

Extensive prophylactic central and lateral neck lymph-node compartment dissections for patients with papillary thyroid cancers smaller than 2 cm modifies the indication for ¹³¹I therapy

Bonnet S, Hartl D, Leboulleux S, Baudin E, Lombroso JD, Al Ghuzlan A, Chami L, Schlumberger M, Travaglini JP. Prophylactic lymph node dissection for papillary thyroid cancer less than 2 cm: implications for radioiodine treatment. *J Clin Endocrinol Metab* December 30, 2008. doi:10.1210/jc.2008-1931

SUMMARY

BACKGROUND Prophylactic cervical lymph-node dissection denotes removal of lymph nodes that are considered normal preoperatively or intraoperatively, and therapeutic dissection refers to removal of malignant lymph nodes identified before or during surgery. Although some advocate routine prophylactic cervical-lymph-node central-compartment dissection for patients with papillary thyroid cancer (PTC), this remains controversial. The aim of this retrospective study was to quantify the role of prophylactic central and lateral neck lymph-node compartment dissection, and to describe its role in staging small tumors and treating them with ¹³¹I.

METHODS Patients selected for study had PTCs 1 to 1.9 cm designated as stage T1N0 according to the 6th edition of the American Joint Commission on Cancer (AJCC) TNM classification (T denotes tumor; N lymph node, and M distant metastases [<https://www.protocols.fccc.edu/fccc/pims/staging/thyroid.html>]).

All had negative results on neck ultrasonography preoperatively and had total thyroidectomy, prophylactic bilateral level VI, and ipsilateral level III and IV cervical-lymph-node compartment dissections (Figure 1) that were extended to levels II and V when tumor was found in the superior pole of the thyroid or when metastases were found in level III or IV. Radioiodine therapy was not administered when a patient had no adverse prognostic factors such as lymph-node metastases, no tumor extension beyond the thyroid capsule, vascular invasion, unfavorable histology such as tall-cell carcinoma, or T1 <10-mm tumors with lymph-node micrometastases or when the patient was 18 years of age or younger. The others were treated with 30 to 100 mCi of ¹³¹I (1.1 to 3.7 GBq) after levothyroxine withdrawal or recombinant human thyrotropin (rhTSH) administration. All patients had follow-up for at least 1 year. Paralysis of the recurrent laryngeal nerve or hypoparathyroidism was considered permanent if it persisted for longer than 1 year. A serum thyroglobulin (Tg) ≤0.9 ng/ml was considered undetectable.

RESULTS A total of 115 patients were studied (99 women [86%], 16 men [14%]; mean age, 48.5 years; range, 18 to 73 years; median, 50 years). Mean PTC size was 13.1 mm (range, 1-19) on ultrasound and 12.5 mm (range, 1 to 19) on final pathology, and was smaller than 10 mm in 51 patients (44%). The tumor was unifocal in 73 patients (64%), multifocal and bilateral in 25 (22%), and multifocal but unilateral in 17 (15%), extended beyond the thyroid capsule (pT3) in 33 (29%), and showed vascular invasion in 7 (6%) (Figure 2). Two had diffuse sclerosing variant PTC. Bilateral prophylactic central neck dissection was performed in all of the patients; prophylactic ipsilateral dissections were performed in 96 (94%) and bilateral

level III-IV dissections were performed in 6 (6%). Ipsilateral level II-III-IV-V dissections were performed in 13 patients, 10 of whom (77%) had ipsilateral and 3 (23%) bilateral tumors (Figure 3). The mean number of central lymph nodes dissected per patient was 12 (range, 2 to 26; median, 7) and the mean number of lymph nodes per patient was 5 (range, 1 to 11; median, 2). Among the metastatic lymph nodes, 14.8% had extracapsular extension. The

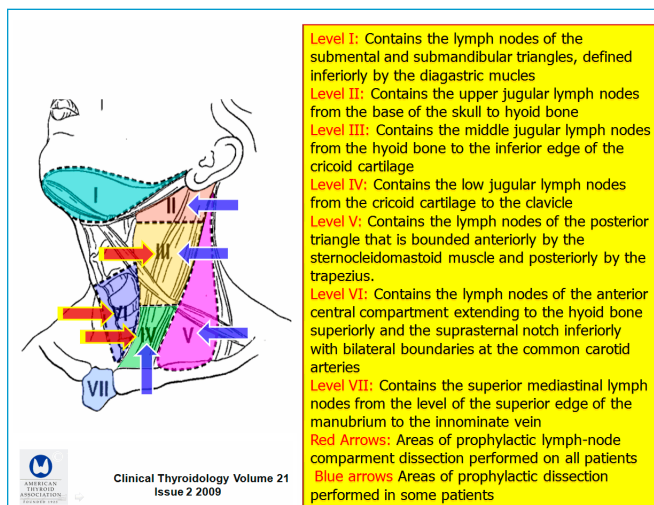


Figure 1. The cervical lymph-node compartments. Prophylactic ipsilateral cervical-lymph-node compartments III-IV and bilateral compartment VI dissections were performed in all patients (red arrows). Some underwent further prophylactic dissections in levels II-III-IV-V because of metastases in other neck compartments (blue arrows).

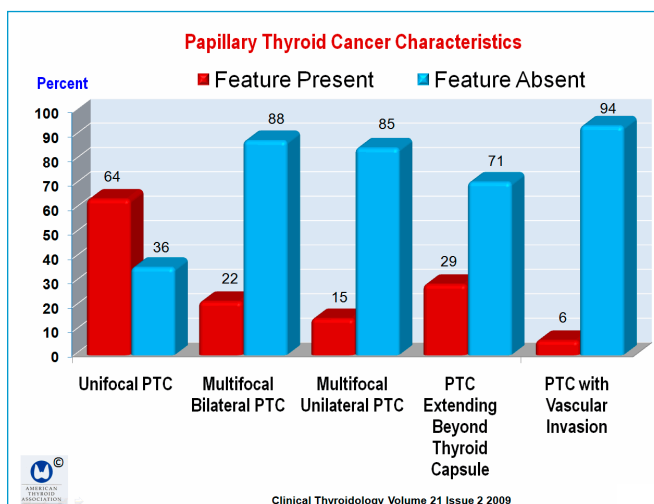


Figure 2. The characteristics of papillary thyroid cancers found at initial surgery.

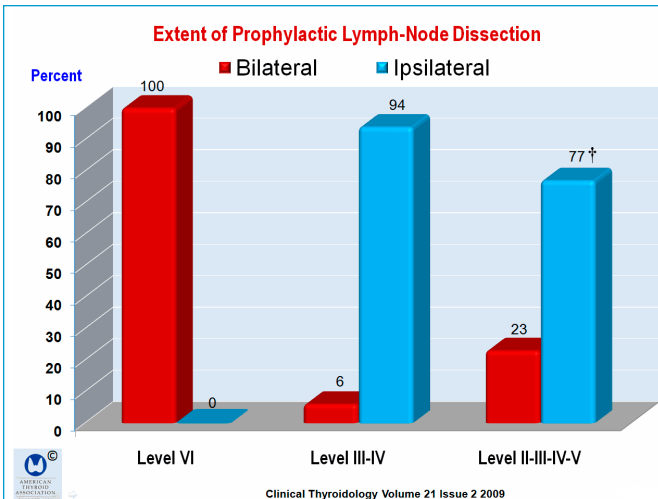


Figure 3. The extent of prophylactic lymph-node dissection. The indications for 10 patients with ipsilateral level II-III-IV-V dissections were PTC in the superior thyroid pole or metastatic lymph-node metastases in levels III-IV. Bilateral dissections in II-III-IV-V were performed in because of contralateral involvement in the same compartments. This figure is derived from data in Table 2 in Bonnet et al.

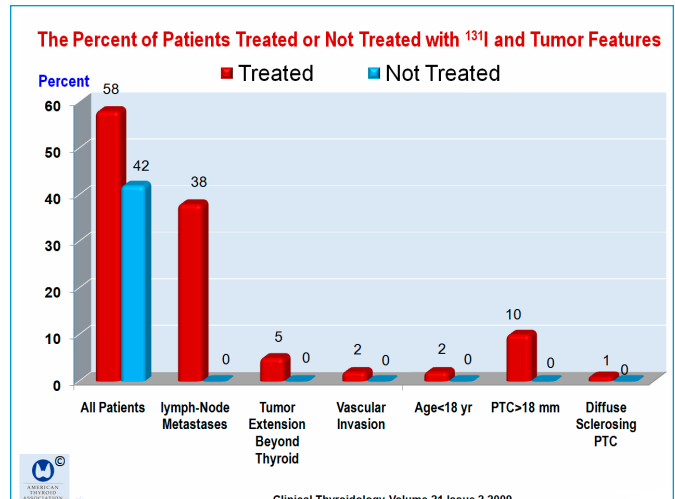


Figure 5. The indications for 131I therapy.

In all, 48 patients (42%) were not treated with 131I. Of this group, 44 (92%) had no lymph-node metastases or adverse prognostic factors, which included 31 tumors <10 mm and 13 >10 mm; 4 had a PTC <10 mm with micrometastases (Figure 5). In all, 67 patients (58%) had 131I therapy for the following adverse prognosis factors: lymph-node metastases in 44 patients (38%), PTC >18 mm in 12 (10%), tumor extension beyond the thyroid capsule in 6 (5%), vascular invasion in 2 (2%), diffuse sclerosing variant of PTC in 1 (0.9%), and age <18 years in 2 (2%). Using the European consensus recommendations, lymph-node status modified the decision for postsurgical 131I ablation for 25 of 115 patients (21.7%), 13 with T >10 mm and 12 with T <10 mm. Excluding the 33 patients with pT3 tumors, the indication for 131I remnant ablation was modified in 25 of 82 patients (30.5%) with pT1 tumors. On the posttreatment whole-body scan, 59 patients (51%) had foci of 131I uptake in the thyroid bed thought to be thyroid remnant. Radioiodine uptake was found in the central neck in 2 patients and in the lateral neck in 6, 1 of whom also had diffuse lung uptake.

One year after surgery, 1 patient (0.9%) had persistent laryngeal palsy and another (0.9%) had persistent hypoparathyroidism; no patients had suspicious cervical lymph nodes on ultrasound. Serum Tg levels during thyroid hormone suppression or rhTSH stimulation levels of Tg was undetectable ($\leq 0.9 \mu\text{IU/ml}$) on levothyroxine or after rhTSH stimulation in 97% of patients who had been treated postoperatively with 131I.

CONCLUSION Prophylactic central and ipsilateral lateral neck dissection for PTC smaller than 2 cm facilitates the accurate selection of patients for 131I ablation and modifies the indication for 131I in 30% of patients with T1 tumors.

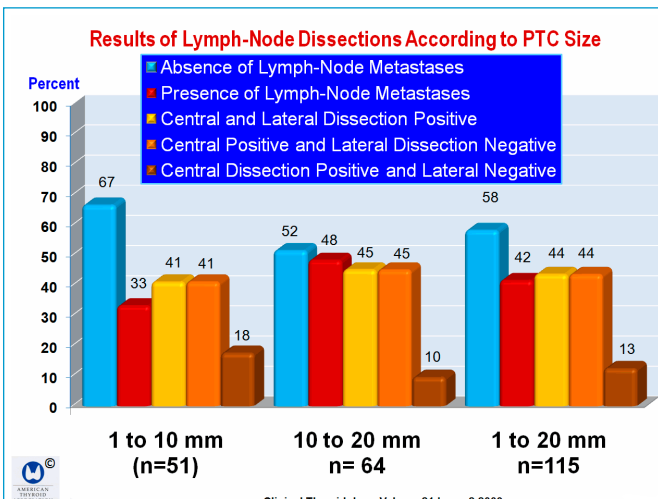


Figure 4. The results of lymph-node compartment dissections according to tumor size. This figure is derived from data in Table 3 in Bonnet et al.

results of lymph-node dissection according to PTC size are shown in Figure 4.

Univariate analysis identified the following prognostic factors for lymph-node involvement: age younger than 50 years ($P = 0.001$) and tumor extension beyond the thyroid capsule ($P = 0.031$), but multivariate analysis identified only age (odds ratio, 5.657; $P < 0.001$) and tumor extension (odds ratio, 2.477; $P = 0.48$) as significant factors for lymph-node metastases.

COMMENTARY

Slow growth and a favorable prognosis for survival characterize the clinical behavior of small PTCs with regional lymph-node metastases; however, the major challenge is to control locoregional recurrence, which happens with surprisingly high frequency. The rates of PTC lymph-node metastases in both low- and high-risk patients range from 25% to 60%, depending on the extent of surgery (1-3). Although lymph-node metastases are widely regarded to increase local recurrence rates without affecting survival, several studies suggest otherwise. A study of prophylactic lymph-node dissection in 342 patients with PTC found that systematic compartment-oriented dissection of lymph-node metastases improved recurrence ($P<0.0001$) and survival ($P<0.005$) especially in patients with T1 to T3 tumors (AJCC) (4). A study of almost 10,000 patient records maintained in the Surveillance, Epidemiology, and End Results (SEER) registry found that 14-year survival of patients with and without lymph-node metastases was 82% and 79%, respectively ($P<0.05$) (5). A more recent study (6) of the SEER registry records of 33,088 patients found that lymph-node metastases in patients 45 years or older with PTC, and patients of all ages with follicular thyroid cancer were associated with a 46% increased risk of death ($P<0.001$).

The ATA guidelines under revision suggest that prophylactic central-compartment neck dissection (ipsilateral or bilateral) may be performed in patients with PTC with clinically uninvolved central neck lymph nodes, especially for advanced primary tumors (T3 or T4), which is a Grade C recommendation (Expert Opinion), and that near-total or total thyroidectomy without prophylactic central neck dissection may be appropriate for small (T1 or T2) noninvasive clinically node-negative PTCs and most follicular cancers (Grade C recommendation). The ATA guidelines also suggest preoperative cervical ultrasonography in all patients undergoing thyroidectomy. Although ultrasonography may identify suspicious cervical lymphadenopathy in up to half the cases, potentially altering the surgical approach in many patients, it has serious limitations in evaluating extracapsular invasion of the thyroid in deep locations in the neck and lymph-node metastasis in the central neck, which may lower the sensitivity of ultrasonography as much as 35% (7). There is controversy about prophylactic lymph-node dissections, especially in lymph-node compartment level VI. A systematic review of central

lymph-node dissection by White et al. (8) found that systematic compartment-oriented central lymph-node dissection may decrease recurrence of PTC and likely improves disease-specific survival (Grade C recommendation) and that adding central lymph-node dissection to total thyroidectomy can significantly reduce serum Tg levels. They also concluded that there may be a higher rate of permanent hypoparathyroidism and unintentional permanent laryngeal nerve injury when compartment-oriented central lymph-node dissection is performed. Further, reoperation in the central neck compartment for recurrent PTC may increase the risk for hypoparathyroidism and unintentional nerve injury as compared with total thyroidectomy with or without central lymph-node dissection (Grade C recommendation) supporting a more aggressive initial operation (12).

The Bonnet study is a remarkable contribution that shows how meticulous lymph-node compartment dissection provides explicit information about initial tumor stage, which was far greater than T1N0 in a number of cases. The findings at surgery modified the decision for remnant ablation in 30% of the patients. No ^{131}I was administered to 42% of the patients, and 58% were treated with ^{131}I . The tumor was found to be unifocal in 64%, multifocal and bilateral in 22% and multifocal but unilateral in 17 (15%), and extended beyond the thyroid capsule (pT3) in 29%, and showed vascular invasion in 6%. None of this was suspected preoperatively. Prophylactic dissection resulted in unambiguous ^{131}I treatment of patients with lymph-node metastases while forgoing ^{131}I therapy for those without residual locoregional tumor. Whether patients will accept such extensive surgery for what is traditionally thought to be low-risk tumor remains to be seen.

Another important matter is that surgeons may not embrace this approach, as it likely prolongs the operative time for thyroidectomy. The surprising thing, however, is how prophylactic compartment dissection remarkably changed the stage of the disease, as compared with preoperative ultrasonography. Advocates of postsurgical radiation should recognize that the Bonnet study points the way to accurate selection of patients for ^{131}I therapy after surgery when tumors are metastatic or invasive.

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References

1. Chow SM, Law SC, Chan JK, et al. Papillary microcarcinoma of the thyroid--prognostic significance of lymph node metastasis and multifocality. *Cancer* 2003;98:31-40.
2. Wada N, Duh QY, Sugino K, et al. Lymph node metastasis from 259 papillary thyroid microcarcinomas: frequency, pattern of occurrence and recurrence, and optimal strategy for neck dissection. *Ann Surg* 2003;237:399-407.
3. Pereira JA, Jimeno J, Miquel J, et al. Nodal yield, morbidity, and recurrence after central neck dissection for papillary thyroid carcinoma. *Surgery* 2005;138:1095-101.
4. Scheumann GF, Gimm O, Wegener, G et al. Prognostic significance and surgical management of locoregional lymph node metastases in papillary thyroid cancer. *World J Surg* 1994;18:559-68.
5. Podnos YD, Smith D, Wagman LD, et al. The implication of lymph node metastasis on survival in patients with well-differentiated thyroid cancer. *Am Surg* 2005;71:731-4.
6. Zaydfudim V, Feuer ID, Griffin MR, et al. The impact of lymph node involvement on survival in patients with papillary and follicular thyroid carcinoma. *Surgery* 2008;144:1070-8.
7. Shimamoto K, Satake H, Sawaki A, et al. Preoperative staging of thyroid papillary carcinoma with ultrasonography. *Eur J Radiol* 1998;29:4-10.
8. White ML, Doherty GM, Gauger PG. Evidence-based surgical management of substernal goiter. *World J Surg* 2008;32:1285-300.