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Controversial Issues in Thyroid Cancer Management

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ABSTRACT

The lack of prospective randomized clinical trials for most management topics in differentiated thyroid cancer force us to make management recommendations based on retrospective observational data which is often incomplete, subject to selection bias, and conflicting. Therefore, it is not surprising that many aspects of thyroid cancer management remain controversial and not well defined.

This review will examine the controversies surrounding three important topics in thyroid cancer management: (1) the option of thyroid lobectomy as initial therapy for thyroid cancer, (2) the proper use of preoperative neck imaging to optimize the completeness of the initial surgical procedure, and (3) the selective use RAI therapy as remnant ablation, adjuvant treatment or treatment of known persistent/recurrent disease.

As thyroid cancer management moves toward a much more risk adapted approach to personalized management recommendations, clinicians and patients must balance the risks and benefits of the potential management options to arrive at a management plan that is optimized based on both patient preferences/values and the philosophy/experience of the local disease management team.

INTRODUCTION

Thyroid cancer management has seen a dramatic shift away from a "one size fits all" management approach to a more risk adapted treatment paradigm in which the extent of surgery, the use of radioactive iodine therapy, TSH suppression goals, and follow-up recommendations are individually tailored for each patient (*1-7*). In the past, essentially all patients except those with intrathyroidal papillary microcarcinoma were subjected to high intensity treatment (total thyroidectomy with or without prophylactic central neck dissection, radioactive iodine therapy, prolonged TSH suppression, and highly sensitive follow-up evaluations). More recently, both the ATA and NCCN thyroid cancer guidelines have evolved to allow for low intensity treatment options (observation or thyroid lobectomy without the need for RAI therapy or TSH suppressive therapy) in properly selected patients (*1,5*). Even though these recommendations are often based on limited or conflicting data, the increasing incidence of low risk thyroid cancers which are commonly associated with an indolent disease course, the increasing reliance on neck ultrasonography rather than routine follow-up diagnostic whole body RAI scanning for disease detection, and a more selective use of postoperative radioactive iodine has forced clinicians to seriously question whether or not intensive treatment and follow up is mandatory for all differentiated thyroid cancers greater than 1 cm.

Many clinicians and patients strongly favor high intensity treatment options under the assumption that up front aggressive treatments and early detection of small volume residual disease would lead to improved outcomes. Conversely, advocates of low intensity treatment options are confident that with proper patient selection and follow-up, very similar long term outcomes can be achieved. The effectiveness of the low intensity treatment option is rooted in the following general assumptions:

- The vast majority of low risk differentiated thyroid cancer patients will do exceptionally well with disease specific survival rates in excess of 99% and structural disease recurrence rates of < 5-10% following either low intensity or high intensity treatments.
- Delayed intervention (surgery, radioactive iodine therapy), when necessary, is effective and has no impact on disease specific survival.
- Minimal residual disease is common and of little clinical importance.
- Early detection and treatment of very small volume persistent/recurrent structural disease has little clinical benefit.

Unfortunately, the literature comparing low intensity with high intensity treatments is largely retrospective, observational and devoid of high quality prospective randomized clinical trials. However, it is interesting to note that despite more than three decades of increasingly sensitive disease detection tools (such as high resolution neck ultrasonography and ultrasensitive thyroglobulin assays) which led to even more aggressive therapeutic interventions (such as prophylactic and therapeutic neck dissections for small volume disease and repeated administrations of RAI for biochemical evidence of persistent disease), thyroid cancer mortality remains stable or slightly increased (*8*). Thus, the controversy will continue as thyroid cancer experts review the same body of literature and reach differing conclusions based on their training, clinical perspective, experience, and personal bias.

This review will examine the controversies surrounding three important topics in thyroid cancer management: (1) the option of thyroid lobectomy as initial therapy for thyroid cancer, (2) the proper use of preoperative neck imaging to optimize the completeness of the initial surgical procedure, and (3) the selective use RAI as remnant ablation, adjuvant treatment or treatment of known persistent/recurrent disease.

When is Thyroid Lobectomy a Reasonable Initial Management Strategy in Differentiated Thyroid Cancer?

The controversy: whether or not total thyroidectomy should be recommended as the primary surgical procedure in all differentiated thyroid cancers with primary tumors greater than 1 cm in maximal dimension.

Position 1: Total thyroidectomy should be recommended for all differentiated thyroid cancers with primary tumors greater than 1 cm in maximal dimension as complete removal of the thyroid gland may improve survival, decrease recurrence, allow for routine use of radioactive iodine therapy, and facilitate detection of recurrent/persistent disease during follow-up. The increased risk of surgical complications associated with total thyroidectomy can be minimized if the procedure is done by experienced surgeons.

Position 2: Total thyroidectomy is not required for differentiated thyroid cancers with primary tumors < 4 cm in maximal dimension that appear to be confined to the thyroid gland on appropriate pre-operative evaluations as thyroid lobectomy is associated with the same excellent overall survival as complete removal of the thyroid gland, a lower risk of surgical complications, and may avoid the need for full replacement dose thyroid hormone replacement therapy in properly selected patients. While the recurrence rate may be slightly higher after lobectomy, appropriate follow-up procedures can easily identify the few patients that demonstrate recurrent structural disease recurrence making subsequent salvage therapy very effective.

The primary point of controversy with regard to initial surgical management revolves around recommendation 35B in the American Thyroid Association (ATA) guidelines that allows for a thyroid lobectomy in patients with tumors between 1 and 4 cm without evidence of

extrathyroidal extension or metastatic disease (Table 1) (*1*). While the National Comprehensive Cancer Network (NCCN) guidelines have long allowed for thyroid lobectomy in this setting, the ATA guidelines had previously strongly recommended total thyroidectomy for tumors > 1 cm (*5,9,10*). This was largely based on the assumption that nearly all of these patients would require postoperative radioactive iodine therapy and was further strengthened by the Bilmoria paper in 2007 that demonstrated a statistically significant improvement in overall survival within this size range (10 year survival of 98.4% for total thyroidectomy vs. 97.1% for thyroid lobectomy, $p< 0.05$) (*11*). Since that publication, multiple other studies have demonstrated no statistically significant survival benefit for total thyroidectomy versus lobectomy in tumors less than 4 cm when patients are properly selected and the statistical analysis controls for important confounding variables (Table 2). The specifics the various retrospective studies examining this issue are extensively reviewed in the text of the ATA guidelines and will not be repeated here (*1*).

Even though total thyroidectomy may not be associated with a proven overall survival benefit in properly selected patients with 1-4 cm intrathyroidal primary tumors, there are still valid reasons to consider a bilateral surgical procedure for individual patients. As noted in recommendation 35B, total thyroidectomy would be the preferred operation if the disease management team thinks that radioactive iodine therapy will be necessary postoperatively based upon either disease features and/or patient preferences. This wording provides the flexibility to actively incorporate the thought processes of the local disease management team and patient preferences into the decision about whether or not a thyroid lobectomy would be the most appropriate surgery for that individual patient.

Furthermore, since papillary thyroid carcinoma is known to be a multifocal disease, it is not surprising that total thyroidectomy is associated with a slightly lower risk of recurrence than a thyroid lobectomy. However, with proper patient selection, locoregional recurrence rates of less than 1-4% can be achieved in experienced centers that couple high quality preoperative imaging (primarily neck ultrasonography) with appropriate clinical judgment (*7,12-14*). Furthermore, salvage therapy is very effective in the few low risk patients that experience structural disease recurrence after low intensity therapy resulting in the same excellent survival rates that would have been expected from up front high intensity therapy.

It is also important for patients to understand that even if the preoperative plan is to proceed with a thyroid lobectomy, there are intraoperative and postoperative findings that may necessitate conversion to a total thyroidectomy. Patients are encouraged to empower the surgeon to convert the surgery from a lobectomy to a total thyroidectomy based on intra-operative findings. Likewise, it is important to emphasize that a final decision regarding the appropriateness of thyroid lobectomy as the initial surgical procedure can only be determined once the final histopathology report has been received a week or two after surgery. Early completion thyroidectomy after lobectomy is only required in 5-6% of our patients (*7,12-14*). However, in disease management teams which are more aggressive in the use of radioactive iodine for intermediate risk features, early completion thyroidectomy may be required up to 20% of the time (*15-17*).

Using a clinical decision-making framework based on what we have previously published for active surveillance of very low risk thyroid cancers, we examine three critical inter-related domains to determine if the patient would be an appropriate candidate for thyroid lobectomy (*18*).

Pre-operative Imaging and Clinical Findings.

The preoperative neck ultrasonography as well as the patient's history and physical exam are carefully reviewed. Any indication of gross extrathyroidal extension, loco-regional or distant metastasis leads to a recommendation for total thyroidectomy. Furthermore, the presence of multiple nodules in the contralateral lobe or extensive non-specific findings on ultrasonography (such as chronic lymphocytic thyroiditis or atypical cervical lymph nodes) would increase the likelihood that a total thyroidectomy would be recommended in an effort to make follow-up evaluations easier.

Successful use of thyroid lobectomy as the initial treatment option is also significantly enhanced when experienced multidisciplinary management teams integrate sound clinical judgment with high quality pre-operative neck ultrasonography in the decision making process. In the absence of high quality neck ultrasonography, in particular with regard to the evaluation of abnormal cervical lymph nodes, the selection of appropriate patients for thyroid lobectomy will be suboptimal.

Medical Team Characteristics.

It is important to understand the philosophy of the local disease management team with regard to the use of radioactive iodine in patients that demonstrate intermediate risk histological features that were not apparent on preoperative imaging (e.g., minor extrathyroidal extension, very small volume lymph node metastasis, and vascular invasion). Disease management teams that use radioactive iodine aggressively for intermediate risk factors will be expected to have a higher immediate completion thyroidectomy rate then centers that use radioactive iodine much

more selectively. This does not preclude the use of lobectomy as initial therapy, but the patient needs to understand what the likelihood is that unexpected histologic findings could lead to an early completion thyroidectomy to allow for post-operative RAI therapy.

*Patient Characteristics***.**

In many practices, patients are actively involved in shared decision-making making with the disease management team to explore the risk and benefits of both surgical options. Some patients, referred to as medical maximalists (*19*), have a strong preference for a total thyroidectomy in an effort to minimize the recurrence rate and maximize the sensitivity for detection of disease during follow-up (these patients often also often opt for routine use of radioactive iodine after surgery). Conversely, medical minimalists often chose thyroid lobectomy. They value the function of the contralateral lobe in order to avoid thyroid hormone replacement if at all possible. They are willing to accept the possibility that additional future treatments may be necessary but will opt for the least aggressive initial therapeutic option that is associated with excellent outcomes. Likewise, they are minimalist in their approach to identifying and treating small volume disease in the future and therefore do not require initial therapies designed simply to facilitate high-sensitivity follow-up. Thus medical minimalists are often good candidates for low intensity treatment options.

In summary, in the absence of a proven survival benefit to the routine use of total thyroidectomy in well differentiated thyroid cancers in the 1-4 cm range, thyroid lobectomy continues to be a very viable treatment option for properly selected patients. Proper patient

selection requires high quality pre-operative evaluations coupled with a thorough understanding of both the medical team characteristics and the patient preferences. By integrating the multiple important factors encompassed in each of these three domains, the patient and the disease management team can arrive at an appropriate initial management and follow-up strategy for each individual patient.

What Pre-operative Imaging is Recommended Prior to Initial Thyroid Surgery?

The controversy: whether or not CT scans with iodinated contrast agents should always be avoided prior to thyroid surgery.

Position 1: CT scans with iodinated contrast should always be avoided prior to thyroid surgery to avoid a delay in post-operative radioactive iodine administration.

Position 2: CT scans with iodinated contrast should routinely be performed in patients with locally aggressive disease and/or clinically apparent cervical lymph node metastases to optimize pre-operative planning and completeness of surgery. Imaging studies that optimize initial surgery are more important than early administration of radioactive iodine post-operatively.

One of the primary goals of initial therapy is to "remove the primary tumor, disease that has extended beyond the thyroid capsule, and clinically significant lymph node metastases" (*1*). Thus, preoperative evaluations must include anatomical assessments of the thyroid and neck in order to appropriately plan surgical interventions.

Neck ultrasonography is now widely used as the primary tool for evaluating not only thyroid nodules but also for examining cervical lymph nodes. Both the NCCN and the ATA guidelines recommend preoperative ultrasound to evaluate cervical lymph nodes in all patients undergoing thyroidectomy for malignant or suspicious for malignancy findings (Table 3). While extensive bilateral neck dissections can identify subclinical microscopic cervical lymph node metastasis in as many as 70-80% of patients (*20*), preoperative neck ultrasonography identifies suspicious cervical lymphadenopathy in about 20-30% of cases (*21-26*). As a result, routine use of preoperative ultrasound potentially alters the surgical management approach in at least 20% of the cases (*21,23,27*). Routine pre-operative ultrasonographic neck evaluations allow for a more complete initial surgical dissection which is expected to decrease subsequent recurrence rates and to facilitate the effectiveness of radioactive iodine therapy.

In addition to the routine use of neck ultrasonography in the preoperative evaluation of thyroid cancer, there are circumstances in which additional cross-sectional imaging with CT or MRI scanning are likely to yield important additional anatomic information (*1*). Clinical findings that would warrant additional cross-sectional imaging beyond ultrasonography include hoarseness, progressive dysphagia, a mass fixed to surrounding structures on exam, hemoptysis, stridor, rapid progression or enlargement of the tumor, sonographic suspicion of gross extra thyroid extension, or bulky cervical lymphadenopathy. In these patients, CT scan of the neck and chest with intravenous contrast is routinely recommended to carefully evaluate the lymph node basins as they extend from high in the neck down through the supraclavicular areas and into the upper mediastinum.

Unlike previous additions of the ATA guidelines that recommended avoiding iodinated intravenous contrast in the preoperative setting, recommendation 33A in the current guideline

clearly recommends the use of contrast when these high risk situations are identified or suspected (Table 3) (*1*). While there is no question that the use of iodinated contrast may delay the administration of postoperative radioactive iodine, it is thought that the "benefit gained from improved anatomic imaging generally outweighs any potential risk of a several week delay in radioactive iodine imaging or therapy." While the ATA guidelines correctly pointed out that urinary iodine levels usually return to normal within 4-8 weeks following IV contrast administration (*28*), the precise time period necessary to ensure that the previous contrast will no effect on subsequent radioactive iodine therapy has not been precisely defined. There remains some concern that even though the urinary iodine has returned normal, residual iodine in thyroid tissues could decrease the effectiveness of radioactive iodine therapy. Nonetheless, since a complete and comprehensive surgical removal of the thyroid and local regional metastasis is such an important component to the initial therapy, the use of intravenous contrast is justified in patients that present with high risk disease in order to optimize surgical planning. A delay in the administration of therapeutic radioactive iodine for for several months postoperatively is acceptable in order to achieve this potential benefit. Delaying radioactive iodine for a few months after intravenous contrast has not been associated with impairment in the effectiveness of radioactive iodine when used either as ablation, adjuvant therapy, or treatment of known disease.

Additional preoperative imaging is seldom indicated in the evaluation of most patients with differentiated thyroid carcinoma except in the case of patients that present with clinical signs or symptoms of distant metastasis. While 18 FDG PET scanning is a valuable tool for both initial staging and follow-up, its use is largely restricted to radioactive iodine refractory disease and seldom plays a role in preoperative staging for differentiated thyroid cancer (*1*).

What is the Role for Post-operative Radioactive Iodine Therapy?

The controversy: whether or not post-operative radioactive iodine therapy should be routinely recommended after total thyroidectomy for patients with differentiated thyroid cancer.

Position 1: Radioactive iodine therapy should be routinely recommended to all patients with differentiated thyroid cancer (except patients with intrathyroidal papillary microcarcinoma) to improve disease specific survival, decrease disease recurrence, facilitate initial staging and allow for highly sensitive follow-up testing.

Position 2: Radioactive iodine therapy should be used selectively in patients with differentiated thyroid cancer based on individual assessments of risk of disease recurrence, risk of disease specific mortality, post-operative disease status, likelihood that radioactive iodine will have a significant impact on clinical outcomes, the need for additional post-operative staging, the need for highly sensitive follow-up evaluations, the side effect profile of radioactive iodine, the treatment philosophy of the local disease management team, and consideration of the patients preferences and values.

Recommendations with regard to the indications for postoperative radioactive iodine therapy continue to be some of the most controversial of issues in the management of differentiated thyroid cancer. To help frame a rational discussion, the goals of radioactive iodine therapy should be described as either remnant ablation, adjuvant treatment, or treatment of known residual/recurrent disease (Table 4) (*29*). With this nomenclature, the term "radioactive iodine therapy" is used as a general term that encompasses the specific goals of remnant ablation, adjuvant treatment, and treatment of known residual/recurrent disease. It is important to

remember that since adjuvant treatment is given for a risk, rather than for demonstrable disease, it is accepted that a proportion of patients who receive adjuvant treatment will already have been cured by their primary surgery. Therefore, selection for adjuvant treatment involves both an assessment of risk of recurrence or disease specific mortality and a prediction of the likelihood that the proposed adjuvant treatment will have a meaningful impact on these event rates.

Several aspects of the current literature make it exceedingly difficult to confidently determine whether or not radioactive iodine therapy will have a significant impact on recurrence or disease specific survival (Fig.1) (*30*). As a result, most guidelines provide general advice as to which intermediate risk patients may or may not benefit from radioactive iodine while giving definitive recommendations for only those patients with very low or high risk disease.

Prior to making specific recommendations with regard to the potential benefit of radioactive iodine therapy in the postoperative setting, the ATA guidelines specifically recommend a careful evaluation of the postoperative disease status to determine whether or not additional therapies or imaging may be appropriate. (Table 5) (*1*). This will provide information to determine whether the goal of RAI therapy is ablation, adjuvant treatment, or treatment of known residual/recurrent disease and thereby help determine the need for RAI therapy and the specific activity that should be administered to best achieve that goal.

Even though the ATA guidelines fully endorse the importance of postoperative disease status evaluation as a key factor in the decision-making process, the recommendations with regard to when clinicians should consider ablation or adjuvant therapy are largely based on ATA and TNM risk stratification (Table 6) (*1*). However, the ATA guidelines also recognize that "in addition to standard clinicopathologic features, local factors such as the quality of preoperative

and postoperative ultrasound evaluations, availability and quality of thyroglobulin measurements, experience of the operating surgeon, and clinical concerns of the local disease management team may also be considerations in postoperative radioactive iodine decision-making." (*1*). In addition, the wording in recommendations 51A and 51C also emphasizes that "patient preferences are relevant to radioactive iodine decision-making" (Table 6).

From a practical standpoint, evaluation of at least 9 key factors are required to determine whether or not post-operative radioactive iodine therapy is likely to be beneficial for a specific patient. These include:

- Assessment of risk of disease recurrence
- Assessment of risk of disease specific mortality
- Evaluation of post-operative disease status (including the presence/absence of anti-thyroglobulin antibodies)
- Assessment of the likelihood that radioactive iodine therapy will have a significant impact on the outcomes of interest (recurrence, disease specific mortality)
- Assessment of the likelihood that RAI therapy will significantly improve initial staging
- Assessment of the need to use RAI in order to facilitate highly sensitive follow-up evaluations
- Consideration of the potential side effect profile of radioactive iodine therapy
- Consideration of patient preferences and values

- Consideration of local factors such as the quality of ultrasound evaluations and thyroglobulin measurements, the experience of the operating team and the treatment philosophy of the disease management team

This management approach generally leads to recommendations for observation in ATA low risk patients that have no evidence of persistent disease after an appropriate initial thyroid surgery and to RAI therapy in most ATA high risk patients either for adjuvant therapy or for treatment of known disease (Table 6) (*1*). Radioactive iodine treatment should be "considered" in ATA intermediate risk level differentiated thyroid cancer patients (Recommendation 51D). Whether or not radioactive iodine treatment is recommended in the ATA intermediate risk patients will depend upon an assessment of their risk of recurrence and disease specific mortality coupled with a careful postoperative disease status evaluation. Many ATA intermediate risk patients will have persistent small volume structural disease or abnormal postoperative thyroglobulin values that indicate persistent disease and thus would be candidates for treatment of known persistent disease with radioactive iodine. If the postoperative evaluation demonstrates no evidence of biochemical or structural disease, then consideration is given as to whether or not remnant ablation or adjuvant therapy would be appropriate. The ATA intermediate risk patients deemed to have a structural disease recurrence of about 5% or less would be considered for observation or possibly remnant ablation to facilitate initial staging and follow-up. Patients classified as having a higher risk of recurrence would be considered for adjuvant therapy in an effort to decrease the risk of recurrence and potentially improve overall survival based on whether or not the tumor is likely to be responsive to radioactive iodine. This logic integrates

risk of recurrence, risk of disease specific mortality, postoperative disease status and the likelihood that adjuvant treatment would be effective into the decision-making process.

With regard to recommendations pertaining to administered activities, the ATA guidelines endorse approximately 1,110 MBq of radioactive iodine as a reasonable choice for routine remnant ablation in low risk patients (Recommendation 55A) (Table 7) (*1*). Higher administered activities are recommended when the goal is to achieve adjuvant therapy. Unfortunately, the currently available literature does not provide adequate guidance with regard to the optimal administered activity that should be used in patients in the adjuvant therapy setting. Therefore, based primarily on expert opinion, the recommended activity for adjuvant therapy could vary anywhere between 1,110 MBq and 5,550MBq depending on the multiple factors listed above and the recommendation of the local disease management team (Recommendation 55B and 56). For patients with known persistent/recurrent disease, administered activities in the 3,700 to 7,400 MBq range are generally recommended except in the elderly were maximum administered activities should generally not exceed 5,550MBq (*1*).

CONCLUSIONS

In conclusion, while many areas of controversy remain in the management of thyroid cancer, there are far more areas where general agreement has been achieved among all specialties. By carefully exploring the logic and rationale that underlies the decision-making that goes into management recommendations with regard to the extent of initial of initial surgery, the completeness of preoperative imaging, and the role of radioactive iodine therapy, clinicians can better understand the unique viewpoint that each specialty brings to this complex issue. It also

allows us to further define specific areas where additional research is necessary for us to develop definitive recommendations. It is only through proactive, purposeful, and inclusive interdisciplinary cooperation that this field can be moved forward as we strive to optimize the intensity of therapy and follow up for each individual patient with thyroid cancer.

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514 **Figure 1: Factors that make interpretation of the current literature difficult**

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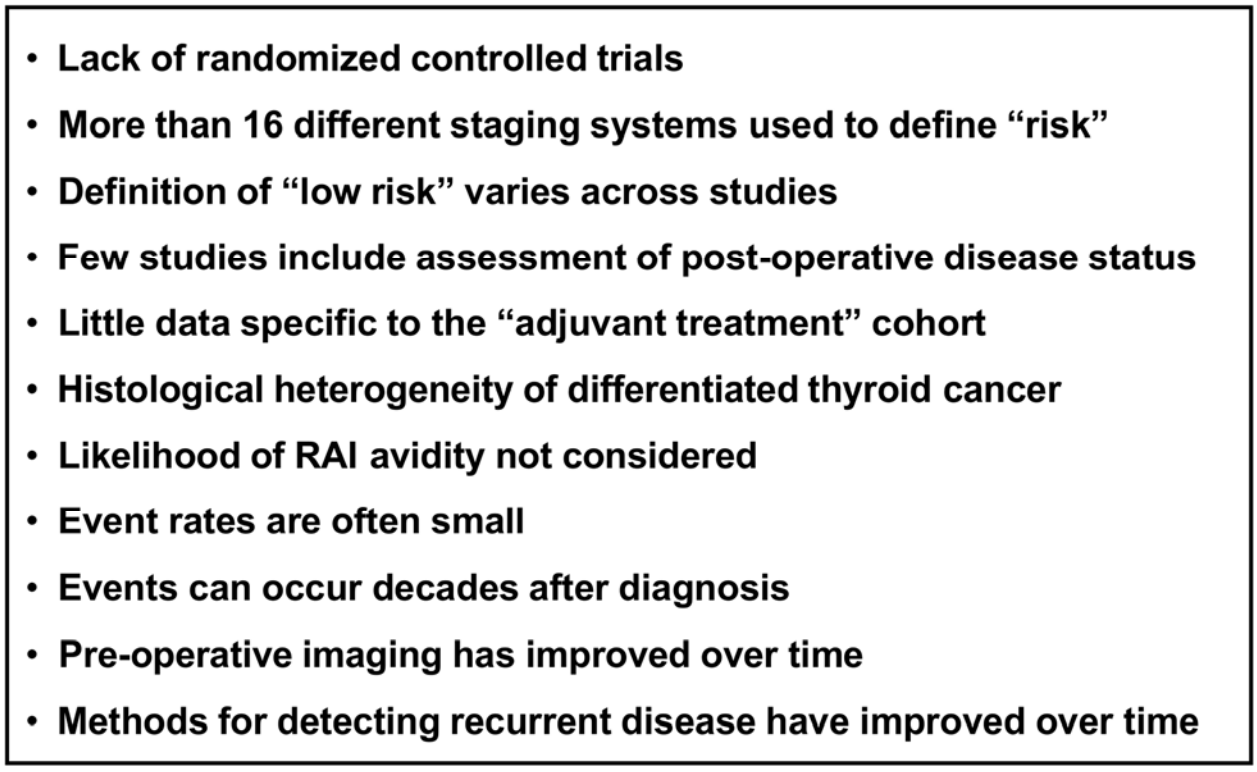

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517 **Figure 1 Legend: Factors that make interpretation of the current literature difficult.**
518 Multiple factors make it difficult to use the numerous retrospective, observational studies to
519 arrive at definite conclusions regarding the optimal use of RAI therapy (Adapted from Sacks et
520 al (*30*)).

521

Table 1: Operative approach for a biopsy diagnostic for follicular cell derived malignancy (*1*)

Recommendation 35A	For patients with thyroid cancer greater than 4 cm, or with gross extrathyroid extension (clinical T4), or clinically apparent metastatic disease to nodes (clinical N1) or distant sites (clinical N1), the initial surgical procedure should in clude a near-total or total thyroidectomy and gross removal of all primary tumor unless there are contraindications to this procedure. (Strong recommendation, Moderate quality evidence)
Recommendation 35B	For patients with thyroid cancer > 1 cm and < 4 cm without extrathyroidal extension, and without clinical evidence of any lymph node metastases (cN0), the initial surgical procedure can be either a bilateral procedure (near-total or total thyroidectomy) or a unilateral procedure (lobectomy). Thyroid lobectomy alone may be sufficient initial treatment for low risk papillary and follicular carcinomas; however, the treatment team may choose total thyroidectomy to enable radioactive iodine therapy or to enhance follow-up based on disease features and/or patient preferences. (Strong recommendation, Moderate quality evidence)
Recommendation 35C	If surgery is chosen for patients with thyroid cancer < 1 cm without extrathyroidal extension and cN0, the initial surgical procedure should be a thyroid lobectomy unless there are clear indications to remove the contralateral lobe. Thyroid lobectomy alone is sufficient treatment for small, unifocal, intrathyroidal carcinomas in the absence of prior head and neck irradiation, familial thyroid carcinoma, or clinically detectable cervical nodal metastases. (Strong recommendation, Moderate quality evidence)

526 Table 2

Study	N (source)	Survival Benefit for Total Thyroidectomy (< 4 cm)
Bilmoria, et al (*11*)	52,173 (NCDB)	Yes
Adam, et al (*31*)	61,775 (NCDB)	No
Haigh, et al (*32*)	5,432 (SEER)	No
Barney, et al (*33*)	23,605 (SEER)	No
Mendelsohn, et al (*34*)	22,724(SEER)	No
Nixon, et al (*12*)	889 (Single center)	No
Matsuzua, et al (*35*)	1,088 (Single center)	No

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528 **Table 2 Legend: Outcomes: Total thyroidectomy vs thyroid lobectomy.** When adjusted for
529 clinically relevant confounding clinicopathological features, multiple retrospective studies
530 demonstrate no significant difference in survival in differentiated thyroid cancer patients treated
531 with either thyroid lobectomy or total thyroidectomy. NCDB (National Cancer Database), SEER
532 (Surveillance, Epidemiology, and End Results Program).

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Table 3: What is the role of preoperative staging with diagnostic imaging and laboratory test? (*1*)

Recommendation 32A	Preoperative neck ultrasound for cervical (central and especially lateral neck compartments) lymph nodes is recommended for all patients undergoing thyroidectomy for malignant or suspicious for malignancy cytologic or molecular findings. (Strong recommendation, Moderate quality evidence)
Recommendation 32B	Ultrasound guided fine-needle aspiration of sonographically suspicious lymph nodes ≥ 8-10 mm in the smallest diameter should be performed to confirm malignancy if this would change management. (Strong recommendation, Moderate quality evidence)
Recommendation 32C	The addition of fine-needle aspiration thyroglobulin washout in the evaluation of suspicious cervical lymph nodes is appropriate in selected patients, but interpretation may be difficult in patients with an intact thyroid gland. (Week recommendation, Low quality evidence)
Recommendation 33A	Preoperative use of cross-sectional imaging studies (CT, MRI) with intravenous contrast is recommended as an adjunct to ultrasound for patients with clinical suspicion for advanced disease, including invasive primary tumor, or clinically apparent multiple or bulky lymph node involvement. (Strong recommendation, Low quality evidence)
Recommendation 33B	Routine preoperative 18 FDG-PET scanning is not recommended. (Strong recommendation, Low quality evidence)

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540 **Table 4: Goals of radioactive iodine therapy in differentiated thyroid cancer (*1*)**

Radioactive Iodine Therapy	Goal	Potential Benefits
Remnant ablation	Destroy residual normal thyroid tissue remaining after total thyroidectomy	Improve initial staging Facilitate highly sensitive follow up
Adjuvant treatment	Destroy subclinical microscopic tumor deposits that may or may not be present	Decrease recurrence Improve disease specific survival
Treatment of known residual/recurrent disease	Destroy known residual/recurrent disease	Achieve excellent response (remission) Improve disease specific survival Improve progression free survival

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Table 5: Should postoperative disease status be considered in decision-making for radioactive iodine therapy for patients with differentiated thyroid cancer? (*1*)

Recommendation 50A	Postoperative disease status (i.e., the presence or absence of persistent disease) should be considered in deciding whether additional treatment (e.g., RAI, surgery, or other treatment) may be needed. (Strong recommendation, Low quality evidence)
Recommendation 50B	Postoperative serum thyroglobulin (on thyroid hormone therapy or after TSH stimulation) can help in assessing the persistence of disease or thyroid remnant and predicting potential future disease recurrence. The thyroglobulin should reach its nadir by 3 to 4 weeks postoperatively in most patients (Strong recommendation, Moderate quality evidence)
Recommendation 50C	The optimal cutoff for postoperative serum thyroglobulin or state in which it is measured (on thyroid hormone therapy or after TSH stimulation) to guide decision-making regarding RAI administration is not known. (No recommendation, Insufficient evidence)
Recommendation 50D	Postoperative diagnostic radioactive iodine whole body scans may be useful when the extent of the thyroid remnant or residual disease cannot be accurately ascertained from the surgical report or neck ultrasonography, and when the results may alter the decision to treat or the activity of radioactive iodine that is to be administered. Identification and localization of uptake foci may be enhanced by concomitant single photon emission computed tomography-–computed tomography (SPECT/CT). When performed, pre-therapy diagnostic scan should utilize ^{123}I (1.5 to 3 mCi) or a low activity of ^{131}I (1 to 3 mCi) with the therapeutic activity optimally administered within 72 hours of the diagnostic activity. (Week recommendation, Low quality evidence)

Table 6: What is the role of radioactive iodine (including remnant ablation, adjuvant therapy, or therapy for persistent disease*) after thyroidectomy in the primary management of differentiated thyroid cancer? (*1*)

Recommendation 51A	Radioactive iodine remnant ablation is not routinely recommended after thyroidectomy for ATA low risk differentiated thyroid cancer patients. Consideration of specific features of the individual patient that could modulate recurrence risk, disease follow-up implications, and patient preferences are relevant to radioactive iodine decision-making. (Week recommendation, Low quality evidence)
Recommendation 51B	Radioactive iodine remnant ablation is not routinely recommended after lobectomy or total thyroidectomy for patients with unifocal papillary microcarcinoma, in the absence of other adverse features. (Strong recommendation, Moderate quality evidence)
Recommendation 51C	Radioactive iodine remnant ablation is not routinely recommended after thyroidectomy for patients with multifocal papillary microcarcinoma in the absence of other adverse features. Consideration of specific features of the individual patient that could modulate recurrence risk, disease follow-up implications, and patient preferences are relevant to radioactive iodine decision-making. (Week recommendation, Low quality evidence)
Recommendation 51D	Radioactive iodine adjuvant therapy should be considered after total thyroidectomy in ATA intermediate risk level differentiated thyroid cancer patients. (Week recommendation, Low quality evidence)
Recommendation 51E	Radioactive iodine adjuvant therapy is routinely recommended after total thyroidectomy for ATA high risk differentiated thyroid cancer patients. (Strong recommendation, Moderate quality evidence)

*As described in the text, "radioactive iodine therapy" is used as a general term that encompasses the specific goals of either remnant ablation, adjuvant treatment, and treatment of known residual/recurrent disease.

Table 7: ATA guidance regarding recommended administered activity when radioactive iodine is used for remnant ablation, adjuvant treatment, or treatment of known residual disease (*1*)

Recommendation 55A	If radioactive iodine remnant ablation is performed after total thyroidectomy for ATA low risk thyroid cancer or intermediate risk disease with lower features (i.e., low-volume central neck nodal metastasis with no other known gross residual disease or any other adverse features), a low administered activity of approximately 30 mCi is generally favored over higher administered activities. (Weak recommendation, Low quality evidence)
Recommendation 55B	Higher administered activities may need to be considered for patients receiving less than total or near total thyroidectomy in which a larger remnant is suspected or and which adjuvant therapy is intended. (Weak recommendation, Low quality evidence)
Recommendation 56	When radioactive iodine is intended for initial adjuvant therapy to treat suspected microscopic residual disease, administered activities above those used for remnant ablation up to 150 mCi are generally recommended (in the absence of known distant metastases). It is uncertain whether routine use of higher administered activities (> 150 mCi) in this setting will reduce structural disease recurrence for T3 and N1 disease. (Weak recommendation, Low quality evidence)
Recommendation 77B	The selection of RAI activity to administer for pulmonary micrometastasis can be empiric (100 to 200 mCi, or 100 to 150 mCi for patients ≥ 70 years old) or estimated by dosimetry to limit whole body retention to 80 mCi at 48 hours and 200 cGy to the bone marrow. (Strong recommendation, Moderate quality evidence)
Recommendation 78	Radioiodine avid macronodular metastasis may be treated with radioactive iodine and treatment may be repeated when objective benefit is demonstrated (decrease in the size of the lesions, decreasing thyroglobulin), but complete remission is not common and survival remains poor. The selection of RAI activity to administer can be made empirically (100-200 mCi) or by lesion dosimetry or whole body dosimetry if available to limit whole body retention to 80 mCi at 48 hours and 200 cGy to the bone marrow. (Weak recommendation, Low quality evidence)
Recommendation 79	With regard to treatment of bone metastases, the RAI activity administered can be given empirically (100 to 200 mCi) or determined by dosimetry (Weak recommendation, Low quality evidence)