Published in final edited form as:

Br J Surg. 2016 February ; 103(3): 218–225. doi:10.1002/bjs.10036.

Outcomes for patients with papillary thyroid cancer who do not undergo prophylactic central neck dissection

I. J. Nixon¹, L. Y. Wang¹, I. Ganly¹, S. G. Patel¹, L. G. Morris¹, J. C. Migliacci¹, R. M. Tuttle², J. P. Shah¹, and A. R. Shaha¹

¹Head and Neck Surgery, Memorial Sloan Kettering Cancer Center, New York, USA

²Department of Endocrinology, Memorial Sloan Kettering Cancer Center, New York, USA

Abstract

Background—The role of prophylactic central neck dissection (CND) in the management of papillary thyroid cancer (PTC) is controversial. This report describes outcomes of an observational approach in patients without clinical evidence of nodal disease in PTC.

Methods—All patients who had surgery between 1986 and 2010 without CND for PTC were identified. All patients had careful clinical assessment of the central neck during preoperative and perioperative evaluation, with any suspicious nodal tissue excised for analysis. The cohort included patients in whom lymph nodes had been removed, but no patient had undergone a formal neck dissection. Recurrence-free survival (RFS), central neck RFS and disease-specific survival (DSS) were calculated using the Kaplan–Meier method.

Results—Of 1798 patients, 397 (22.1 per cent) were men, 1088 (60.5 per cent) were aged 45 years or more, and 539 (30.0 per cent) had pT3 or pT4 disease. Some 742 patients (41.3 per cent) received adjuvant treatment with radioactive iodine. At a median follow-up of 46 months the 5-year DSS rate was 100 per cent. Five-year RFS and central neck RFS rates were 96.6 and 99.1 per cent respectively.

Conclusion—Observation of the central neck is safe and should be recommended for all patients with PTC considered before and during surgery to be free of central neck metastasis.

Introduction

Lymph node metastasis in papillary thyroid cancer (PTC) is common^{1–3}. In contrast to other human malignancies, regional metastases are not always associated with disease-specific mortality. In patients under 45 years of age there is little influence on survival. Older patients and those with clinically detectable disease in the lateral neck have higher rates of distant failure and disease-related death⁴. Although most nodal metastases have little impact on survival, they have been associated with higher rates of recurrence^{5,6}.

Correspondence to: Dr I. J. Nixon, Head and Neck Surgery, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10021, USA (iainjnixon@gmail.com).

Disclosure

The authors declare no conflict of interest.

Management for patients who present with clinical evidence of nodal disease involves total thyroidectomy and a compartment-oriented neck dissection. Management of the clinically node-negative neck is controversial. In this situation, occult metastases are common⁷. Centres that routinely perform prophylactic central neck dissection (CND) report rates of subclinical disease of up to 40 per cent. Controversy stems from the uncertainty about the impact of such microscopic nodal disease.

Although prophylactic CND does not lead to improved survival rates, some authors recommend the procedure in order to improve risk stratification and target patients with occult nodal disease for more aggressive therapy in the form of radioactive iodine (RAI) administration⁸. It has been suggested that following prophylactic CND, in contrast to total thyroidectomy alone, postoperative thyroglobulin levels are lower, facilitating follow-up⁹. By removing occult disease, recurrence rates should theoretically be reduced, and outcomes improved¹⁰.

Authors who oppose prophylactic CND highlight the low rates of persistent disease or central neck recurrence following observation alone^{11,12}.

Although this issue could be resolved with a prospective randomized clinical trial, it has been calculated¹³ that more than 5000 patients would have to be recruited, making such a trial impractical. Thus, at present, clinicians have to rely on observational studies with analysis of high-quality data to plan treatment and advise patients.

The Memorial Sloan Kettering Cancer Center (MSKCC) has previously reported¹² the outcomes of patients managed at this institution who had no nodes included in a total thyroidectomy specimen. This historical cohort excluded all patients who had any nodal tissue excised, including those who had negative frozen-section biopsies, and any patient with nodes detected on histopathological examination of the perithyroid tissue.

The aim of this study was to report the long-term outcomes of a large, updated cohort of clinically node-negative (cN0) patients with PTC. The patients underwent total thyroidectomy and postoperative observation of the central neck, in order to determine the rates of recurrence and reoperation.

Methods

Following institutional review board approval, the MSKCC institutional database of patients who had primary treatment for differentiated thyroid cancer between 1986 and 2010 was analysed. Patients with non-papillary histology were excluded, as were patients with distant metastases at presentation and those with less than total thyroidectomy or lateral neck dissection. In addition, patients who underwent a CND were excluded. At MSKCC, prophylactic CND is not practised. Therapeutic CND is performed based on preoperative and intraoperative assessment of the central neck. Frozen-section examination is used generously. If nodes are thought macroscopically suspicious and frozen-section findings confirm malignancy, appropriate CND is performed.

Details of patients, surgery and adjuvant therapy were extracted. Histopathological data included primary tumour size, presence of extrathyroidal extension, and presence of nodal tissue and any evidence of nodal metastasis. The TNM stage was reported. All patients were assigned a risk stratification category using both the MSKCC GAMES (gender, age, metastasis, extrathyroidal extension, size) system for predicting risk of death from disease¹³ and the American Thyroid Association system for predicting recurrence risk⁶.

During the early years of the study, ultrasound imaging was not used routinely for preoperative assessment. Patients were assessed in the clinic and again during the procedure, and, if no suspicious nodal disease was identified, no central compartment neck dissection was performed. During the study interval, the use of ultrasonography has become routine. Postoperative thyroid-stimulating hormone suppression was used for all patients, aiming for a level between 0.1 and 0.5 μ units/ml. The use of thyroglobulin and ultrasound imaging for post-treatment assessment has become standard over the past 10–15 years. Before that, however, it was not used. No patient included in this study underwent a formal prophylactic CND. However, in contrast to the previous publication from MSKCC¹², some patients had incidental nodal tissue removed that was later analysed and included in the histological report. This included patients who had nodes excised in the perithyroid soft tissues, and those who had node samples sent for analysis during surgery.

Outcomes were analysed to identify local, regional and distant recurrence as well as death from disease. All recurrences were agreed by the disease management team. Locoregional recurrences were confirmed on cytological or histological examination. Distant recurrence was determined by imaging studies including RAI uptake scans, CT, PET, or cytological and histopathological evidence where available. Isolated biochemical recurrence was not included in the absence of cytological confirmation, as practice patterns changed significantly during the follow-up and this information was not available for all patients.

Statistical analysis

Statistical analysis was carried out using SPSS® version 21 (IBM, Armonk, New York, USA). Variables were compared within groups using Pearson's χ^2 test. Survival outcomes were analysed using the log rank test for univariable analysis. Cox regression was used in univariable and multivariable models and results presented as hazard ratios (HRs) with 95 per cent c.i. Variables included in the multivariable model (age, sex and extrathyroidal extension) were selected as known risk factors for recurrence as recognized in the recent British Thyroid Association guidelines¹⁴. $P < 0.050$ was considered statistically significant.

Results

During the study period, 3665 patients had primary treatment for differentiated thyroid cancer at MSKCC. Some 1798 patients (49.1 per cent) with PTC who underwent total thyroidectomy and observation of the central neck were eligible for the study (Fig. 1). The median follow-up for the entire patient cohort was 46 (range 1–320) months.

Patient and tumour characteristics for 1798 patients selected for neck observation are shown in Table 1. These characteristics were compared with those for 338 patients selected to have

central compartment neck dissection. Patients managed by neck observation alone were more likely to be 45 years of age or older, to have less advanced pT and pN category, and less likely to receive adjuvant RAI.

The median age of the neck observation cohort was 49 (range 12–89) years. Some 397 patients (22.1 per cent) were men and 539 (30.0 per cent) had pT3 or pT4 tumours. Following histopathological analysis, 260 patients (14.5 per cent) were found to have evidence of metastatic nodal disease either in perithyroid tissues or in nodes removed from the central or lateral compartments. Some 243 (13.5 per cent) of these patients had nodes with metastasis in the perithyroid tissue (pN1a). Seventeen patients (0.9 per cent) had nodal tissue sampled from the lateral neck that was shown to be positive on histopathology (pN1b). Of the 864 patients with a diagnosis of pN0 and 260 patients with pN1 disease on histopathology, 341 (39.5 per cent) and 151 (58.1 per cent) respectively had nodes excised separately from the thyroid surgical specimen. None of these patients underwent formal CND or lateral neck dissection. Patients with pN1 disease had low-volume neck disease that was resected from the neck at the time of primary thyroid surgery. The remaining patients either had nodes removed with no evidence of metastatic disease (pN0: 864 patients, 48.1 per cent) or no nodal tissue present in the surgical specimen (pNx: 674 patients, 37.5 per cent). Some 742 patients (41.3 per cent) received adjuvant RAI. When stratified by RAI *versus* no RAI, the patients who received RAI were more likely to be men, aged 45 years or above, and have advanced pT and pN stage (Table 2).

The 5-year disease-specific survival (DSS) rate was 100 per cent. There were 48 recurrences during follow-up (8 local, 35 regional, 8 distant), with some patients having more than one type of recurrence. The 5-year recurrence-free survival (RFS) rate was 96.6 per cent.

In univariable analysis, reduced 5-year RFS was associated with male sex (93.9 per cent *versus* 97.4 per cent in women; $P = 0.004$), extrathyroidal extension (92.5 per cent *versus* 98.4 per cent in those with no extension; $P < 0.001$), advanced T category (86.4 per cent in patients with pT4 disease *versus* 96.9 per cent in those with pT1–3 disease; $P < 0.001$) (Fig. 2), and nodal disease (91 per cent for pN1 disease *versus* 98 per cent for pN0 or pNx disease; $P < 0.001$).

Factors predictive of RFS are shown in Table 3. Men and patients with extrathyroidal extension had a worse outcome. Age 45 years or over was not predictive of recurrence in the multivariable model.

The 5-year regional RFS rate was 97.5 per cent. Of the 35 regional recurrences, 23 were in the lateral neck alone, seven in the central neck alone, and five in both the central and lateral neck. The 5-year RFS rate for the central neck was 99.1 per cent.

Analysis of factors predictive of regional RFS is shown in Table 4. In univariable analysis, male sex, extrathyroidal extension, advanced T category, nodal disease and RAI use were significant. As seen in Table 2, RAI was used more commonly in high-risk patients; the 5-year RFS rate was 94.7 per cent in these patients. In multivariable analysis, male sex and extrathyroidal extension remained predictive.

Univariable analysis of patients with central neck node recurrence specifically showed male sex (97.7 per cent *versus* 99.5 per cent for women; $P=0.003$), pN1 category (96.4 per cent *versus* 99.7 per cent for pN0/pNx; $P<0.001$) and RAI administration (98.6 per cent *versus* 99.6 per cent with no RAI use; $P=0.034$) to be associated with poor outcome in this group (log rank test). There were insufficient events to support multivariable analysis of central neck recurrence. Only 12 (0.7 per cent) of the 1798 patients in this cohort had recurrence in the central neck nodes. Of these, seven patients had pT3 disease and nine had metastatic nodal tissue excised at the time of surgery (pN1a). Ten of these 12 patients had been treated with RAI following initial surgery. Eleven of the 12 patients went on to have central neck surgery for recurrent disease and one received RAI following cytological confirmation of recurrence. Although pT4 disease was uncommon (33 patients, 1.8 per cent), there was an association with lateral neck recurrence: four patients with pT4 disease developed recurrence in the lateral neck during follow-up.

No patient had a recurrent laryngeal nerve palsy or permanent hypocalcaemia, and all patients are currently alive with no evidence of disease.

Discussion

The authors have previously reported results from a group of patients with cN0 disease who had no nodal tissue excised from the central compartment following total thyroidectomy for PTC (pNx)¹². This study suggested that outcomes were excellent without prophylactic CND. In routine clinical practice, however, not all patients managed without prophylactic CND actually have pNx disease. Many patients have nodal tissue excised from the perithyroid tissue or during operative sampling. The present study broadened the inclusion criteria to include all patients who were managed without prophylactic CND to reflect standard clinical practice. In addition, the institutional database has been updated to include an additional 5 years of practice.

The present report is of 1798 patients managed over a 25-year period with a specific focus on the follow-up status of those who did not undergo CND. This cohort included 84.2 per cent of patients who were treated for PTC at MSKCC during this interval. Some 14.5 per cent of the cohort had incidental positive nodal disease identified on histological analysis. The majority of positive nodes were in the central neck. However, 0.9 per cent were in the lateral neck. These patients had small-volume nodal disease, and no patient underwent a formal neck dissection. More than 80 per cent of reoperations for thyroid cancer are performed within the first 2 years of postoperative follow-up¹⁵, suggesting that the median follow-up of 46 months reported here should be adequate to identify the majority of recurrences in this cohort.

With a 5-year DSS and RFS rates of 100 and 96.6 per cent respectively, outcomes in this group were excellent. Only 12 patients had recurrence in the central neck (less than 1 per cent). All were salvaged successfully and are alive with no evidence of disease at the time of writing.

It is widely accepted that metastasis to regional nodes is common in patients with PTC³. Despite this, most patients who present with PTC will have excellent outcomes¹⁶. Few patients die from disease, recurrences are uncommon, and almost all can be salvaged successfully with appropriate surgery^{17,18}. The incongruity between high rates of occult metastasis and excellent outcomes shows that the majority of metastases do not progress to clinically significant disease. Although most authors agree that elective lateral neck dissection should not be recommended, the situation in relation to the central neck is controversial. Clinical examination, ultrasound assessment and even intraoperative examination of the central compartment are all unreliable predictors of microscopic metastatic disease^{15,19}.

Advocates of prophylactic CND highlight rates of histologically identified metastatic nodes of up to 40 per cent⁷. This occult node disease results in the upstaging of patients aged 45 years or more by International Union Against Cancer/American Joint Committee on Cancer (UICC/AJCC) criteria^{20,21}, which may influence decisions regarding adjuvant RAI treatment in up to one-third of patients⁸. Prophylactic CND has been associated with lower postoperative rates of raised thyroglobulin levels^{9,22}, which suggests that the burden of persistent disease is lower following prophylactic CND, perhaps resulting in improved outcomes.

However, prophylactic CND has never been shown to improve survival. Although experts appear able to perform CND with minimal long-term complications, evidence that these outcomes can be replicated by community surgeons is lacking^{23,24}. Even in high-volume cancer centres, rates of hypocalcaemia and recurrent laryngeal nerve injury have been shown to be greater following prophylactic CND compared with thyroidectomy alone²⁵.

The clinical value of upstaging this group of patients by identifying microscopic nodal disease is highly questionable¹², particularly given the current appreciation of the small but significant side-effects of adjuvant RAI^{26–31}. Of note, those groups who have reported large series of revisional surgery in the central neck have found high rates of disease in areas not normally included in prophylactic CND.

This study does have limitations. The patient group was managed over a 25-year period, and although ultrasound imaging was not used in the early years of the study, in later years it became a routine part of preoperative clinical assessment. It is therefore likely that suspicious disease was identified before operation in an increasing number of patients treated in the later years of the study. However, if anything, this strengthens the results, as even patients in the early part of the study, who were likely to have had disease that today would be identified and resected, had excellent outcomes. In this investigation, structural recurrence was chosen as an endpoint as data were available throughout the study interval.

The presence of a preoperative diagnosis of malignancy was not recorded in the institutional database. Some patients may have had diagnostic surgery, although standard practice at MSKCC is to perform diagnostic lobectomy rather than total thyroidectomy, as reported here. The majority of patients who undergo treatment in this institution have a diagnosis of cancer before referral. Some patients with multinodular disease may have undergone

diagnostic total thyroidectomy and had malignancy confirmed on histological analysis. Nonetheless, at MSKCC, even when malignancy is confirmed before surgery, CND is not performed unless evidence of regional metastasis is confirmed.

As an international tertiary referral centre, MSKCC has a large cohort of patients who visit from outside the local area of the institution. Although many patients return regularly for review by the disease management team, some are inevitably lost to follow-up. For this reason, the median follow-up was only 46 months. This relatively short follow-up may result in some late recurrences being missed. However, although late recurrences are reported, the majority of recurrent disease will be identified within the first 5 years of follow-up^{18,32}.

Frozen-section analysis is in routine use within MSKCC. However, the number of patients who had frozen-section examination of nodal tissue was not included in the data collected, and so was not available for analysis. Although frozen section is used, the presence of PTC in a macroscopically normal central neck lymph node is not used as an indicator for therapeutic CND. However, it is possible that this practice influenced the results.

The institutional database does not contain information that allowed the authors to determine whether the nodes excised were included in the perithyroid tissue or were sampled selectively during thyroidectomy. Seventeen patients (0.9 per cent) had pN1b disease. It is standard practice at MSKCC to perform therapeutic neck dissection when lateral neck disease is identified. These patients had small-volume nodal metastases, and a decision was made not to perform formal neck dissection.

The introduction of routine serial ultrasound imaging and thyroglobulin administration during the follow-up of these patients with PTC has also impacted on postoperative outcomes. Such investigations were not employed during the early years of the study, and it is conceivable that patients lost to follow-up before the routine use of such investigations may have harboured occult persistent nodal disease.

This study has important clinical implications. Survival cannot be improved for patients with no evidence of regional metastasis by the practice of prophylactic CND. The study adds follow-up data to cohorts such as that reported by Monchik and colleagues¹¹, who concluded that prophylactic CND is not required in selected low-risk patients with PTC.

Adjuvant treatment with RAI was used more commonly in high-risk patients. However, even in the higher-risk patients selected for RAI, recurrence rates were low (5.3 per cent at 5 years).

More than half (7 of 12) of the patients with recurrence in the central neck had pT3 disease. In the present study pT4 disease was uncommon, and was associated with lateral neck rather than central neck recurrence. However, low rates of recurrence, even in the presence of extra-thyroidal extension, support the approach of observation of the lateral neck despite locally advanced disease.

Less than 10 per cent of patients with pN1 disease will have recurrence at 5 years. In this study, all patients with central neck recurrence were able to be salvaged.

The results of the present study show that patients with PTC with no preoperative evidence of metastasis to the central neck, who are selected for observation rather than prophylactic CND, have an excellent outcome.

References

1. Shaha AR, Shah JP, Loree TR. Patterns of nodal and distant metastasis based on histologic varieties in differentiated carcinoma of the thyroid. *Am J Surg*. 1996; 172:692–694. [PubMed: 8988680]
2. Roh JL, Park JY, Park CI. Total thyroidectomy plus neck dissection in differentiated papillary thyroid carcinoma patients: pattern of nodal metastasis, morbidity, recurrence, and postoperative levels of serum parathyroid hormone. *Ann Surg*. 2007; 245:604–610. [PubMed: 17414610]
3. Randolph G, Duh QY, Heller KS, Livolsi VA, Mandel SJ, Steward D, et al. The prognostic significance of nodal metastases from papillary thyroid carcinoma can be stratified based on the size and number of metastatic lymph nodes, as well as the presence of extranodal extension at a surgical affairs committee's taskforce on thyroid cancer nodal surgery. *Thyroid*. 2012; 22:1144–1152. [PubMed: 23083442]
4. Cady B, Sedgwick CE, Meissner WA, Bookwalter JR, Romagosa V, Werber J. Changing clinical, pathologic, therapeutic, and survival patterns in differentiated thyroid carcinoma. *Ann Surg*. 1976; 184:541–553. [PubMed: 984923]
5. Hughes CJ, Shaha AR, Shah JP, Loree TR. Impact of lymph node metastasis in differentiated carcinoma of the thyroid: a matched-pair analysis. *Head Neck*. 1996; 18:127–132. [PubMed: 8647677]
6. Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid*. 2009; 19:1167–1214. [PubMed: 19860577]
7. Hartl DM, Leboulleux S, Al Ghuzlan A, Baudin E, Chami L, Schlumberger M, et al. Optimization of staging of the neck with prophylactic central and lateral neck dissection for papillary thyroid carcinoma. *Ann Surg*. 2012; 255:777–783. [PubMed: 22418010]
8. Hughes DT, White ML, Miller BS, Gauger PG, Burney RE, Doherty GM. Influence of prophylactic central lymph node dissection on postoperative thyroglobulin levels and radioiodine treatment in papillary thyroid cancer. *Surgery*. 2010; 148:1100–1106. [PubMed: 21134539]
9. Popadich A, Levin O, Lee JC, Smooke-Praw S, Ro K, Fazel M, et al. A multicenter cohort study of total thyroidectomy and routine central lymph node dissection for cN0 papillary thyroid cancer. *Surgery*. 2011; 150:1048–1057. [PubMed: 22136820]
10. Scheumann GF, Gimm O, Wegener G, Hundeshagen H, Dralle H. Prognostic significance and surgical management of locoregional lymph node metastases in papillary thyroid cancer. *World J Surg*. 1994; 18:559–567. [PubMed: 7725745]
11. Monchik JM, Simon CJ, Caragacianu DL, Thomay AA, Tsai V, Cohen J, et al. Does failure to perform prophylactic level VI node dissection leave persistent disease detectable by ultrasonography in patients with low-risk papillary carcinoma of the thyroid? *Surgery*. 2009; 146:1182–1187. [PubMed: 19958947]
12. Nixon IJ, Ganly I, Patel SG, Morris LG, Palmer FL, Thomas D, et al. Observation of clinically negative central compartment lymph nodes in papillary thyroid carcinoma. *Surgery*. 2013; 154:1166–1172. [PubMed: 24238042]
13. Shaha AR, Shah JP, Loree TR. Risk group stratification and prognostic factors in papillary carcinoma of thyroid. *Ann Surg Oncol*. 1996; 3:534–538. [PubMed: 8915484]
14. Perros P, Boelaert K, Colley S, Evans C, Evans RM, Gerrard Ba G, et al. British Thyroid Association. Guidelines for the management of thyroid cancer. *Clin Endocrinol (Oxf)*. 2014; 81(Suppl 1):1–122. [PubMed: 24989897]
15. Moreno MA, Edeiken-Monroe BS, Siegel ER, Sherman SI, Clayman GL. In papillary thyroid cancer, preoperative central neck ultrasound detects only macroscopic surgical disease, but negative findings predict excellent long-term regional control and survival. *Thyroid*. 2012; 22:347–355. [PubMed: 22280230]

16. Nixon IJ, Ganly I, Patel SG, Palmer FL, Whitcher MM, Ghossein R, et al. Changing trends in well differentiated thyroid carcinoma over eight decades. *Int J Surg.* 2012; 10:618–623. [PubMed: 23128246]
17. Onkendi EO, McKenzie TJ, Richards ML, Farley DR, Thompson GB, Kasperbauer JL, et al. Reoperative experience with papillary thyroid cancer. *World J Surg.* 2014; 38:645–652. [PubMed: 24305931]
18. Young S, Harari A, Smooke-Praw S, Ituarte PH, Yeh MW. Effect of reoperation on outcomes in papillary thyroid cancer. *Surgery.* 2013; 154:1354–1361. [PubMed: 24238053]
19. Hwang HS, Orloff LA. Efficacy of preoperative neck ultrasound in the detection of cervical lymph node metastasis from thyroid cancer. *Laryngoscope.* 2011; 121:487–491. [PubMed: 21344423]
20. American Joint Committee on Cancer. *AJCC Cancer Staging Manual.* 7th. New York: Springer; 2010.
21. Bozec A, Dassonville O, Chamorey E, Poissonnet G, Sudaka A, Peyrottes I, et al. Clinical impact of cervical lymph node involvement and central neck dissection in patients with papillary thyroid carcinoma: a retrospective analysis of 368 cases. *Eur Arch Otorhinolaryngol.* 2011; 268:1205–1212. [PubMed: 21607578]
22. So YK, Seo MY, Son YI. Prophylactic central lymph node dissection for clinically node-negative papillary thyroid microcarcinoma: influence on serum thyroglobulin level, recurrence rate, and postoperative complications. *Surgery.* 2012; 151:192–198. [PubMed: 21497873]
23. Ahn D, Sohn JH, Park JY. Surgical complications and recurrence after central neck dissection in cN0 papillary thyroid carcinoma. *Auris Nasus Larynx.* 2014; 41:63–68. [PubMed: 23886706]
24. Giordano D, Valcavi R, Thompson GB, Pedroni C, Renna L, Gradoni P, et al. Complications of central neck dissection in patients with papillary thyroid carcinoma: results of a study on 1087 patients and review of the literature. *Thyroid.* 2012; 22:911–917. [PubMed: 22827494]
25. Ywata de Carvalho A, Chulam TC, Kowalski LP. Long-term results of observation vs prophylactic selective level VI neck dissection for papillary thyroid carcinoma at a cancer center. *JAMA Otolaryngol Head Neck Surg.* 2015; 141:599–606. [PubMed: 25997016]
26. Almeida JP, Sanabria AE, Lima EN, Kowalski LP. Late side effects of radioactive iodine on salivary gland function in patients with thyroid cancer. *Head Neck.* 2011; 33:686–690. [PubMed: 21484917]
27. Iyer NG, Morris LG, Tuttle RM, Shaha AR, Ganly I. Rising incidence of second cancers in patients with low-risk (T1N0) thyroid cancer who receive radioactive iodine therapy. *Cancer.* 2011; 117:4439–4446. [PubMed: 21432843]
28. Lee SL. Complications of radioactive iodine treatment of thyroid carcinoma. *J Natl Compr Canc Netw.* 2010; 8:1277–1286. [PubMed: 21081784]
29. Grewal RK, Larson SM, Pentlow CE, Pentlow KS, Gonen M, Qualey R, et al. Salivary gland side effects commonly develop several weeks after initial radioactive iodine ablation. *J Nucl Med.* 2009; 50:1605–1610. [PubMed: 19759114]
30. Sawka AM, Thabane L, Parlea L, Ibrahim-Zada I, Tsang RW, Brierley JD, et al. Second primary malignancy risk after radioactive iodine treatment for thyroid cancer: a systematic review and meta-analysis. *Thyroid.* 2009; 19:451–457. [PubMed: 19281429]
31. Molinaro E, Leboeuf R, Shue B, Martorella AJ, Fleisher M, Larson S, et al. Mild decreases in white blood cell and platelet counts are present one year after radioactive iodine remnant ablation. *Thyroid.* 2009; 19:1035–1041. [PubMed: 19772430]
32. Durante C, Montesano T, Torlontano M, Attard M, Monzani F, Tumino S, et al. PTC Study Group. Papillary thyroid cancer: time course of recurrences during postsurgery surveillance. *J Clin Endocrinol Metab.* 2013; 98:636–642. [PubMed: 23293334]

Fig. 1.

Flow chart showing how the final cohort was derived. Values in parentheses are ranges.

*Some patients had more than one reason for exclusion. Information is also provided on the nodal yield in patients who did not undergo neck dissection

No. of patients

pT1–T3	1765	1358	1157	931	734	562
pT4	33	28	21	16	16	12

Fig. 2. Kaplan–Meier plot showing recurrence-free survival rates stratified by T category (pT1–pT3 versus pT4). $P < 0.001$ (log rank test)

Table 1Overall group stratified by central neck dissection *versus* no central neck dissection

	CND (<i>n</i> = 338)	No CND (<i>n</i> = 1798)	<i>P</i> *
Age (years)			<0.001
< 45	196 (60.0)	710 (39.5)	
≥ 45	142 (42.0)	1088 (60.5)	
Sex ratio (F : M)	250 : 88	1401 : 397	0.080
Extrathroidal extension			<0.001
None	187 (55.3)	1332 (74.1)	
Microscopic	88 (26.0)	339 (18.9)	
Macroscopic	63 (18.6)	127 (7.1)	
T category			<0.001
pT1	125 (37.0)	1044 (58.1)	
pT2	52 (15.4)	215 (12.0)	
pT3	140 (41.4)	506 (28.1)	
pT4	21 (6.2)	33 (1.8)	
N category			<0.001
pN0	103 (30.5)	864 (48.1)	
pNx	4 (1.2)	674 (37.5)	
pN1a	196 (58.0)	243 (13.5)	
pN1b	35 (10.4)	17 (0.9)	
Radioactive iodine			<0.001
Yes	229 (67.8)	742 (41.3)	
No	109 (32.2)	1056 (58.7)	

Values in parentheses are percentages. CND, central neck dissection.

* χ^2 test.

Table 2Patients without central node dissection stratified by radioactive iodine treatment *versus* no treatment

	No RAI (n = 1056)	RAI (n = 742)	P*
Age (years)			0.031
< 45	395 (55.6)	315 (44.4)	
≥ 45	661 (60.8)	427 (39.2)	
Sex			<0.001
F	864 (61.7)	537 (38.3)	
M	192 (48.4)	205 (51.6)	
T category			<0.001
pT1	809 (77.5)	235 (22.5)	
pT2	96 (44.7)	119 (55.3)	
pT3	150 (29.6)	356 (70.4)	
pT4	1 (3)	32 (97)	
N category			<0.001
pN0	573 (66.3)	291 (33.7)	
pNx	423 (62.8)	251 (37.2)	
pN1a	59 (24.3)	184 (75.7)	
pN1b	1 (6)	16 (94)	
GAMES			<0.001
High	105 (30.1)	244 (69.9)	
Intermediate	602 (64.8)	327 (35.2)	
Low	349 (67.1)	171 (32.9)	
ATA risk			<0.001
Low	810 (76.0)	256 (24.0)	
Intermediate	225 (37.2)	380 (62.8)	
High	21 (16.5)	106 (83.5)	

Values in parentheses are percentages. RAI, radioactive iodine; GAMES, gender, age, metastasis, extrathyroidal extension, size (Memorial Sloan–Kettering Cancer Center risk stratification system¹³); ATA, American Thyroid Association risk stratification system⁶.

* χ^2 test.

Table 3

Cox regression analysis of factors predictive of recurrence-free survival at 5 years

	Univariable analysis		Multivariable analysis	
	Hazard ratio	<i>P</i>	Hazard ratio	<i>P</i>
Age (years)				
< 45	1.00 (reference)		1.00 (reference)	
45	0.93 (0.53, 1.65)	0.810	0.74 (0.42, 1.32)	0.314
Sex				
F	1.00 (reference)		1.00 (reference)	
M	2.31 (1.30, 4.12)	0.005	2.40 (1.34, 4.28)	0.003
Extrathyroidal extension				
No	1.00 (reference)		1.00 (reference)	
Microscopic/macroscopic	3.92 (2.19, 7.01)	<0.001	4.12 (2.29, 7.40)	<0.001
T category				
pT1–pT3	1.00 (reference)			
pT4	7.57 (3.21, 17.86)	<0.001		
N category				
pN0/pNx	1.00 (reference)			
pN1	4.90 (2.78, 8.63)	<0.001		
Radioactive iodine				
Yes	1.00 (reference)			
No	0.25 (0.12, 0.53)	<0.001		

Values in parentheses are 95 per cent c.i.

Table 4

Cox regression analysis of factors predictive of regional recurrence-free survival

	Univariable analysis		Multivariable analysis	
	Hazard ratio	<i>P</i>	Hazard ratio	<i>P</i>
Age (years)				
< 45	1.00 (reference)		1.00 (reference)	
45	0.85 (0.44, 1.65)	0.628	0.65 (0.34, 1.28)	0.215
Sex				
F	1.00 (reference)		1.00 (reference)	
M	2.11 (1.06, 4.18)	0.033	2.22 (1.12, 4.41)	0.023
Extrathyroidal extension				
No	1.00 (reference)		1.00 (reference)	
Microscopic/macroscopic	6.22 (2.99, 12.96)	<0.001	6.63 (3.17, 13.88)	<0.001
T category				
pT1–pT3	1.00 (reference)			
pT4	6.32 (2.23, 17.91)	0.001		
N category				
pN0/pNx	1.00 (reference)			
pN1	6.46 (3.30, 12.64)	<0.001		
Radioactive iodine				
Yes	1.00 (reference)			
No	0.18 (0.07, 0.47)	<0.001		

Values in parentheses are 95 per cent c.i.