Surgical Decision Making in the Management of Well-Differentiated Thyroid Cancer

Natalya Chernichenko · Ashok R. Shaha

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Abstract The incidence of thyroid cancer in the United States has been increasing. The biologic behavior of well-differentiated thyroid cancer (WDTC) can vary from indolent tumor to an aggressive disease with invasion of critical structures and/or widespread distant metastasis. Therefore, the risk stratification is crucial in understanding the biology of thyroid cancer, its prognosis and appropriate therapeutic interventions. In fact, understanding the nuances of biological behavior of thyroid carcinomas lays the foundation for the idea of selective surgical management of this disease.

Keywords well-differentiated thyroid cancer · management

Introduction

The incidence of well-differentiated thyroid cancer has increased substantially over the past three decades, and an estimated 48,020 cases were diagnosed in the United States in 2011. In fact, thyroid cancer is the fastest increasing cancer in both men and women. The biologic behavior of WDTC can vary from an indolent tumor, incidentally detected at autopsy, to an aggressive disease with invasion into critical structures in the neck or widespread distant metastases with a 5-year survival of less than 50 %. [1, 2] Of note, the increasing incidence of thyroid cancer in the United States is predominantly due to the increased detection of small (<2 cm) well-differentiated cancers. [3] Given that majority of deaths from thyroid cancer are related to

anaplastic or medullary thyroid cancer, it is not surprising that this increase in the incidence of thyroid cancer has no significant impact on disease specific mortality. Given this increase in detection of subclinical thyroid cancer, it is crucial for a surgical oncologist to understand the principles of selective surgical management of well-differentiated thyroid carcinoma based on tumor biological behavior. Treatment recommendations should reflect clinical balance between estimation of the aggressiveness of the disease and effectiveness, as well as possible complications, of the proposed intervention.

Prognostic Factors and Risk Group Stratification

The risk stratification is crucial in understanding the biology of thyroid cancer, its prognosis and appropriate therapeutic intervention. The prognostic factors in thyroid cancer have been well described and validated in recent literature by the work done at Mayo Clinic, Lahey Clinic, and Memorial Sloan-Kettering Cancer Center. These prognostic factors include age, gender, size of primary tumor, extrathyroidal extension, histology and distant metastasis. [4] At Memorial Sloan-Kettering Cancer Center we divide thyroid cancer patients into low-, intermediate-, high-risk groups. [4, 5] *Low-risk group* patients are young (under 45 years), have small tumors (less than 4 cm in diameter) without extrathyroidal extension, well-differentiated histology and no evidence of distant metastasis. *High-risk group* patients are older (over 45 years old), have larger tumors (more than 4 cm in diameter) with extrathyroidal extension, poorly differentiated histology or presence of distant metastasis. The *intermediate risk group* includes young patients with aggressive primary tumors or older patients with favorable primary tumors.

N. Chernichenko · A. R. Shaha (✉)
Department of Surgery, Memorial Sloan-Kettering Cancer Center,
1275 York Avenue, C-1076,
New York, NY 10021, USA
e-mail: shahaa@mskcc.org

Treatment failure in the low-risk group usually occurs with regional metastasis, which is curable. [6, 7] Treatment failure in the high-risk group patients, on the other hand, occurs with local recurrence and distant metastasis, which is unlikely to be curable, leading to disease specific mortality [8]. From prognostic perspective, the long-term survivals in low-, intermediate- and high-risk groups were shown to be 99 %, 87 %, and 57 % respectively.[4] Understanding the nuances of biological behavior of thyroid carcinoma lays the foundation for the idea of selective surgical management of this disease: applying appropriate surgical procedure and, if needed, adjuvant therapy based on the aggressiveness of the cancer. With this in mind, the surgical treatment of thyroid cancer can be discussed in terms of treatment of the primary tumor, treatment of central and lateral neck nodes, and management of locally aggressive thyroid cancer.

Primary Thyroid Tumor

Surgical options in the management of well-differentiated thyroid cancer include thyroid lobectomy and total thyroidectomy. The extent of thyroid resection should be individualized based on the risk group stratification. There is a general agreement that patients in the high-risk group should undergo total thyroidectomy. Total thyroidectomy in this group will not only facilitate complete surgical resection of the disease, but also will allow postoperative radioactive iodine (RAI) ablation with subsequent adjuvant RAI treatment. When total thyroidectomy is undertaken, it should be a true extracapsular resection without leaving any thyroid tissue behind.

Surgical management of low- and intermediate-risk groups is a subject of controversy. On the one hand, thyroid lobectomy minimizes overtreatment, thus allowing a select group of patients to avoid lifetime thyroid supplementation in follow-up. In addition, complications of total thyroidectomy, such as recurrent laryngeal nerve injury and temporary or permanent hypoparathyroidism could be avoided. On the other hand, the complication rate of total thyroidectomy in the hands of experienced thyroid surgeons is not higher than that in thyroid lobectomy. The additional pros of total thyroidectomy in this scenario are the ease of radioactive iodine scanning/ablation and the ease of follow-up of patients with thyroglobulin. But do these patients really benefit from total thyroidectomy and/or RAI? Obviously, the best approach to address this question is to perform a prospective randomized clinical trial. In the absence of such trial, however, we must rely on a careful analysis of retrospective data. A matched pair analysis of patients undergoing lobectomy compared to those undergoing total thyroidectomy showed that long-term survival, local recurrence rate, the rate of regional and distant metastasis were

comparable in these two groups, regardless of the extent of surgical resection at initial treatment [6]. According to this study by *Shah et al.*, both thyroid lobectomy and total thyroidectomy appear to render similar long-term results in low- and selected intermediate-risk group of patients. Based on this study, we advocate the selective use of thyroid lobectomy in management of WDTC. Obviously, in the absence of high quality prospective data, the philosophy of extent of thyroidectomy will depend on surgical center, surgeon and patient preference.

Looking forward, we need to identify molecular signatures for diagnosis and prognosis of patients at high risk of death. This will allow us to identify a relatively few low- and intermediate-risk patients with more aggressive thyroid carcinomas; therefore, requiring a more aggressive surgical resection initially. Numerous published reports appreciate that initiation and progression of thyroid cancer involve multiple genetic and epigenetic alterations, leading to activation of the MAPK and PI3K-AKT signaling pathways. Common mutations found in thyroid cancer are point mutations of the *BRAF* and *RAS* genes as well as *RET/PTC* and *PAX8/PPAR γ* [9]. In a recent report, a molecular-pathologic score was developed based on several molecular and histopathologic features that correlated with a more aggressive behavior. This scoring system relies on *BRAF* mutation status and three histopathologic features -superficial tumor location, intraglandular tumor spread/multifocality, and tumor fibrosis, to assign tumors to one of three risk categories [10]. Notably, neither mutational status, nor histologic features alone were adequate to provide accurate risk stratification. This score allows practical and simple scoring system for clinical risk stratification of thyroid papillary microcarcinomas. While this scoring system needs additional validation and is not ready for widespread use, it is definitely a step in the right direction.

Metastatic Neck Disease

WDTC metastasizes to regional lymphatics in a well-established manner. For most patients with thyroid cancer, the first echelon lymph nodes are perithyroidal, tracheoesophageal and superior mediastinal. Lymph node metastasis subsequently spread to lower and upper jugular lymph nodes. Microscopic occult metastases are quite common and reported to be present in as many as 50–60 % of patients with papillary carcinoma and a clinically negative neck [11]. Moreover, with the recent increasing use of preoperative ultrasound, a large number of patients with WDTC are noted to have nodal metastasis. It is well-documented that nodal metastasis has no major impact on outcome of well-differentiated thyroid cancer, which is a unique feature of thyroid cancer [12–14]. Therefore, an elective neck

dissection is not recommended in the absence of clinically or radiographically documented disease. On the other hand, every patient undergoing surgery for thyroid cancer should have a thorough central compartment evaluation. If suspicious enlarged lymph nodes are encountered, histologic evaluation should be obtained intraoperatively. If positive, a comprehensive central compartment neck dissection should be carried out. Presence of positive lymph nodes in the central compartment is not an indication for lateral neck dissection. Obviously, when cervical node metastases are documented clinically or radiographically, systemic clearance of lymph nodes is indicated. Standard radical neck dissection is rarely performed for WDTC. On the other end of the spectrum, is a “berry picking” operation, which was popular in the past. However, it leads to multiple recurrences, requiring re-operation with increased morbidity and, therefore, is best avoided. The standard procedure for therapeutic lateral neck nodal clearance is modified radical neck dissection, with the removal of lymph nodes at levels II, III, IV, and V. The incidence of metastasis at level I and IIb is quite low. In order to avoid the risk of injuring marginal mandibular and spinal accessory nerves, these regions do not need to be dissected routinely.

Locally Aggressive Thyroid Cancer

The majority of patients with thyroid carcinoma have well-differentiated papillary and follicular tumors with an excellent overall prognosis and survival. However, 6–13 % of these tumors can present with extrathyroidal extension [15–17]. Extrathyroidal extension has been well-recognized as a poor prognostic indicator, with 10-year overall survival rates dropping to 45 % in patients who have extrathyroidal extension compared to 91 % for those who have well-encapsulated tumors [16]. The most commonly involved structures in patients with locally invasive thyroid cancer are strap muscles (53 %), recurrent laryngeal nerve (47 %), trachea (37 %), esophagus (21 %), lateral neck structures including the great vessels and vagus nerve (30 %), and larynx (12 %) [18]. Involvement of anterior structures, such as strap muscles, has no major prognostic implications, as they can be easily resected. However, when tumor invades posterior structures, surgical resection may be difficult and overall outcome may be quite poor.

The prime objective of the surgical management of locally invasive thyroid carcinoma is complete surgical excision with no gross residual disease. Patients with signs and symptoms of locally invasive disease should undergo a thorough preoperative work-up in order to delineate the extent of the disease and guide surgical management. In

addition history, physical exam and fiberoptic laryngoscopy, this work-up may need to include imaging studies such as ultrasound, CT and/or MRI. Of note, CT scan should be performed with contrast, as it will give better information about the extent of the disease and help surgeon, preoperatively and intraoperatively, making certain important and critical decisions regarding tumor excision. The contrast iodine dye will delay postoperative RAI ablation for a few weeks, but the information provided by the CT scan is very crucial. If there is any concern then MRI should be obtained with contrast. PET scan is generally not recommended in the initial evaluation unless there is concern about tumor resectability, suspicion of distant metastasis or concern about aggressive histology. Preoperative FNA may be able to distinguish well-differentiated papillary carcinoma from more aggressive types of thyroid cancer.

If tumor invades recurrent laryngeal nerve and the nerve is known to be paralyzed preoperatively, then it should be sacrificed in order to achieve a gross tumor resection. When recurrent laryngeal nerve invasion is identified in a patient with normal preoperative vocal cord function, the nerve can frequently be spared. Even though this approach in combination with RAI may achieve adequate local control, care should be taken to weigh in all other factors related to the tumor and the patient. Tumors with more aggressive and/or poorly differentiated histology are less sensitive to RAI and will require nerve sacrifice to achieve gross tumor resection.

Understanding the pattern of tracheal invasion is the key in designing an oncologically sound surgical approach. The staging system for tracheal involvement proposed by Shin et al. [19] can help in operative decision making for tracheal involvement. According to this classification, Stage 0 disease is confined to the substance of the thyroid. Stage I disease invades through the capsule of the thyroid gland and abuts but does not invade the external perichondrium of the trachea. Stage II disease invades between the rings of cartilage or causes minor cartilage destruction. Stage III disease invades through the cartilage or between the cartilaginous rings into the lamina propria of the tracheal mucosa or in the submucosal area. Stage IV disease is a full-thickness invasion with expansion of tracheal mucosa that is visible through a bronchoscope as a nodule or ulcerated mass. If the tumor is adherent to the tracheal wall, it can be easily shaved off. Careful bronchoscopy to rule out tracheal mucosal or submucosal involvement is a key factor in decision-making, as stage IV tracheal invasion cannot be shaved off the trachea without leaving residual macroscopic disease. Most importantly, if all gross residual disease cannot be removed with this method, this procedure should be abandoned in favor of more aggressive approach. If the tumor is invading the trachea with submucosal or intraluminal extension tracheal resection is generally recommended.

Segmental sleeve resection of the trachea is defined as a full-thickness circumferential resection that requires repair using end-to-end anastomosis. Obvious advantages of this approach include a full-thickness specimen that allows thorough evaluation of depth of the invasion and margin status with subsequent risk-stratification, immediate reconstruction of the airway, and rare need for tracheostomy. The key to success of this technique is achievement of tension-free repair of viable tracheal segments and preservation of functional larynx. Therefore, operating surgeon should be aware of the tracheal blood supply, the length of the involved segment, and the status of the recurrent laryngeal nerves. When these considerations are taken into account, operative risk in centers experienced in tracheal surgery is low. However, surgeon experience and expertise is an important factor in best outcome in these complex and challenging situations.

Esophageal invasion is frequently identified concomitantly with tracheal invasion, and, therefore, preoperative rigid esophagoscopy is mandatory. The extent of involvement is usually limited to the muscle layer, while sparing the mucosa. In this case, tumor can be safely resected. Intraluminal involvement will require partial esophagectomy and reconstruction with either regional or free flap.

Larynx invasion can occur via direct invasion through the thyroid cartilage, through cricothyroid membrane, or through the pyriform sinus [20]. The main surgical options in these cases are shave procedures, partial and total laryngectomy. Shave procedures have limited application and should be reserved to well-differentiated tumors without cartilage destruction. A partial laryngectomy can be performed if less than 50 % of laryngeal framework is involved by the tumor, when all gross tumor can be removed and the laryngeal function maintained [21]. Primary total laryngectomy is rarely indicated in well-differentiated thyroid carcinoma. Indications for total laryngectomy include intraluminal hemorrhage, significant laryngeal, pharyngeal or cricoid invasion (>50 %), and contralateral recurrent laryngeal nerve paralysis [22].

The involvement of the carotid artery and prevertebral fascia are generally considered unresectable. Such patients are best considered for palliative management.

Conclusion

The behavior of WDTC varies from indolent tumor behavior, incidentally detected by biopsy, to an aggressive disease with invasion of critical structures and widespread distant metastasis. Therefore, treatment recommendations should reflect clinical balance between our estimation of aggressiveness of the disease, versus the effectiveness and

morbidity of the proposed intervention. The understanding the biological behavior of thyroid carcinoma lays the foundation of selective surgical management.

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