

The Pros and Cons of Prophylactic Central Compartment Lymph Node Dissection for Papillary Thyroid Carcinoma

Ernest L. Mazzaferri, M.D., MACP,¹⁻³ Gerard M. Doherty, M.D.,⁴ and David L. Steward, M.D., FACS^{5,6}

Introduction

Ernest L. Mazzaferri, M.D., M.A.C.P.

A well-established feature of papillary thyroid carcinoma (PTC) is its propensity to metastasize to cervical lymph nodes in the central and lateral compartments. Currently, there is no non- or minimally invasive method that is completely reliable for detecting all of the metastases that are present. Therefore, some have advocated prophylactic cervical lymph node dissection as part of the operative procedure for PTC. There is no unanimity, however, on the efficacy and safety of prophylactic cervical lymph node dissection for this tumor. At the recent National Thyroid Cancer Workshop II,* two distinguished surgeons, Dr. Gerard M. Doherty from the University of Michigan and Dr. David L. Steward at the University of Cincinnati, were invited to debate the pros and cons of prophylactic cervical lymph node dissection. More specifically, Dr. Doherty was asked to take the positive view and Dr. Steward the contrary view concerning prophylactic central compartment (Level VI) dissection (CLND). By definition, this is a total compartment dissection that is performed when there is no preoperative or intraoperative evidence of cervical lymph-node metastases. Each participant was asked to marshal the case for one side and not necessarily reflect their personal views. To help them prepare, they were given the following hypothetical case to consider.

A 22-year-old woman is referred by her endocrinologist for surgical management of an asymptomatic 2-cm PTC diagnosed 1 week before. There is no family history of thyroid cancer, and she has had no exposure to radiation. Her thyroid-stimulating hormone (TSH) level is 1.7 (IU/mL). Repeat neck ultrasonography reveals a single 2-cm right lobe thyroid nodule with a hazy border and no lateral or central neck lymph-node abnormalities. The question posed to the debat-

ers is: What are the pros and cons of prophylactic level VI lymph-node dissection for this patient?

After the workshop, these surgeons, who are recognized authorities on the surgical management of thyroid cancer, were asked to prepare written commentary based on their presentations. What follows are two concise, carefully articulated, literature-based reviews that support each side of the debate.

Pro

Gerard M. Doherty, MD

Cervical lymph node metastases are common in PTC, occurring in 20% to 50% of patients using standard pathologic techniques (1). Micrometastases are even more common in PTC. One series found micrometastases in nearly 90% of examined nodes (2). Nodal metastases are known to correlate significantly with the persistence and recurrence of PTC (3).

However, it has traditionally been accepted that regional lymph node metastases in PTC may increase regional recurrence rates but do not ultimately affect survival (4–6), as attested by the omission of regional lymph node metastases in the AMES,[†] AGES,[‡] and MACIS[§] prognostic scoring systems (7–9). However, among other data, a large population-based study demonstrating greater mortality associated with regional lymph node metastases (10) has challenged this view. Hence, there has been a recent focus on the role of operative management of cervical lymph node metastases during the initial operation for thyroid cancer (1).

The only area of significant current controversy is the utility of prophylactic CLND. The term “prophylactic” denotes

[†]Classification based on age of the patient when the tumor is discovered, metastases of the tumor to different sites other than neck lymph nodes, extent of primary tumor, and size of the tumor.

[‡]Classification based on age of patient, tumor grade, extent, and size.

[§]Classification based on metastasis, age, completeness of resection, invasion, and size.

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¹Emeritus Professor of Medicine, College of Medicine, Ohio State University, Columbus, Ohio.

²Courtesy Professor of Medicine, University of Florida, Gainesville, Florida.

³University of Florida, Gainesville, Florida.

⁴NW Thompson Professor of Surgery, Head, Section of General Surgery, Residency Program Director, Surgery, University of Michigan, Ann Arbor, Michigan.

⁵Department of Otolaryngology – Head and Neck Surgery, Division of Endocrinology; and ⁶Department of Medicine; University of Cincinnati Academic Health Center, Cincinnati, Ohio.

removal of lymph nodes that appear normal according to palpation and imaging studies preoperatively and intraoperatively. In contrast, "therapeutic" dissection denotes removal of lymph nodes that likely contain metastatic disease based on palpation or imaging studies. There is universal agreement that lymph node involvement should always be assessed using preoperative examination and ultrasound, and intraoperative inspection, and that evidence of central compartment node (Level 6) involvement should prompt therapeutic complete dissection of the nodes in that compartment, rather than "berry-picking." It is also accepted that prophylactic dissection of the lateral neck compartments (Levels 1–5) is not necessary, because those compartments of the neck are not violated during thyroidectomy and so could be dissected at a later time without increased risk due to the reoperative field. The important remaining question is whether removal of normal-appearing nodes from the central compartment during thyroidectomy has benefit. Some evidence for this has been extensively catalogued previously (11).

Arguments for Prophylactic Dissection. The rationales for prophylactic central neck dissection are as follows. Each is considered, in order, in the following paragraphs.

- Lymph node metastases have a negative effect on patient outcome.
- Lymph node metastases in the central neck cannot be reliably identified at operation.
- Meticulous central neck node dissection has a beneficial effect on subsequent course.
- Central neck dissection can be performed safely.
- Reoperation for central neck recurrence has greater morbidity.

Nodal metastases have been regarded as innocuous for patients with PTC, but this turns out not to be true when studied more carefully. For example, in a recent, carefully performed retrospective analysis with long patient follow-up, Swedish investigators demonstrated that lymph node metastases were associated with diminished survival, even when adjusted for TNM staging (10). In addition, lymph node metastases are associated with a greater risk of locoregional recurrence (5, 12, 13) in some, but not all, studies (7, 9, 14). Although the data are conflicting, the existence of excellent data showing greater risk should outweigh the lack of such a finding in studies underpowered to identify this.

One strategy to avoid prophylactic dissection is to actively evaluate the central compartment for metastasis and perform therapeutic dissection if the nodes are involved. However, the central compartment nodes cannot be sensitively assessed using preoperative ultrasound examination (14, 15) or intraoperative examination (15, 16). Without the ability to reliably identify node metastasis using ultrasound or surgery, this assessment strategy cannot replace prophylactic dissection. Actively seeking node involvement to guide the extent of surgery is preferable, however, if prophylactic dissection is not chosen routinely.

No prospective, randomized data exist to explain the effect of CLND on recurrence or disease-specific mortality in PTC. One prospective Swedish study with contemporaneous controls provides the best available data (17) to support improvement in survival. This study details the surgical and disease outcomes from a prospectively studied group of 195

patients with PTC and compares them with contemporaneous outcomes from other Scandinavian populations (Norway and Finland). All patients in the Swedish cohort had meticulous CLND and radioiodine only if there was substantial cervical uptake on radioiodine scan; 6% of the patients received radioiodine. Median follow-up was 13 years, and 37% of the patients were American Joint Committee on Cancer (AJCC) stage III, compared with 19% to 28% Stage III and 10- to 11.5-year median follow-up in the comparison cohorts. Death due to thyroid cancer occurred in 1.6% of the Göteborg cohort, compared with 8.4% to 11.1% in the comparison groups. Four retrospective cohort studies (level IV) also exist (18–21), with mixed results, with two supporting improvement with node dissection and two showing no difference. One retrospective cohort study provides related evidence using thyroglobulin levels as a surrogate endpoint (22). This study retrospectively examined 447 patients with clinically node-negative PTC. Fifty-six patients underwent total thyroidectomy plus ipsilateral CLND, and 391 patients had total thyroidectomy alone. Both groups had equivalent tumor sizes and MACIS scores, and both groups were treated with radioactive iodine, with the mean dose not different between the two groups. Postablation serum levels of thyroglobulin, a marker for residual PTC, were lower in those with CLND ($p = 0.02$), and more patients with CLND had undetectable thyroglobulin levels (72% vs 43%; $p < 0.001$). On balance, there is some evidence to support improvement in outcome by including dissection, and only underpowered studies that show no difference.

Operative morbidity is one concern about including routine prophylactic central neck dissection in thyroid cancer treatment. Total thyroidectomy without lymph node dissection performed by surgeons experienced in the procedure results in permanent hypoparathyroidism in 1% to 2% of patients and permanent nerve injury (recurrent laryngeal, external branch of the superior laryngeal) in 1% to 2% of patients. No high-level evidence exists to define whether the addition of CLND to total thyroidectomy for PTC confers greater risk of permanent hypoparathyroidism or permanent nerve injury. An expert series with liberal use of parathyroid autotransplantation did not find greater morbidity (22), although other studies are mixed in their information regarding greater risk of permanent hypoparathyroidism (14, 23–27). The morbidity appears to be related to surgical skill and experience, but selected surgeons can safely perform central node dissection.

One thing that is clear is that reoperation in the central neck compartment for recurrent PTC has greater risk of hypoparathyroidism and unintentional nerve injury than initial total thyroidectomy with or without CLND (28–32). This supports more-aggressive initial surgery in cohorts of patients in whom central neck recurrence is sufficiently likely to require reoperation in some fraction if not initially cleared of disease.

Conclusion (Dr. Doherty). The application of prophylactic central neck dissection to patients with differentiated thyroid cancer (DTC) is a controversial area in thyroid cancer management. As with many issues regarding the management of DTC, there are no level one data to support or refute the hypothesis that central neck dissection at the time of initial thyroid cancer treatment is beneficial, but in expert surgical hands, the addition of central neck node dissection to

total thyroidectomy should carry no greater patient risk and probably has benefit for disease-free and possibly overall survival in patients who are at some risk of recurrence. Finally, the value of identifying patients who are definitively node negative is not clear, but dissection may also benefit them by defining a group that can receive limited or no adjuvant therapy and who may require less-intensive follow-up.

Con

David L. Steward, M.D., F.A.C.S.

Treatment decisions necessarily involve a balance of risk to the patient from disease with risk and benefit to the patient from its treatment. This balance involves concepts of beneficence and nonmaleficence, with the latter summed up succinctly in the Hippocratic Oath, "*primum, non nocerum,*" or first, do no harm.

By definition, prophylactic CLND implies removal of lymph node-bearing tissue from the central compartment in the absence of clinically detectable nodal metastasis using all available modalities (preoperative and intraoperative inspection, palpation, and imaging). In contrast, a therapeutic dissection involves removal in the presence of clinically detectable nodal metastasis. The rationale for prophylactic neck dissection is based upon suspicion of a high incidence of occult (subclinical) nodal metastasis, often microscopic. However, the decision to perform prophylactic central neck dissection can not be justified solely upon the discovery of subclinical nodal metastasis. Were that sufficient justification, then prophylactic lateral compartment neck dissections should also be performed for every patient with PTC based upon the known high incidence of occult nodal metastasis in the lateral compartment as well. In fact, the prognosis of clinically detectable (macroscopic) nodal metastasis may differ from clinically occult (microscopic) nodal metastasis (33, 34). As such, justification for prophylactic central neck dissection needs to be based upon evidence of patient benefit exceeding harm. With regard to thyroid carcinoma, clinical benefit is measured primarily in terms of lower recurrence and mortality rates, whereas harm is measured in terms of higher complication rates, including recurrent laryngeal nerve injury and hypoparathyroidism.

The following careful analysis of the literature on the topic fails to demonstrate evidence of benefit from prophylactic central neck dissection. In contrast, it demonstrates clear and consistent evidence of harm, primarily transient hypoparathyroidism. The likelihood of harm is clearly and consistently proportional to the extent of surgery, increasing progressively from total thyroidectomy alone to concomitant unilateral and finally bilateral central neck dissection. Moreover, the likelihood of permanent morbidity resulting from routine prophylactic central neck dissection may be higher in the hands of less-experienced surgeons than is reported in published series by experienced high-volume surgeons. Given the lack of measurable benefit and clear evidence of harm, prophylactic central neck dissection cannot be routinely recommended. Without evidence of collective benefit from routine prophylactic central neck dissection, justification of a prophylactic procedure for all is invalid. Rather, a needs-based paradigm of performing a therapeutic procedure for the minority who present with or subsequently develop clinically detectable nodal metastasis appears most rational.

Evidence of Benefit? The evidence of mortality benefit from central neck dissection for PTC is limited to one published study with two significant limitations (17). The first limitation is that no distinction was made between patients undergoing therapeutic and prophylactic central neck dissection; thus conclusions cannot be made from this study regarding benefit of prophylactic central neck dissection. The second limitation is with the validity of the mortality rate comparison. The study by Tissel *et al.* (17) retrospectively evaluated 195 patients from Sweden, of whom approximately 175 underwent pretracheal and paratracheal central neck dissection and total or near-total thyroidectomy. Radioiodine was administered in approximately 5% of patients. All-cause mortality was reported as 26%, and disease-specific mortality was 4%. Disease-specific mortality after exclusion of those with distant metastasis at initial staging was reported as 1.6%. Comparison was made with two previously published Scandinavian studies from Norway and Finland assessing the utility of the then new TNM classification system, with reported disease-specific mortality rates of 8.4% and 11%, respectively (35, 36). No statistical comparison was made between these mortality rates, but the authors concluded that the differences were significant and due to routine central neck dissection.

In the Norwegian study by Salvesen *et al.* (37) that specifically assessed results from surgical treatment of the same series of patients compared above (35), all-cause mortality in PTC was reported to be 16% and disease-specific mortality to be 9%. However, 12 of 15 patients who died from PTC had only palliative operations because of initial extent of primary tumor (37). Exclusion of these 12 patients would give a disease-specific mortality from PTC of 1.9% (3/155), which is similar to that reported by Tissel *et al.* (17) of 1.6% after exclusion of those with distant metastases at presentation. The patients who underwent surgery with curative intent underwent total or subtotal thyroidectomy with node plucking for clinically detectable nodal metastasis, with approximately 40% of patients undergoing radioiodine therapy (37). Thus, comparison of the outcomes from the Tissel *et al.* (17) study and the Salvesen *et al.* study (37) addressing results of surgical treatment reveal no obvious difference in disease-specific mortality for those treated surgically with curative intent (1.6% vs. 1.9%), although a much higher proportion of patients in the latter study underwent postoperative radioiodine therapy (5% vs. 40%).

A comparison between the study from Finland by Kukkonen *et al.* (36) (1956–1979) and the study by Tissel *et al.* (17) (1970–1989) is more problematic for the following two reasons. First, the study period differed significantly between these two, in contrast to the study periods of Salvesen *et al.* (37) (1971–1989) and Tissel *et al.* (17) (1970–1989). Second, the study by Kukkonen *et al.* (36) did not attempt to evaluate the effect of surgery on survival. Data regarding extent of thyroidectomy were limited, and data regarding node removal and radioiodine therapy were not available or not provided.

The recent study by Sywak *et al.* (22) is also used as evidence supporting prophylactic CLND for PTC (11). This retrospective study reported a higher rate of undetectable post-radioiodine-ablation TSH-stimulated thyroglobulin levels for those undergoing total thyroidectomy with prophylactic unilateral CLND ($n = 56$) (72%) than for those undergoing total

TABLE 1. COMPARISON OF REPORTED COMPLICATION RATES BETWEEN TOTAL THYROIDECTOMY AND TOTAL THYROIDECTOMY WITH CENTRAL NECK DISSECTION IN VARIOUS STUDIES

Complication	TT	TT + CLND	P-Value	Study	
		%			
Recurrent laryngeal nerve injury -Transient	4.1	7.3	0.39	Roh, 2008 (40)	
	1.3	5.4	0.06	Roh, 2007 (38)	
	1.0	1.8	0.62	Sywak, 2006 (22)	
	6.0	4.0		Henry, 1998 (24)	
	-Permanent	2.7	3.6	0.75	Roh, 2007 (38)
		1.3	0	0.34	Palestini, 2008 (39)
1.0		0	0.45	Sywak, 2006 (22)	
0		0		Henry, 1998 (24)	
Hypoparathyroidism -Transient	14	44	0.015	Roh, 2007 (38)	
	10	31	0.001	Palestini, 2008 (39)	
	13	27	0.003	Palestini, 2008 (39)	
	8	18	0.02	Sywak, 2006 (22)	
	8	14		Henry, 1998 (24)	
	-Permanent	0	5.0	0.06	Roh, 2007 (38)
		2.7	0	0.20	Palestini, 2008 (39)
		0.5	1.8	0.27	Sywak, 2006 (22)
		0	4.0		Henry, 1998 (24)

TT, total thyroidectomy; TT + CLND, total thyroidectomy with central neck dissection.

thyroidectomy alone (n = 391) (43%, $p < 0.001$). However, there were no significant differences reported in locoregional recurrence rates (3.6% vs. 5.6%) or disease-specific mortality rates (0% vs. 0%), despite significantly shorter median follow-up duration (25 vs. 70 months) in the prophylactic CLND group. Time-adjusted rates of recurrence to account for the difference in duration of follow-up were not performed or reported.

Two other studies have evaluated prophylactic CLND for PTC without demonstrating evidence of lower recurrence or mortality rates. The prospective study by Roh *et al.* (38) found no significant difference in recurrence rate (4.1% and 1.2%, respectively, $p = 0.37$) or disease-specific mortality rate (0% and 0%) between those undergoing total thyroidectomy alone (n = 73) and those undergoing total thyroidectomy with central neck dissection (n = 82). A distinction was made between patients undergoing CLND for therapeutic (n = 42) and prophylactic (n = 40) reasons (38). The retrospective study by Bardet *et al.* (33) demonstrated no significant difference in recurrence rates for those without macroscopic nodal metastasis (n = 427) who underwent total thyroidectomy alone (3%), total thyroidectomy with bilateral central and lateral neck dissection (0%), and total thyroidectomy with other node dissection (5%, $p = 0.12$).

Evidence of Harm? There is a large body of evidence documenting consistently greater morbidity rates for patients undergoing CLND along with thyroidectomy than total thyroidectomy alone (22, 24, 33, 38–40). The reported complication rates are summarized in Table 1, with every study demonstrating greater rates of temporary hypoparathyroidism with central neck dissection. The extent of surgical treatment of thyroid carcinoma is associated with a greater rate of hypoparathyroidism when CLND is added to thyroidectomy (41). Further study has demonstrated significantly higher rates of hypoparathyroidism in patients undergoing bilateral

CLND than unilateral CLND, with no significant difference in rates of undetectable thyroglobulin levels, recurrence, or mortality (14, 42, 43).

Summary (Dr. Steward). Review of the current literature finds no evidence of benefit in terms of lower recurrence or mortality rates for thyroidectomy with prophylactic CLND than for thyroidectomy without CLND for the management of PTC, although clear and consistent evidence demonstrates greater rates of transient hypoparathyroidism resulting from prophylactic central neck dissection. As a result, utilitarian justification for routine prophylactic central neck dissection is invalid. A needs-based paradigm of therapeutic central neck dissection appears to be the most reasonable. The concept of distributive justice suggests that it is better overall for the small minority of patients who subsequently develop central nodal metastasis to undergo therapeutic reoperation by more experienced central neck surgeons than for all patients to undergo prophylactic operation, with the majority by less experienced surgeons.

The apparent discordance between the relatively high rates of occult nodal metastasis detected by prophylactic central neck dissection and the relatively low rates of recurrence after thyroidectomy without nodal dissection may be related to postoperative radioiodine administration. The sole justification for prophylactic CLND at this time may be to subject patients to a greater risk of temporary hypoparathyroidism in hopes of avoiding risk from subsequent radioiodine therapy for patients with pathologically negative nodes to whom radioiodine would not be given otherwise. In such cases, the additional risk of bilateral central dissection is unjustified. The validity of this paradigm requires further study (44). Future study may also identify a subset of higher-risk patients for whom prophylactic CLND may be beneficial. This could include those diagnosed preoperatively with advanced T-stage or molecular mutations with

high risk of nonradioiodine avid nodal metastasis, mutations of v-raf murine sarcoma viral oncogene homolog B1 (BRAF).

Summary

Ernest L. Mazzaferri, M.D., M.A.C.P.

It is important to recognize that the 10-year mortality rates for PTC are low, in the range of 7%; however, the recurrence rates are high with this disease, causing considerable anxiety and morbidity for the patient. This is the main challenge in managing the majority of patients with this disease. Prophylactic neck dissection for small papillary carcinomas, which is an important factor in reducing tumor burden, remains controversial. The two summaries by Drs. Steward and Doherty define the depth of the controversy over this aspect of management.

Dr. Steward makes the strong point that prophylactic central compartment dissection cannot be justified based on a high likelihood of finding tumor by removing subclinical central compartment lymph-node metastases without using the same argument for dissecting the ipsilateral lateral compartment, which has an equally high possibility of metastases. The second point Dr. Steward argues is that careful analysis of the literature fails to demonstrate evidence of benefit measured in terms of enhanced survival or tumor recurrence, which per se renders prophylactic surgery invalid. His third major point is that the rates of permanent recurrent laryngeal nerve injury and permanent hypoparathyroidism are as high as 3.6% and 5%, respectively, with total thyroidectomy and central lymph node compartment dissection. These arguments provide little enthusiasm for routinely performing this surgery.

Dr. Doherty makes the strong point that cervical lymph-node metastases are found in as many as half the patients with papillary cancer using standard pathology techniques, which correlates with tumor persistence and recurrence and may be associated with lower survival rates. The second point that Dr. Doherty argues is that central compartment lymph-node metastases cannot be accurately accessed before or during surgery using preoperative ultrasonography or intraoperative examination. The third important point is that, excluding underpowered studies, there is some evidence to support improvement in outcome with central compartment dissection, which in the hands of experienced surgeons is associated with a 1% to 2% rate of permanent recurrent laryngeal nerve injury and hypoparathyroidism, compared with much higher complication rates with reoperation of the central neck compartment.

In many ways, the debate concerning prophylactic lymph-node dissection is reminiscent of the widely divergent opinions that prevailed for 30 years or more concerning the efficacy and risk of total thyroidectomy for PTC (5, 8, 45–48) until a study in 2007 by Bilimoria *et al.* (49) of 52,173 patients found that total thyroidectomy results in significantly lower recurrence rates and significantly higher survival rates for PTCs of 1 cm or larger than with lobectomy, largely putting to rest the arguments about the efficacy and safety of total thyroidectomy for PTCs of 1 cm or larger.

Conclusion (Dr. Mazzaferri). There seems little doubt that cervical lymph-node metastases from PTC are common and

are not always entirely innocuous. Given the high odds of leaving residual central compartment lymph-node metastases by forgoing prophylactic lymph-node surgery, two options are left for the patient: watchful waiting, which in some cases may span decades, or empiric radioiodine therapy, which may eradicate the thyroid remnant and smaller lymph-node metastases. However, the efficacy of remnant ablation continues to be debated for small tumors, mainly because of the small risk for radiation-induced second cancers, which appears to be ¹³¹I dose-dependent (50).

A recent study by Bonnet *et al.* (44) provides important information concerning prophylactic neck compartment dissections as it relates to the extent of initial surgery and the use of postoperative ¹³¹I remnant ablation. Although ¹³¹I ablation is not uniformly recommended for tumors smaller than 10 mm, its use is debated for papillary tumors between 10 and 20 mm in diameter. In a study from the Institut Gustave Roussy, Bonnet *et al.* (44) retrospectively studied 115 patients with PTCs of 2 cm or smaller without ultrasonographically detectable cervical lymph-node metastases who were treated with total thyroidectomy and complete prophylactic central and ipsilateral lateral neck compartment dissection. Nearly half (43%) the patients were found to have lymph-node metastases. Radioiodine was not given to 42% of the patients who had tumors smaller than 20 mm without lymph-node metastases, whereas the remaining 58% were treated with ¹³¹I if they had lymph-node metastasis, thyroid extracapsular tumor invasion, or unfavorable histologic subtypes. Lymph-node status played a major role in defining the indication for ¹³¹I. Of the 30.5% of the cases classified as T1, 12 patients had tumors smaller than 10 mm with lymph-node metastases that were subsequently treated with ¹³¹I, whereas 13 others with tumors 10 to 20 mm in diameter without lymph-node metastases did not receive ¹³¹I therapy. Permanent vocal cord paralysis occurred in 0.9%, and hypoparathyroidism occurred in another 0.9% of the patients. After 1 year of follow-up, cervical ultrasonography was normal in all patients, and recombinant human TSH-stimulated thyroglobulin was undetectable in 97% of the patients. The authors concluded that precise lymph-node staging produced using prophylactic cervical lymph-node dissection for tumors initially staged as T1N0* modified the indication for ¹³¹I ablation for 30% of the patients.

Taken together, the role of prophylactic central and ipsilateral lateral neck compartment dissections have a broad effect on identifying the extent of locoregional lymph-node metastases, a concept that must be examined within the framework of potential complications and patient acceptance of extensive surgery for relatively low-grade tumors. However, prophylactic surgery may help patients chose between small amounts of ¹³¹I (when it is necessary) in the range of 30 to 50 mCi for remnant ablation that may well reduce the rate of persistent or recurrent locoregional tumor to near zero.

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Address correspondence to:
Ernest L. Mazzaferri, M.D.
University of Florida
Gainesville, FL 32611

E-mail: mazz01@ufl.edu

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