation, laser ablation, and microwave ablation. There clearly is a learning curve for these techniques, and physician commitment is essential. Alcohol injection is another technique commonly used for nodal metastasis and, according to some reports, for primary tumors also.

BRAF-based targeted therapies have shown remarkable impact in the outcome of patients with anaplastic thyroid cancer, with excellent temporary response in reports from MD Anderson and other centers [16]. Whether this will be reflected in the long-term outcome and survival remains to be seen. The new ATA guidelines on anaplastic thyroid cancer were just published with an enormous wealth of information on the evaluation and management of anaplastic thyroid cancers, including ethical considerations in these most aggressive and lethal human tumors.

Complications of Thyroid Surgery

The success of thyroid surgery revolves mainly around managing potential complications. Thyroid surgery complications are directly proportional to the extent of thyroidectomy and inversely proportional to the surgeon experience. Major complications are related to postoperative hematoma leading

to airway issues, nerve injury, and temporary or permanent hypoparathyroidism. Superior laryngeal nerve injury is not as well described as recurrent laryngeal nerve injury, but it can be especially detrimental to professionals who use their voices daily, such as teachers, professors, lawyers, and singers. Every thyroid surgeon should be familiar with parathyroid autotransplantation if the parathyroid gland appears traumatized or compromised with its blood supply. Prior to autotransplantation, it is important to send a small piece of the parathyroid gland to confirm whether it is truly a parathyroid and not metastatic thyroid cancer. There appears to be sizable interest in the recent literature on autofluorescence imaging for identification of parathyroid glands during thyroidectomy and preserving its function, but whether these techniques will become common remains unclear.

Overall, thyroid cancer is a highly treatable tumor with excellent outcome. However, we do need to recognize the risk factors and identify who is likely to recur and succumb to thyroid cancer. Understanding the biology of thyroid cancer, analyzing the prognostic factors, and following a risk-based treatment plan are the key to optimizing outcomes and avoiding over- and undertreatment and treatment-related medical and surgical complications. Although thyroid surgery was once considered a "horrid butchery," William Halsted's statement that thyroid surgery represents "the supreme triumph of the surgeon's art" is much more appropriate.

Declarations

Competing Interests The authors no competing interests.

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