

# Shifting Paradigms and Debates in the Management of Well-differentiated Thyroid Cancer

Ashok R Shaha

Attending Surgeon, Professor of Surgery, Memorial Sloan Kettering Cancer Center, Head and Neck Service, 1275 York Avenue, New York, NY 10065

**Correspondence:** Ashok R Shaha, Attending Surgeon, Professor of Surgery, Memorial Sloan Kettering Cancer Center, Head and Neck Service, 1275 York Avenue, New York, NY 10065, Phone: (212)639-7649, Fax: (212)717-3302 e-mail: shahaa@mskcc.org

## Abstract

The incidence of thyroid cancer has almost quadrupled over the past 30 years in the United States, a large number of which are less than 2 cm in size. There have been several paradigms in the management of well-differentiated thyroid cancer. The common debate in the past was total vs less than total thyroidectomy, however recently there is more interest in evaluation of fine needle aspiration of thyroid nodules, and intraoperative management in relation to the central compartment. The debate about elective central compartment nodal dissection vs observation has generated considerable controversy in the recent literature. Postoperative follow-up with thyroglobulin and ultrasound has become the mainstay of postoperative evaluation. Radioactive iodine ablation has been used in selected patients with advanced or aggressive thyroid cancer. While risk stratification continues to be an important facet in the evaluation of thyroid cancer, low risk patients are rarely offered radioactive iodine ablation. Understanding of the details of the histopathology is crucial, especially dividing the patients between well-differentiated and poorly differentiated thyroid cancer. PET scanning has been useful in the follow-up of patients with poorly differentiated, insular or tall cell thyroid cancer. External radiation therapy is used in selected patients where gross residual disease was present or there are painful bony metastases. Considerable research has been undertaken to identify specific molecular markers and their applicability for targeted therapy. This manuscript describes the current debates and shifting paradigms in the management of well-differentiated thyroid cancer.

**Keywords:** Thyroid cancer, thyroid surgery, postop surveillance, PET scan, thyroglobulin, neck nodes.

## INTRODUCTION

The incidence of well-differentiated thyroid cancer is rapidly rising in the United States and worldwide. In 1974, approximately 8,000 new patients with thyroid cancer were seen in the US. Incidence has almost quadrupled over the last 30 years. Approximately 37,000 new patients with thyroid cancer are now seen annually in the US, and a large percentage of these are incidentalomas of the thyroid smaller than 2 cm. Interestingly, mortality from thyroid cancer has essentially remained unchanged over the last 30 years. The majority of deaths from thyroid cancer are due to anaplastic or medullary thyroid cancer. With this rising incidence, there has been more interest in the early diagnosis, treatment and follow-up of thyroid cancer along with greater public awareness.

The management of well-differentiated thyroid cancer continues to be, and has always been, a subject of major controversy with interesting debates taking place in national and international meetings.<sup>1,2</sup> The focus of most of these debates used to be the extent of thyroidectomy: total versus less-than-total. The controversy mainly revolved around the best outcome in low risk thyroid cancer patients and higher incidence of

complications related to total thyroidectomy, such as nerve injury and temporary and permanent hypoparathyroidism. With technical expertise and better intraoperative monitoring of the nerves along with parathyroid autotransplantation in selected cases, the complication rate for total thyroidectomy has been considerably reduced and the focus of the debate has thus changed. The increased involvement of endocrinologists in thyroid cancer and preference for radioactive iodine ablation, the common use of ultrasound in preoperative evaluation of thyroid nodules showing bilateral thyroid nodules in a large number of patients, and patients' insistence on total thyroidectomy for follow-up with radioactive iodine ablation and thyroglobulin have ended that debate. However, newer controversial issues have evolved, such as fine needle aspiration biopsy and cytological interpretation, preoperative ultrasound imaging of the neck nodes and FNA of suspicious nodes, intraoperative decisions regarding prophylactic central compartment dissection, the extent of neck dissection for lateral neck disease and the role of radioactive iodine ablation in low risk thyroid cancer patients. During postoperative follow-up, the role of thyroglobulin and ultrasound finding of tiny lymph

nodes in the paratracheal area have become a subject of major debate. Some of these issues will be discussed in detail in this article.

## EVALUATION OF THE THYROID NODULE

The overall increase in the incidence of thyroid cancer is probably related to incidentalomas of the thyroid. These are generally tumors which are clinically not palpable and most commonly seen on imaging studies. The CT scan of the neck and chest, ultrasound of the carotid, and MRI scan of the spine are the most common investigations where thyroid nodules may be noted. The best investigation for these patients is ultrasound and ultrasound-guided needle biopsy. However, if the ultrasonographic features are not suspicious and the lesion is <1 cm, it may be appropriate to keep the patient under observation. PET incidentalomas are commonly seen nowadays in patients undergoing work-up for other malignant tumors. A focal PET uptake in the thyroid is always of concern, and appropriate further investigations including ultrasound and ultrasound-guided needle biopsy should be considered. The incidence of malignancy in focal PET positive thyroid lesions exceeds 35-40%. Interestingly, 50% of these patients with malignant lesions are noted to have a high grade malignancy or Hurthle cell lesions. TSH measurement is an important investigation in the preoperative evaluation of the thyroid nodule to see if the nodule is hyperfunctioning. If the TSH value is very low, the general consensus is to consider a thyroid scan to see if it is a hot nodule and treat the patient accordingly. The incidence of thyroid cancer is very low with hot nodules. However, if the nodule is clinically palpable or >3 cm, due consideration should be given to surgical excision of the thyroid nodule or evaluation with a needle biopsy.

There continues to be considerable debate about the interpretation of a fine needle aspiration biopsy. The British Thyroid Association has made sincere efforts to standardize the cytology report from THY1 to THY5. However, there are still considerable differences of opinion amongst prominent cytologists concerning reporting of needle biopsy results. The diagnosis of follicular lesion or follicular neoplasm continues to be a subject of controversy which leads to difficulties in making appropriate recommendations for or against surgical intervention. However, other parameters such as the size of the thyroid nodule, suspicious ultrasound characteristics such as irregular halo, punctate calcification and intratumoral hypervascularity should also be considered in the evaluation of thyroid nodules. The role of additional biologic markers and immunohistochemistry remains unclear and is only used for study purposes. A preoperative calcitonin assay in every thyroid nodule is not indicated unless there is a strong family history or a cytological interpretation leads to the suspicion of medullary carcinoma of the thyroid. The incidence of medullary carcinoma of the thyroid in the US is approximately 2-3% and routine calcitonin assay does not appear to be cost effective. Preoperative evaluation of the neck with ultrasound is

considered to be the investigation of choice to evaluate the neck nodes in patients proven to have papillary carcinoma of the thyroid. The central compartment neck nodes are difficult to evaluate in the presence of a thyroid tumor, however the lateral neck nodes are easy to evaluate. If there is a suspicious or complex lateral neck node recognized at the preoperative evaluation, due consideration may be given to therapeutic neck dissection. A preoperative fine needle aspiration biopsy is quite helpful. There is great interest in interpretation of fine needle aspiration biopsy samples with cytological analysis and needle wash thyroglobulin assay. If the thyroglobulin level is high in the needle washed sample, it is interpreted as positive for papillary carcinoma of the thyroid. If the ultrasound is suggestive of bilateral thyroid nodularity, the general consensus is to consider total thyroidectomy irrespective of the extent of the disease on the ipsilateral side.

## INTRAOPERATIVE MANAGEMENT

The major debate in intraoperative management now revolves around prophylactic elective nodal dissection of the central compartment. The incidence of nodal metastasis in papillary carcinoma ranges between 40-60%. However, the biologic impact of such nodal metastasis is minimal with essentially no major impact on long-term survival. In low risk patients, the presence of microscopic nodal metastasis does not alter long term survival, even though it may have some impact on regional recurrence. The bulkier or large nodal metastases, especially in older individuals, may have some impact on long-term survival and recurrence. One needs to be aggressive in the evaluation and management of neck nodes in high-risk thyroid cancer patients.<sup>3,4</sup> The preference for elective or prophylactic central compartment node dissection is based on the low incidence of complications in experienced surgical hands and the chances that future central compartment recurrence may be avoided with prophylactic central compartment dissection. However, neither of these issues have been studied in a prospective manner. There appears to be a higher incidence of complications of temporary and permanent nerve injury and temporary and permanent hypoparathyroidism with routine central compartment dissection. Even with generous use of autotransplantation of the lower parathyroid gland, there seems to be a 25-40% incidence of temporary hypoparathyroidism in prophylactic neck dissection and a 3-5% incidence of permanent hypoparathyroidism. In view of this, the opponents of prophylactic central compartment neck dissection believe that removal of the nonsuspicious central compartment nodes is unlikely to have a major impact on long-term prognosis and is unlikely to alter the chances of recurrence in the central compartment, as there may be additional lymph nodes in the paratracheal area which may not have been removed. The general consensus is to undertake appropriate evaluation of the central compartment during the primary surgery, and removal of the lymph nodes which appear to be suspicious or enlarged primarily based on frozen section diagnosis. The incidence of

Hashimoto's thyroiditis is quite high in North America and a majority of these patients are likely to harbor mildly enlarged paratracheal lymph nodes. Caution should be used to avoid routine paratracheal dissection to diminish complications from the procedure.

The presence of extrathyroidal extension requires meticulous surgical resection of all gross tumor.<sup>5</sup> The functioning structures, such as the recurrent laryngeal nerve, should be preserved. However, if the tumor is invading the trachea, appropriate surgical resection will require sleeve resection and anastomosis. Tumors invading the cricoid cartilage may be difficult to resect and reconstruct. Generally patients presenting with extrathyroidal extension are older individuals with a more aggressive histology of thyroid tumors. There is a higher incidence of local recurrence, nodal metastasis and distant metastasis in patients presenting with extrathyroidal extension. External radiation therapy may be necessary in individuals where there is gross tumor left behind, or high grade histology with a high likelihood of tumor recurrence.

### POSTOPERATIVE EVALUATION AND FOLLOW-UP

Debate also continues regarding the management of post-total thyroidectomy hypocalcemia. There has been interest in discharging these patients home the day after surgery with large doses of calcium and occasionally vitamin D, and gradually tapering them off calcium supplementation. The issue of routine placement of drains after total thyroidectomy seems to be resolved, as the majority of surgeons avoid routine drainage after total thyroidectomy. Randomized prospective trials have not shown a higher incidence of complications or wound hematomas without the use of drains. Most patients are discharged within 24 hours after surgery. There has been some interest in outpatient surgery or sending patients home within 23 hours. Obviously this is more emotional and related to the facilities of the institution and the practice of the individual surgeon and insurance bias. However, the majority of surgeons would prefer the patient be observed in the hospital for a period of 24 hours, the period which is most critical in the patient's recovery mainly due to postoperative hematoma. Postoperative hematoma occurs in 1-2% of thyroidectomy patients and can be quite disastrous if not attended to in a timely manner. Post-thyroidectomy hematoma may lead to airway issues and prompt intervention to evacuate the hematoma and maintenance of airway is essential.

The final pathology details are critical, especially in relation to the histopathological evaluation. Even though papillary carcinoma is the most common variant, it is very important for the pathologist to define the type of papillary carcinoma. Further details on tall cell, insular or poorly differentiated carcinoma are critical in the postoperative management of patients, especially the role of radioactive iodine ablation and postoperative follow-up with PET scans, etc.<sup>6</sup> Understanding extrathyroidal extension is the most important prognostic feature in the initial surgical procedure for patients with well-differentiated thyroid

carcinoma. Minor extrathyroidal extension suggests involvement of perithyroidal adipose tissue and is not as critical as gross involvement of the surrounding structures such as tracheal wall, esophageal musculature or recurrent laryngeal nerve. Preoperative evaluation of vocal cord function is necessary and intraoperative evaluation of the extent of extrathyroidal extension is essential. Appropriate surgical excision should include removal of all gross tumor, preservation of vital structures such as the trachea, esophagus, and larynx. Sacrifice of the recurrent laryngeal nerve should be undertaken after evaluation of the opposite tracheoesophageal groove area and selectively resecting functioning nerve, only if gross tumor is likely to be left behind. Generally a functioning nerve rarely needs to be sacrificed in well-differentiated thyroid carcinoma, however in older individuals the tumor may be more aggressive histologically and may require appropriate surgical resection of the involved organs. Laryngectomy is rarely necessary and the esophageal mucosa is rarely involved by the tumor. A majority of the time the esophageal musculature can be easily resected with no functional disadvantage to the patient. The tumor may be adherent to the trachea, but if the tumor does not directly involve the submucosa or the intraluminal extension, a tracheal shave can be easily performed. If, however, the tumor involves the tracheal lumen, the patient will require appropriate sleeve resection and primary anastomosis. Approximately 4-6 rings of the trachea can be easily resected and reconstruction performed with laryngeal drop by sectioning the strap muscles attached to the hyoid.<sup>5</sup>

Minimally invasive follicular cancer and Hurthle cell tumors always generate considerable debate, even amongst pathologists. The most important prognostic feature in these lesions is the extent of capsular and vascular invasion. If there is minimal capsular invasion, these are generally considered to be nonthreatening malignancies and survival is almost 100%. However, the major prognostic feature is widely invasive follicular cancers with major vascular invasion. Such patients definitely require completion thyroidectomy and radioactive iodine ablation.

### RADIOACTIVE IODINE ABLATION

Decisions regarding the use of radioactive iodine ablation have been studied extensively in the last two decades. Data from the Mayo Clinic has made it very clear that radioactive iodine ablation is not necessary in low-risk patients. The outcome in patients with low-risk thyroid cancer is so good, with 98% long term survival, that radioactive iodine ablation is unlikely to be beneficial and may cause complications and long-term sequelae. Thyroglobulin follow-up is commonly used after total thyroidectomy.<sup>7-9</sup> There is considerable interest in stimulated thyroglobulin levels with recombinant TSH. Any definite rise in thyroglobulin level in the follow-up period is likely to represent recurrent tumor either in the thyroid bed or in the paratracheal or lateral neck nodes. It is important to distinguish thyroid bed recurrence compared to paratracheal nodal or lateral

nodal recurrence. Thyroid bed recurrence is primarily related to initial extrathyroidal extension of disease, aggressive histology or inadequate surgery. Overall control of thyroid bed recurrence is difficult, requiring a more involved surgical intervention. Lateral nodal disease can be easily resected with an appropriate modified neck dissection or compartment-oriented neck dissection, especially the lymph nodes at levels II, III, IV and V. Paratracheal nodal recurrence has become a therapeutic challenge, especially small subcentimeter lymph nodes. It is very important to understand the biology of well-differentiated thyroid cancer, as 40-60% of patients will have microscopic positive nodal disease. Finding a tiny lymph node in the central compartment in the postoperative period is not uncommon, however surgical intervention in these cases may cause more harm to the patient's parathyroid function or recurrent laryngeal nerve. It may be appropriate to follow these patients with serial ultrasound and if there is a major change noted in the size of the recurrent disease, then surgical intervention may be considered. Neural monitoring may be helpful in recurrent paratracheal disease and central compartment clearance.

### USE OF EXTERNAL RADIATION THERAPY

External radiation therapy is used in selected patients with high grade histology, gross residual tumor, high likelihood of tumor recurrence due to initial extent of the disease or unsatisfactory surgery. There is a general consensus that radiation therapy will enhance local control in such situations. Radiation therapy is also used for relief of pain from bony metastasis. Intensity modulated radiation therapy (IMRT) is commonly used now to minimize local complications related to external RT.

### PET SCANNING IN FOLLOW-UP

PET scanning has become an important investigation in the follow-up of patients with high grade histology, Hurthle cell tumors or where no demonstrable disease is noted with rising thyroglobulin. The initial histological aggressiveness of the tumor is crucial to determine the use of PET scanning in follow-up. Patients with recurrent thyroid cancer who are PET positive do much worse compared to PET negative patients. The extent of PET positivity and the standard uptake value are also important as a prognostic marker.

### ULTRASOUND FOLLOW-UP

Ultrasound at intervals of 8-12 months in the initial follow-up period of 4-5 years is important to evaluate the possibility of nodal or central compartment recurrence. It is an excellent tool to evaluate and monitor recurrent disease. Fine needle aspiration biopsy will confirm the diagnosis and the occasional use of

alcohol injection. However alcohol injection and radiofrequency ablation appear to be investigatory approaches at this time.

### TARGETED THERAPIES

There has been great interest in the molecular biology of thyroid cancer and the BRAF mutation. Patients presenting with an advanced recurrent tumor where no definitive therapeutic modality is available, such as surgery, radioactive iodine ablation, external RT, standard chemotherapy, may be appropriate candidates for experimental treatments such as Sorafenib, histone deacetylase, and antiangiogenic modalities such as EGFR inhibitors. However, these therapeutic approaches are under investigation at this time and should only be used on a protocol basis.

### SUMMARY

Thyroid cancer continues to be a subject of debate and decision making depends upon the treating physician, philosophy of the individual institution, and the anxiety shown by the patient. Certain decisions are generally made by the patients themselves from a Google search, while the multidisciplinary approach by endocrine surgeons and endocrinologists is crucial in an effort to offer the best treatment for the patient's cancer and avoid unnecessary or nonbeneficial additional treatment. It is important to appreciate that the treatment of thyroid cancer patients should adhere to risk group stratification and prognostic factors which have been recognized world wide in various series such as age, gender, distant metastasis, grade of the primary tumor, extrathyroidal extension and size of the tumor and completeness of resection. Risk stratification into low, intermediate and high-risk is crucial, both in terms of prognosticating individual patient and the treatment choices.<sup>7</sup> Thyroid cancer is a continuum of diseases from papillary carcinoma to tall cell, insular, moderately differentiated, poorly differentiated and anaplastic thyroid cancer. It is amazing that in the same organ, there is the human cancer with the best prognosis: papillary carcinoma with survival exceeding 95%, and there is the human cancer with the worst prognosis: anaplastic thyroid cancer with a mortality rate of 95%. As the tumor progresses from well-differentiated to poorly differentiated, radioactive iodine avidity goes down while the PET positivity goes up and mortality increases considerably. The treatment of well-differentiated thyroid cancer requires a multidisciplinary team approach, with active involvement of a competent thyroid surgeon, endocrinologists, and nuclear physicians. The treatment should be balanced against the outcome, prognosis, risk stratification and complications. Let the punishment fit the crime, and remember: *Primum non nocere* – first do no harm.

## REFERENCES

1. Shaha AR. Implications of prognostic factors and risk groups in the management of differentiated thyroid cancer. *Laryngoscope* 2004;114:393-402.
2. Shaha AR. Controversies in the management of thyroid nodule. *Laryngoscope* 2000;110(2 Pt 1):183-93.
3. Sugitani I, Kasai N, Fujimoto Y, Yanagisawa A. A novel classification system for patients with PTC: Addition of the new variables of large (3 cm or greater) nodal metastases and reclassification during the follow-up period. *Surgery* 2004;135:139-48.
4. Grubbs EG, Evans DB. Role of lymph node dissection in primary surgery for thyroid cancer. *J natl Compr Canc Netw* 2007;5:623-30.
5. Patel KN, Shaha AR. Locally advanced thyroid cancer. *Curr Opin Otolaryngol Head Neck Surg* 2005;13:112-16.
6. Cohen EG, Tuttle RM, Kraus DH. Postoperative management of differentiated thyroid cancer. *Otolaryngol Clin North Am* 2003;36:129-57.
7. Shaha A. Treatment of thyroid cancer based on risk groups. *J Surg Oncol* 2006;94:683-91.
8. Mazzaferri EL, Jhiang SM. Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. *Am J Med* 1994;97(5):418-28.
9. Hay ID, Bergstralh EJ, Goellner JR, et al. Predicting outcome in papillary thyroid carcinoma: Development of a reliable prognostic scoring system in a cohort of 1779 patients surgically treated at one institution during 1940 through 1989. *Surgery* 1993;102(6):947-53.