Surgery 165 (2019) 12–16

Contents lists available at ScienceDirect

Surgery

journal homepage: www.elsevier.com/locate/surg

NIFT-P: Are they indolent tumors? Results of a multi-institutional study ☆

Nathalie Chereau, MD[a,*], Tristan Greilsamer, MD[b], Eric Mirallié, MD[b], Samira M. Sadowski, MD[c], Marc Pusztaszeri, MD[c], Frederic Triponez, MD[c], Grégory Baud, MD[d], Francois Pattou, MD, PhD[d], Niki Christou, MD, PhD[e], Muriel Mathonnet, MD, PhD[e], Laurent Brunaud, MD, PhD[f], Nicolas Santucci, MD[g], Pierre Goudet, MD[g], Carole Guérin, MD[h], Frédéric Sebag, MD, PhD[h], Gianluca Donatini, MD, PhD[i], Jean-Louis Kraimps, MD, PhD[i], Frédérique Tissier, MD[j], Charlotte Lussey-Lepoutre, MD, PhD[k], Laurence Leenhardt, MD, PhD[l], Fabrice Menegaux, MD, PhD[a]

[a] *Sorbonne Université, Pitié Salpêtrière Hospital, Paris, France*
[b] *Clinique de Chirurgie Digestive et Endocrinienne (CCDE), Institut des maladies de l'Appareil Digestif (IMAD), Hôtel Dieu, CHU Nantes, France*
[c] *University Hospital of Geneva and Faculty of Medicine of Geneva, Geneva, Switzerland*
[d] *Claude Huriez University Hospital, Lille, France*
[e] *University Hospital of Limoges, France*
[f] *University of Lorraine, Brabois Hospital, Vandoeuvre-les-Nancy, France*
[g] *University Hospital of Dijon, France*
[h] *University of Aix Marseille, La Conception Hospital, France*
[i] *University of Poitiers, Jean Bernard Hospital, France*
[j] *Sorbonne Université, Department of Pathology,Pitié-Salpêtrière Hospital, Paris, France*
[k] *Sorbonne Université, Department of Nuclear medicine, Pitié-Salpêtrière Hospital, Paris, France*
[l] *Sorbonne Université, Thyroid and Endocrine Tumors Unit, Pitié-Salpêtrière Hospital, Paris, France*

ARTICLE INFO

Article history:
Accepted 9 April 2018
Available online 9 November 2018

ABSTRACT

Background: Encapsulated follicular variant of papillary thyroid carcinoma has recently been reclassified as noninvasive follicular thyroid neoplasm with papillary-like nuclear features on the basis of its highly indolent behavior, as proposed by an international group of experienced thyroid pathologists.
Methods: All patients from 9 high-volume endocrine surgery departments who underwent surgery between 2005 and 2015 and whose final surgical pathology revealed noninvasive follicular thyroid neoplasm with papillary-like nuclear features (>10 mm) were included in this study. The primary outcome was to determine the potential for recurrent disease in these patients.
Results: Among the 363 patients with noninvasive follicular thyroid neoplasm with papillary-like nuclear features, 76% were female with a median age of 50 years (5–86 years); 345 patients (95%) underwent total thyroidectomy. A total of 65 patients had an associated micropapillary thyroid carcinoma. In the group of 133 patients who underwent prophylactic lymph node dissection (37%), 1 patient had a micrometastasis but with an associated micropapillary thyroid carcinoma. Over a median follow-up period of 5 years, 1 patient with an associated micropapillary thyroid carcinoma had recurrent disease at 6 years. All patients with noninvasive follicular thyroid neoplasm with papillary-like nuclear features without micropapillary thyroid carcinoma had no lymph node metastasis or recurrent disease.
Conclusion: We found that noninvasive follicular thyroid neoplasm with papillary-like nuclear features presents with indolent behavior. However, the identification of an associated micropapillary thyroid carcinoma should be carefully evaluated because it could be a factor for lymph node metastasis and/or of recurrence.

☆ Presented at the American Association of Endocrine Surgeons 39th annual meeting in Durham, North Carolina, May 7, 2018.

* Corresponding author: Nathalie Chereau, Hospital Pitié Salpêtrière, Department of General and Endocrine Surgery, 47-83 Boulevard de l'Hôspital, Paris, France, 75013.
E-mail address: nathalie.chereau@aphp.fr (N. Chereau).

https://doi.org/10.1016/j.surg.2018.04.089
0039-6060/

Table 1
Diagnostic criteria for NIFT-P

1. Encapsulation or clear demarcation (thick, thin, or partial capsule or well circumscribed with a clear demarcation from adjacent thyroid tissue)
2. Follicular growth pattern with <1% papillae, no psammoma bodies, 30% solid/trabecular/insular growth pattern
3. Nuclear score 2–3
4. No vascular or capsular invasion
5. No tumor necrosis
6. No high mitotic activity

Note: adapted from Nikiforov et al, 2016

Introduction

The rates for new thyroid cancer cases have been rising 3% per year on average,[1] with papillary thyroid cancer (PTC), the most common histologic type, now accounting for more than 90% of new cases[1]. PTC usually has a favorable outcome, with its 5-year survival rate exceeding 98% (National Cancer Institute Surveillance, Epidemiology, and End Results Program (SEER); Available at: https://seer.cancer.gov/). It has been demonstrated that overdiagnosis or the increased ability to detect and diagnose small indolent tumors[2] is not solely responsible for this increase. A true increase in PTC incidence has been documented, particularly because the follicular variant of papillary thyroid carcinoma (FVPTC) accounts for approximately 10% to 20% of PTC tumors.[3–5] FVPTCs appear to represent a heterogeneous group of carcinomas, including encapsulated/noninvasive and invasive FVPTCs (17% and 4% of FVPTCs, respectively), both of which seem to bear different prognostic and molecular features. Invasive FVPTCs demonstrate a more aggressive behavior characterized by lymph node (LN) metastases, disease recurrence, and (BRAF) mutations.[6] Conversely, noninvasive FVPTCs demonstrate highly indolent behavior and have been reclassified by an international group of experienced thyroid pathologists as noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFT-P).[7] To date, there has not been a large, multicentric evaluation of this reclassification as a nonmalignant condition.

The aims of this study were as to analyze the demographics, characteristics, and pathologic results of NIFT-P and to document the rate of LN metastasis and recurrence using a large prospective patient registry.

Methods

Patients

This was a retrospective, multicenter study of consecutive adult patients surgically treated for indolent tumors and malignant thyroid diagnoses between 2005 and 2015 at high-volume referral centers for endocrine surgery. The data were collected in prospective databases after informed consent was obtained from the patients. Each NIFT-P diagnosis was confirmed by an expert pathologist at each center based on pathologic slides and then reconfirmed by an expert pathologist from Pitié Salpêtrière Hospital who retrospectively reviewed the histologic reports. All criteria for NIFT-P (Table 1) were met in addition to the following selection criteria described by Nikiforov et al[7]: tumor size >1 cm, no vascular or capsular invasion upon adequate tumor sampling (ie, reasonable confidence that the entire tumor capsule was examined), and no other invasive tumors in the gland except single small microcarcinoma.

This study was approved by the French-speaking Association of Endocrine Surgeons, with Institutional Review Board exemption.

Surgery

The operative management was homogeneous among the 9 surgical departments in France and Switzerland.[8] Patients diagnosed with PTC by preoperative ultrasound (US)-guided fine-needle aspiration (FNA) cytology or intraoperative frozen section underwent total thyroidectomy (TT) regardless of the tumor size. Prophylactic lymph node dissection (LND; including almost central [level VI] ± ipsilateral [levels III and IV] lateral LN as routinely performed at Pitié Salpêtrière Hospital) was performed in PTC patients who were preoperatively and intraoperatively classified as node negative (N0). Therapeutic LND was performed in cases of positive LN that were cytologically confirmed preoperatively or intraoperatively with frozen section (N1). Patients who underwent TT for nonmalignant disease but who were then diagnosed with PTC on final pathology did not undergo LND (Nx). If patients underwent thyroid lobectomy for indolent tumors or indeterminate nodules but then a T1b (PTC >1 cm) or higher stage PTC was identified on final pathology, completion thyroidectomy was performed in conjunction with either a prophylactic or therapeutic ipsilateral neck dissection (clearance of tissue from the original operative side), depending on the results of cervical ultrasonography. Patients with incidental T1a tumors (PTC ≤10 mm limited to the thyroid) did not undergo a complete thyroidectomy.

Data collection

The following data were recorded at baseline (ie, immediately after the surgical procedure): patient demographics (age and sex), operative details (lobectomy or TT), and LND performance. Complications after surgery were also recorded, including recurrent laryngeal nerve palsy (permanent if there was no proof of recovery according to laryngoscopy within 6 months of surgery) and hypocalcemia, defined as a serum calcium level <8 mg/dL (normal range, 8.4–10.6 mg/dL) at any time after surgery (permanent if the patient required oral calcium supplements and vitamin D ≥6 months and had a plasma PTH level <8 pg/mL). Tumor characteristics included size, bilaterality, multifocality, and pathologic tumor staging in accordance with the 8th edition of the American Joint Committee on Cancer/Union for International Cancer Control pathologic staging system.[9] For patients who underwent LND, we recorded the number of resected LNs and the number, location (central versus lateral), and laterality (ipsilateral, contralateral, or bilateral) of LN metastases. Molecular markers were not included (too recently implemented at our institutions).

Use of postoperative radioactive iodine (RAI) treatment also was recorded in the database; the dose of RAI administered was determined by consensus through weekly multidisciplinary conferences. The risk categories and postoperative RAI dose were determined according to the American Thyroid Association (ATA) guidelines and the French Societies of Nuclear Medicine and Endocrinology.[10]

Follow-up and recurrence

All patients followed a standardized surveillance schedule, which included physical examination, neck US, serum thyroglobulin (Tg), and Tg autoantibody measurements after stimulation or under suppressive treatment at 6 and 12 months, then annualy for 7 years and every three years therafter. No patients were lost to follow-up.

The potential for recurrent disease was determined by the following[10]: the presence of suspicious LN in the central or lateral neck or abnormal tissue in the thyroid bed with positive FNA biopsy; biochemical evidence of disease (stimulated Tg level >10 ng/mL after thyroid hormone withdrawal or 5 ng/mL after recombinant human thyrotropin administration); progression of basal (unsuppressed) Tg or basal Tg >1 ng/mL using the same assay technique; appearance or progressive increase (>50%) in Tg autoantibodies using the same assay technique; or isolated and repeatedly increased serum Tg levels.

Table 2
Demographic, clinical, operative, and pathologic characteristics of patients who underwent surgery with a final surgical pathology of NIFT-P (2005-2015).

Factor	Total (N = 363)
Sex	
Female	274 (75.5%)
Age at diagnosis	
Median (IQR)	50.1 (14-86)
Thyroid function	
Hypothyroidism	11
Euthyroidism	337
Hyperthyroidism	15
Surgery type	
Lobectomy	18 (5%)
Total thyroidectomy	240 (66.1%)
Lobectomy followed by completion thyroidectomy	105 (28.9%)
Lymph node dissection	
No LN dissection	230 (63.4%)
Prophylactic dissection	133 (36.6%)
Max tumor size	
Median (IQR)	25 (11-90)
Tumor multifocality	
Yes	78 (21.5%)
Tumor bilaterality	
Yes	48 (13.2%)
Associated "classic" PTC microcarcinoma	
Yes	65 (17.9%)
No. of Lymph Nodes Examined (n=133)	
Median (IQR)	8 (1-41)
Central LN	
Negative	132 (36.4%)
Positive	1
Not Examined	230 (63.4%)
Pathologic T	
1	162 (44.6%)
2	150 (41.3%)
3	51 (14%)
Pathologic N	
0	160
1a	1
X	202
Stage AJCC 8th edition	
I	343 (94.5%)
II	20 (5.5%)

Time to recurrence was measured in months from the date of the initial surgery.

Results

A total of 363 patients met the inclusion criteria for our study cohort. The incidence of NIFT-P in our cohort was approximately 6% of the total PTC cases. Patient demographics and clinical characteristics are presented in Table 2. Among 363 NIFT-P patients (76% female), the median age was 50 years (range, 5–86 years) and 345 patients (95%) underwent TT. The median NIFT-P size was 25 mm (range, 11–90 mm), and 14 were multifocal; 65 patients had an associated micro-PTC. Approximately 61% of the patients ($n = 221$) were considered to be young (<55 years) according to the AJCC 8th edition.

The results of FNA before surgery were available for 162 patients (45%). After excluding 27 "non-diagnostic or unsatisfactory FNA" samples (Bethesda I), 14 (10.4%) were categorized as indolent tumors nodules (Bethesda II), 11 (8.1%) were categorized as atypia of undetermined significance (Bethesda III), 31 (23%) were categorized as follicular neoplasm (Bethesda IV), 41 (30.4%) were suspicious for malignancy (Bethesda V), and 38 (28.1%) were malignant (Bethesda VI).

According to the NIFT-P criteria, all tumors were confined to the thyroid and were resected completely with negative surgical margins during the initial surgery. A total of 65 patients had an associated classic micro-PTC. Within the group of 133 patients (37%) who underwent prophylactic LND, 1 patient with an 18-mm NIFT-P had a micro-LN metastasis (2 mm) in the central (level VI) compartment and an associated contralateral classic micro-PTC (6mm). Given the size, we could not determinate if this metastasis was more similar to the NIFT-P or the micro-PTC.

Postoperative complications developed for 60 patients (17%); 47 patients (12.9%) had postoperative hypocalcemia, including 3 with permanent hypoparathyroidism (0.8%), and recurrent laryngeal nerve palsy was diagnosed in 21 patients and was permanent in 2 patients (0.6%).

Adjuvant treatment with RAI therapy was performed in 296 (82%) patients.

The median follow-up was 55 months (interquartile range [IQR] 12–146 months) and only 1 patient experienced recurrence 76 months after initial treatment. This patient had an associated classic micro-PTC (5 mm) contralateral to the NIFT-P (42 mm), with no positive LNs in the initial prophylactic central LND (4 LN examined). The recurrence was located in the central compartment on the side of the NIFT-P, with a centimetric LN and a positive FNA biopsy; thus, reoperation was required. Given the size, we could not determinate if this metastasis was more similar to the NIFT-P or the micro-PTC.

Discussion

The term *NIFT-P* was recently proposed by a group of thyroid pathologist experts to replace the term *carcinoma* and to emphasize its indolent behavior.[7] The goal of this observational study from 9 surgical departments highly specialized in endocrine surgery over a 10-year period was to validate this reclassification as a nonmalignant condition among the patients in our series.

If we accept the new paradigm of excluding NIFT-P from thyroid malignancy, the main challenge is to detect such lesions before surgery. Considering the current knowledge, it is unlikely that US criteria may be sufficient to characterize NIFT-P lesions. Rosario et al[11] found that a US appearance considered to be of low suspicion for malignancy was common in NIFT-P (32.5%) samples, whereas a highly suspicious appearance was uncommon (5%). Another study by Rosario et al[12] also found no significant differences between invasive encapsulated follicular variant of papillary thyroid carcinoma and NIFT-P in a comparative study using the US categories of the ATA. Similarly, FNA results seem to be challenging for improving the diagnosis, mainly because of the evaluation of the capsule and the differentiation of the cytonuclear features of NIFT-P and PTC.[11,13] In their study, the nuclear features of NIFT-P were significantly different from those of indolent tumors nodules but not from those of invasive EFVPTC. Most of the publications have found that most NIFT-P cytologies fall into indeterminate categories or are follicular neoplasms according to the Bethesda system.[14,15] In our retrospective study, only 8% were classified as undetermined significance and 23% as follicular neoplasms, lower than what was found in other series. Likewise, NIFT-P constitutes a more expected proportion of the "malignancies" hidden in suspicion of malignancy (Bethesda V). Interestingly, Cibas et al[16] recently established a risk of malignancy associated with each Bethesda category: first, when NIFT-P is not considered a malignancy, and second, when NIFT-P is still included among the carcinomas. They highlight that a substantial proportion of the cases in the Bethesda V category are likely to be NIFT-P. To avoid false positives in the general category owing to NIFT-P (28% in our study), it also suggests limiting the use of the malignant category to cases with classic features of PTC (true papillae, psammoma bodies, and nuclear pseudoinclusions). Future perspectives include the amelioration of cytological details. Immunohistochemical stains are not required for the diagnosis of NIFT-P. It seems that invasive FVPTC is frequently associated with frequent BRAF oncogenes, making them

similar to conventional PTC, (BRAF-like PTC group), whereas noninvasive EFVPTC predominantly harbor RAS mutations, making them similar to follicular adenoma and follicular carcinoma.[7] The upcoming molecular profiling techniques will undoubtedly be precious additional diagnostic tools in the near future.

In this present study, we reviewed all cases that met the initial criteria described by Nikiforov et al[7] for NIFT-P, excluding infracentimetric tumors. There are few published subcentimeter NIFT-P cases in the literature,[5,17] and it is recognized that not all pathologists currently accept the diagnosis of NIFT-P for subcentimeter tumors. Tumors must be well circumscribed or encapsulated with no invasion through the tumor capsule or tumor-parenchyma interface.

This study has the advantage of using data that involves prophylactic LND allows the estimation of the risk of LN metastasis and recurrence.[18] In our cohort, almost 40% of our patients had LND at their initial operation. Only 1 patient had a central LN involvement, but this patient had an associated classic micro-PTC, and it is unclear if this LN metastasis was related to NIFT-P. For some authors, LN metastases are incompatible with a diagnosis of NIFT-P.[19] In the study by Cho et al[20] evaluating 105 NIFT-P cases, LN micrometastases were noted in 3 cases (3%; 2 entirely lacked papillae). Together with 3 additional studies, 10 cases with central LN metastases associated with NIFT-P have been reported.[21]

Most studies report favorable outcomes for NIFT-P. In Nikiforov's study, encapsulated FVPTC showed no recurrence of disease after surgical management alone, justifying their reclassification using the new NIFT-P terminology.[7] However, it should be noted that patients with a follow-up duration of $<$10 years were excluded, thus creating a selection bias. Nikiforov reports that only 2 cases of recurrence were described in 388 well-encapsulated noninvasive EFVPTC cases in the previous literature; however, 1 of these tumors had been incompletely excised, and the nature of the other case nature remains questionable.[7] Xu et al reported that, similar to their small counterparts, large NIFT-P ($\geq$4 cm) appear to have no risk of recurrence, even when treated conservatively.[22]

However, controversies on the indolent behavior of NIFT-P still remain. After a mean follow up of 5.7 years, Parente et al[23] found 6 (6%) adverse oncologic events (including 1 patient with lung metastasis) compared to none found in the Nikiforov et al cohort.[7] They conclude that the adverse oncologic events seen in this cohort of patients are not consistent with a indolent tumors diagnosis of NIFT-P. As in the present study, most of their patients received adjuvant treatment with RAI ablation. Regarding our multicentric study, it is difficult to conclude to the same adverse oncologic outcome. Only 1 patient had a recurrence, but after reviewing the thyroid specimen, we found an associated classic micro-PTC. Although most micro-PTCs behave in a relatively nonaggressive fashion, we have already demonstrated that some patients may have poor outcomes with extracapsular extension, LN involvement, and distant metastases. Consequently, even though we confirm that NIFT-P shows an indolent behavior that supports conservative surgery alone, we also suggest that an association with a micro-PTC should be treated differently. Moreover, it is unclear how NIFT-P patients should be monitored. Until more data is available, ATA guidelines[24] have proposed "occasional monitoring with serum thyroglobulin and neck US depending upon patient context" without a precise length of follow-up.

One of the limitations of this study is its retrospective design; preoperative ultrasonographic data information and molecular profiles of the tumors were unavailable. Better ultrasonographic characterization and genetic testing should be carried out. However, the aim of the present study was to assess the risk of recurrence of NIFT-P after initial surgery. The long-term follow-up of this study resulted in the greater identification of recurrent disease. Finally, it might affect the ability to determine the true course of NIFT-P as patients now diagnosed with NIFT-P would not undergo RAI and therefore may have a higher recurrence rate than is shown in this group where the majority (82%) received RAI.

In conclusion, we found that NIFT-P presents with nonmalignant behavior. However, the identification of an associated micro-PTC should be carefully evaluated because it could be a factor for LN metastasis or recurrence. Our findings support conservative surgery alone, although further prospective studies are needed to confirm this result.

Conflicts of interest

The authors have indicated that they have no conflicts of interest regarding the content of this article.

References

1. Lim H, Devesa SS, Sosa JA, Check D, Kitahara CM. Trends in thyroid cancer incidence and mortality in the United States, 1974–2013. *JAMA*. 2017;317:1338–1348.
2. Vaccarella S, Franceschi S, Bray F, Wild CP, Plummer M, Dal Maso L. Worldwide thyroid-cancer epidemic. *N Engl J Med*. 2016;375:614–617.
3. Jung CK, Little MP, Lubin JH, Brenner AV, Wells Jr SA, Sigurdson AJ, et al. The increase in thyroid cancer incidence during the last four decades is accompanied by a high frequency of BRAF mutations and a sharp increase in RAS mutations. *J Clin Endocrinol Metab*. 2014;99:E276–E285.
4. Lam AKY, Lo CY, Lam KSL. Papillary carcinoma of thyroid: a 30-yr clinicopathological review of the histological variants. *Endocr Pathol*. 2005;16:323–330.
5. Thompson LD. Ninety-four cases of encapsulated follicular variant of papillary thyroid carcinoma: a name change to noninvasive follicular thyroid neoplasm with papillary-like nuclear features would help prevent overtreatment. *Mod Pathol*. 2016;29:698.
6. Fagin JA, Wells Jr SA. Biologic and clinical perspectives on thyroid cancer. *New N Engl J Med*. 2016;375:1054–1067.
7. Nikiforov YE, Seethala RR, Tallini G, Baloch ZW, Basolo F, Thompson LD, et al. Nomenclature revision for encapsulated follicular variant of papillary thyroid carcinoma: a paradigm shift to reduce overtreatment of indolent tumors. *JAMA Oncol*. 2016;2:1023–1029.
8. Borson-Chazot F, Bardet S, Bournaud C, Conte-Devolx B, Corone C, d'Herbomez M, et al. Guidelines for the management of differentiated thyroid carcinomas of vesicular origin: recommandations pour la prise en charge des cancers thyroïdiens différenciés de souche vésiculaire. *Annales d'Endocrinologie*. 2008;69:472–486.
9. Amin MB, Edge SB, Greene FL, Byr DR, Brookland RK, Washington MK, et al.. *AJCC Cancer Staging Manual*. New York: Springer; 2017.
10. Zerdoud S, Giraudet AL, Leboulleux S, Leenhardt L, Bardet S, Clerc J, et al. Radioactive iodine therapy, molecular imaging and serum biomarkers for differentiated thyroid cancer: 2017 guidelines of the French Societies of Nuclear Medicine, Endocrinology, Pathology, Biology, Endocrine Surgery and Head and Neck Surgery. *Annales d'Endocrinologie*. 2017.
11. Rosario PW, Mourão GF, Nunes MB, Nunes MS, Calsolari MR. Noninvasive follicular thyroid neoplasm with papillary-like nuclear features. *Endocrine-Related Cancer*. 2016;23:893–897.
12. Rosario PW. Ultrasonography and cytology as predictors of noninvasive follicular thyroid (NIFTP) neoplasm with papillary-like nuclear features: importance of the differential diagnosis with the invasive encapsulated follicular variant of papillary thyroid cancer. *Clin Endocrinol (Oxf)*. 2017;87:635–636.
13. Jug R, Jiang X. Noninvasive follicular thyroid neoplasm with papillary-like nuclear features: an evidence-based nomenclature change. *Patholog Res Int*. 2017;2017. 1057252.
14. Maletta F, Massa F, Torregrossa L, Duregon E, Casadei GP, Basolo F, et al. Cytological features of "noninvasive follicular thyroid neoplasm with papillary-like nuclear features" and their correlation with tumor histology. *Human Pathology*. 2016;54:134–142.
15. Faquin WC, Wong LQ, Afrogheh AH, Ali SZ, Bishop JA, Bongiovanni M, et al. Impact of reclassifying noninvasive follicular variant of papillary thyroid carcinoma on the risk of malignancy in the Bethesda System for Reporting Thyroid Cytopathology. *Cancer Cytopathol*. 2016;124:181–187.
16. Cibas ES, Ali SZ. The 2017 Bethesda System for Reporting Thyroid Cytopathology. *Thyroid*. 2017;27:1341–1346.
17. Xu B, Farhat N, Barletta JA, Hung YP, de Biase D, Casadei GP, et al. Should subcentimeter non-invasive encapsulated, follicular variant of papillary thyroid carcinoma be included in the noninvasive follicular thyroid neoplasm with papillary-like nuclear features category? *Endocrine*. 2018;59:143–150.
18. 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.
19. Hung YP, Barletta JA. A user's guide to non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP). *Histopathology*. 2018;72:53–69.

20. Cho U, Mete O, Kim MH, Bae JS, Jung CK. Molecular correlates and rate of lymph node metastasis of non-invasive follicular thyroid neoplasm with papillary-like nuclear features and invasive follicular variant papillary thyroid carcinoma: the impact of rigid criteria to distinguish non-invasive follicular thyroid neoplasm with papillary-like nuclear features. *Mod Pathol*. 2017;30:810.
21. Jiang X, Harrison GP, Datto MB. Young Investigator Challenge: Molecular testing in noninvasive follicular thyroid neoplasm with papillary-like nuclear features. *Cancer Cytopathol*. 2016;124:893–900.
22. Xu B, Tallini G, Scognamiglio T, Roman BR, Tuttle RM, Ghossein RA. Outcome of large noninvasive follicular thyroid neoplasm with papillary-like nuclear features. *Thyroid*. 2017;27:512–517.
23. Parente DN, Kluijfhout WP, Bongers PJ, Verzijl R, Devon KM, Rotstein LE, et al. Clinical safety of renaming encapsulated follicular variant of papillary thyroid carcinoma: is NIFTP truly indolent tumors. *World J Surg*. 2018;42:321–326.
24. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 2015 American Thyroid Association Management Guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association Guidelines Task Force on thyroid nodules and differentiated thyroid cancer. *Thyroid*. 2016;26:1–133.

Discussion

Dr Ashok R Shaha (New York, NY): This is a large series over a long period of time and very well presented. I have 2 questions:

In 2005, we didn't have the term NIFT-P, so you are probably using retrospective data. The critical question is what do you tell the patient? Patients and their families are interested in only 1 question: Do I have cancer or not? And that has implications not only for their emotions but more importantly for the issues of long-term follow-up.

Secondly, I was surprised to see 75% of your patients received RAI. Is that your current philosophy?

Dr Nathalie Chereau: Thank you for your questions. I think what we have to tell the patient is that it's not a nonmalignant tumor as much as an indolent tumor. It's not a cancer, but it is a tumor, and we don't have enough follow-up to say that it's truly indolent tumors.

And for the second question, we do more radioactive iodine in France than in the US for papillary thyroid carcinoma, and we followed French guidelines for this adjuvant therapy at the time of the study.

Dr Quan-Yang Duh (San Francisco, CA): Wonderful job, Nathalie, with this large series. Basically, what you are reminding us is that we have 2 entities here that both have relatively indolent tumors behavior. One is a NIFT-P, and the other 1 is a papillary microcarcinoma.

You made a recommendation that maybe we ought to follow the NIFT-P patients more carefully because some of them will have microscopic papillary thyroid cancer. How aggressively would you follow the patient who has a 6-millimeter microscopic papillary thyroid cancer that you removed? And would the presence of NIFT-P influence that?

Dr Nathalie Chereau: We follow them 6 months, 18 months, 4 years, and 7 years after surgery. At that point, we think that we can stop the specific follow-up.

Dr Quan-Yang Duh (San Francisco, CA): And for the patient that has only papillary microcarcinoma but no NIFT-P, how would you follow that then?

Dr Nathalie Chereau: We check the patient at 6 months, and if blood tests (serum thyroglobulin levels in case of total thyroidectomy) and neck ultrasound are negative, we think that we can stop the follow-up.

Dr Electron Kebebew (Stanford, CA): I too enjoyed your presentation. It's an informative study. I have a comment and a question for you.

It's all in the definition. I shouldn't say this, but all pathologists are not created equally, and there's always some discordance in the interpretation. So my question to you is whether you had at least 2 pathologists looking at each of those cases to make sure that their diagnosis was concordant? I think that will be so critical in defining this new entity.

Dr Nathalie Chereau: Each case was identified by a local pathologist specialized in endocrine tumors, and double-checked by another expert pathologist from Pitié Salpêtrière University Hospital.

Dr Electron Kebebew (Stanford, CA): And did you have any discordance in the diagnosis? If so, how often?

Dr Nathalie Chereau: Yes. I think about 20 patients were excluded because there was significant discordance between the 2 pathologists.

Dr Alberto Treiguer (Porto Alegre, Brazil): I also appreciate your presentation. On our service, we also see the frequent diagnosis of NIFT-P. We are worried about it because it may be a misdiagnosis or they may have microcarcinoma. What we see in our practice is that the pathologists do have variability in diagnosis and we cannot always have it reviewed by multiple pathologists.

So how can we ask for all diagnoses to be double-checked? What would you suggest that we do? Because it all comes down to the patient that's in front of us. They want to know do they have a cancer or not. Are they cured or not? That's the question.

Dr Nathalie Chereau: It's a difficult diagnosis for the pathologist, so we asked them to double-check each case for this study with an extra pathologist. However, since this entity is now well-known, I think that pathologists are aware that it's very important to see no vascular and/or tumor capsule invasion. This includes a careful study of the limits of the tumor (well encapsulated or clear demarcation). It's important to respect the criteria that have been described by Nikiforov et al.

Dr Dina Elaraj (Chicago, IL): Thank you for your very interesting and timely presentation. My question regards your methods.

You reviewed cases from 2005 to 2015. How did you arrive at your final patient cohort? Were these all patients who were initially diagnosed with follicular variant of papillary thyroid cancer and then re-reviewed and reclassified? How exactly was that done?

Dr Nathalie Chereau: Thank you for your question. In each department of the participating centers, we retrospectively reviewed the cases of patients who had surgery for an initially diagnosed encapsulated follicular variant of papillary thyroid carcinoma. From pathology reports, 2 expert pathologists reclassified the tumor based on invasion.