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Incidental Thyroid Papillary Microcarcinoma: Survival and Follow-up

Sophie Gorostis, MD ; Thibaut Raguin, MD; Olivier Schneegans, MD; Catherine Takeda, MD;
 Christian Debry, MD, PhD; Agnès Dupret-Bories, MD, PhD 

Objectives/Hypothesis: The aim was to study the survival of incidental thyroid papillary microcarcinoma patients treated with surgery for benign thyroid disease to validate absence of oncological follow-up and reduce unnecessary health expenses.

Study Design: Retrospective cohort study.

Methods: We analyzed patient's files and interviewed 252 patients by telephone whose cases were submitted to the multidisciplinary meeting of thyroid pathology in Strasbourg, France, for incidental thyroid papillary microcarcinoma without clinical lymph node involvement, between January 1996 and December 2012.

Results: Thirteen patients (5.8%) died while the data were being collected; however, none of the deaths were due to the thyroid pathology, and no patients showed signs of relapse of the thyroidectomy or cervical lymph node level.

Conclusions: Our retrospective study shows that patients with incidental localized thyroid papillary microcarcinoma who underwent surgery without radioactive iodine treatment have an identical survival compared to the general population at the same age to validate absence of oncological follow-up and reduce unnecessary health expenses.

Key Words: Thyroid papillary microcarcinoma, thyroid lobo-isthmectomy, total thyroidectomy, survival.

Level of Evidence: 3

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INTRODUCTION

Although thyroid cancer is the most common cancer of the endocrine system, it only represents 1.2% of all malignant tumors.¹ In France, its incidence is low, estimated at about 8,000 new cases per year.² Thyroid cancer has an excellent prognosis in its differentiated form, with a very low mortality rate in France (i.e., 0.3 per 100,000 people per year or just over 400 deaths per year). This type of cancer is not considered a public health problem because of its low incidence and favorable prognosis and low mortality; however, the increase in its incidence is a medico-economic growth issue.³

The most frequent histological form is papillary carcinoma (85%).⁴ Microcarcinomas are the most frequent and are defined by a size ≤ 10 mm without crossing the gland's capsule.² They are mainly an incidental discovery during the final pathological examination of the parts of partial or total thyroidectomy for patients operated on for benign thyroid pathology. During the past 30 years,

incidence of papillary microcarcinoma has increased in industrialized countries. This evolution is explained by the increase in their diagnosis, mainly due to more diligent pathological analysis.^{2,5} Their mortality rate is less than 1%, which is an excellent prognosis.⁶

The latest US and French recommendations in the event of incidental discovery from a partial thyroidectomy do not recommend radioactive iodine treatment or recurrent node dissection for N0 patients (clinically or by ultrasound), or completion thyroidectomy. They recommend a lobo-isthmectomy in cases of preoperative suspicion of papillary microcarcinoma.⁷

On the other hand, the modalities of the postoperative follow-up are not standardized and are dependent on the centers, surgeons, and doctors.⁸ We carried out a retrospective study from January 1996 to December 2012, in which a thyroid papillary microcarcinoma was an incidental discovery, and evaluated the survival of patients operated on in Alsace, France. Our aim was to study the survival of these patients to validate the methods of the multidisciplinary meeting of thyroid pathology reference center in Alsace, France: the absence of completion thyroidectomy, absence of radioactive iodine treatment, absence of thyroid-stimulating hormone (TSH) suppression, and absence of oncological follow-up of these patients considered cured to reduce unnecessary health expenses (consultations, follow-up, ultrasound).

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From the CHU de Strasbourg, Oto-Rhino-Laryngology (S.G., T.R., C.D.), Strasbourg, France; Service de Médecine Nucléaire (O.S.), Centre Paul Strauss, Strasbourg, France; Service de Gériatrie de la Clinique Sainte Barbe (C.T.), Strasbourg, France; Service d'Otorhinolaryngologie et Chirurgie Cervico-Faciale (A.D.-B.), Institut Claudius Regaud, Institut Universitaire du Cancer de Toulouse Oncopole, Toulouse, France.

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Send correspondence to Sophie Gorostis, MD, CHU de Strasbourg, 1 Avenue Molière, 672098 Strasbourg, France. E-mail: sophie.gorostis@chru-strasbourg.fr

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MATERIALS AND METHODS

All patients' records presented for thyroid carcinoma during the multidisciplinary meeting of thyroid pathology at the Paul Strauss Center, Strasbourg, France, were studied between January 1996 and December 2012. This reference center is the

only one in Alsace listing all of the thyroid carcinomas of the region of Alsace and the east of Moselle, France. During this period, 1,554 patients with a thyroid carcinoma were presented for immediate postoperative treatment.

Among the 1,554 patients, 252 were selected because they had a papillary microcarcinoma incidentally discovered during pathological examination. These lesions were precisely ≤ 10 mm, uni- or multifocal (additional size of ≤ 10 mm), without crossing the thyroid capsule, and without cervical lymphadenopathy detected before or during surgery by clinical examination or cervical ultrasound (pT1aNx or pT1amNx from the *TNM Classification of Malignant Tumours, 7th Edition*). The size reported was determined with the anatomopathological analysis (largest diameter).

All patients underwent preoperative thyroid and cervical ultrasound to eliminate cervical nodes. Among all of the patients, patients with thyroid nodules suspected of malignancy in preoperative treatment with fine-needle aspiration, classified as Bethesda IV, V, or VI, were excluded. Those with a Bethesda classified I, II, or III were included. When extemporaneous examination was in favor of a malignant lesion, the patients were excluded.

The following data were used: patient's age, date of surgery, surgeon's name, date of the multidisciplinary meeting, procedure performed (lobo-isthmectomy, total thyroidectomy, subtotal thyroidectomy), surgical indication, and in particular, toxicity or pretoxic goitre, number of papillary microcarcinoma, histological size, reports of consultations, hospitalizations of thyroid surgery for medium-term surgical outcomes, signs of locoregional or distant recurrence, death, and cause of death.

A telephone survey was developed and used for these 252 patients. This included information on their survival, whether there were signs of a locoregional or distant oncological evolution of their incidental papillary thyroid microcarcinoma, and surgical outcomes (i.e., dysphonia, hypocalcemia). As well as the impact of the intervention and levothyroxine supplementation on daily living. The minimal follow-up was 5 years after the intervention, allowing us to consider these complications as definitive and study medium-term surgical outcomes. We interviewed patients on their oncological history in search of an association with other cancers.

The voice was not objectively assessed. Patients were described as dysphonic when describing a change in their voice compared to the preoperative consultation (modification of the tone or power of the voice, tiredness of the voice, impossibility or difficulty to sing). Hypocalcemia was retained for patients taking calcium supplementation or vitamin D therapy at the time of interview, only when they had been initiated as a result of the intervention.

The patients were asked about whether or not levothyroxine was taken, as well as the experience of this daily hormonal supplementation. In the event of a telephone call failure, the general practitioner was asked the information or helped us contact patients. Regarding the death of the patients, the information was given by the family and then confirmed by family doctor, thus ensuring the absence of a link with the thyroid pathology.

Quantitative variables were described using the usual statistics of position and dispersion (i.e., mean, median, variance, minimum, maximum, and quantiles). Qualitative variables were described using proportions of the modality and cumulative proportions for variables with more than two modalities. All analyses were carried out in R software version 3.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Between January 1996 and December 2012, 1,554 patients were presented with thyroid carcinoma during the multidisciplinary meeting of thyroid pathology at the

Paul Strauss Center. Two hundred fifty-two patients were included, representing 16.2% with a papillary microcarcinoma of incidental discovery, classified as pT1aNx (American Joint Committee on Cancer 7th Edition) or pT1amNx (additional size ≤ 10 mm) and without cervical nodes (clinical or ultrasound). The incidence of these microcarcinomas before 2001 is an average of seven new cases per year, and after 2001 the incidence is of 18 new cases per year.

We were unable to reach 27 patients by telephone or through their general practitioner. Our final study resulted in 225 patients (Fig. 1). Their medical files did not contain any arguments in favor of recurrence or death. The mean age at diagnosis was 65.1 years, with a standard deviation of ± 11.8 years (range, 30–95 years; median age of 66 years). The sex ratio was 0.2 male/female, with 182 women (80.9%) and 43 men. The mean lesion size was 4.4 mm, with a standard deviation of ± 2.5 mm (range, 0.4 mm–10 mm). Multifocality concerned 22 patients, representing 9.8%.

The surgical indications were: 69.3% for euthyroid heteronodular goitre, 15.1% for toxic heteronodular goitre, 8% for single node, and 7.6% for Graves' disease. Among the 225 patients of the cohort, 190 (84.4%) patients had a total thyroidectomy. Partial surgery was performed for 35 patients (15.6%): lobo-isthmectomy in 34 patients and one isthmectomy. Completion thyroidectomy for recurrence of goiter at the level of the remaining lobe involved four of these 35 patients (11.4%), none because of the cancer lesion originally objectified. None of these anatomopathology lesions were found to be malignant.

For 222 patients, the multidisciplinary meeting recommended no further radioactive iodine treatment.

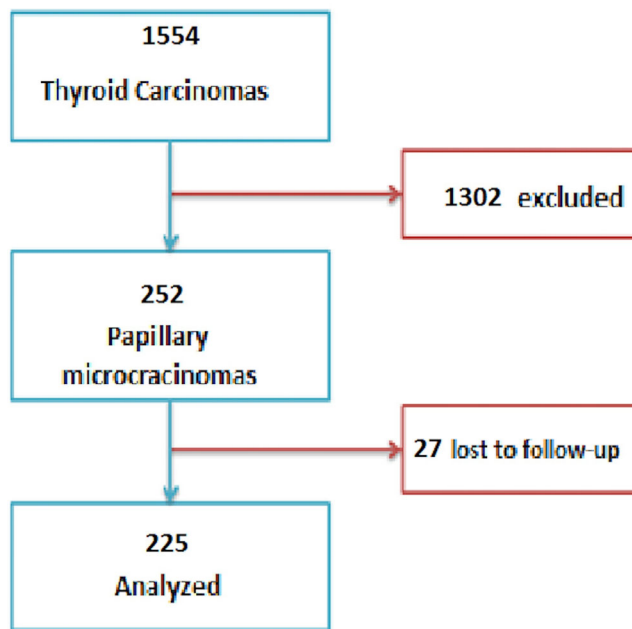


Fig. 1. Flowchart of the process for selection of the patients analyzed in the study. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

Only three (1.3%) were postoperatively administered 100 mCi of radioactive iodine in 1996 and 1997 due to a lesion reaching the upper limit of 10 mm or a doubt on the thyroid capsule crossing. On the entire body scintigraphy following therapy, there was no ganglion metastasis or distant metastasis found (Table I).

The recommendations of the multidisciplinary meeting changed in 2001 to total thyroidectomy. Prior to this date, TSH suppression and regular ultrasound monitoring were recommended. After that date, the experts concluded that no TSH suppression and no oncological follow-up were needed.

In cases of partial surgery, it has always been advised an annual ultrasound monitoring of the remaining lobe to control for the absence of recurrence (goiter and macronodule). The time between diagnosis and our survey was an average of 12 years and 3 months, with a standard deviation of ± 4.8 years (range, 5–19 years. Median = 12 years). While the data were being collected, 13 patients died (5.8%), though none due to their thyroid pathology. None of the patients required intervention at a minimum follow-up of 5 years. None manifested disease or showed signs of relapse at the thyroidectomy or cervical lymph node level. Among the 212 patients who were interviewed, 21 (9.9%) reported a voice complaint, without distinction, of lack of voice projection, tiredness during the day, a lower or monotonous voice, difficulties singing. None complained of dyspnea.

Calcium supplementation or vitamin D treatment was initiated in the immediate aftermath of the operation and continued for 12 patients (5.7%). For the patients treated with lobo-isthmectomy, 46.4% required hormonal supplementation with levothyroxine. Thirty-five out of 197 patients requiring hormone supplementation (17.8%) and considered this treatment to be a problem in their

TABLE I.

Characteristics of Patients Operated on in Alsace With Incidental Papillary Microcarcinomas From January 1996 to July 2015.

Characteristics of Analyzed Patients	Papillary Microcarcinomas
Sex, n (%)	
Women	182 (80.9)
Men	43 (19.1)
Tumor characteristic	
Average size, mm	4.4
Multifocal, n (%)	22 (9.8)
Surgery indications, n (%)	
Euthyroid heteronodular goiter	156 (69.3)
Toxic heteronodular goiter	34 (15.1)
Thyroid nodes	18 (8)
Grave's disease	17 (7.6)
Surgery, n (%)	
Total thyroidectomy	190 (84.4)
Partial surgery (lobo-isthmectomy or isthmectomy)	35 (15.6)
Completion thyroidectomy in a second time	4 (11.4)
Radioactive iodine treatment, n (%)	3 (1.3)

TABLE II.
Medium-term Surgical Outcomes.

Surgery	Hypocalcemia	Dysphonia	Hormonal Supplementation
Total thyroidectomy, n = 180	11	19	180
Partial thyroidectomy, n = 32			
No completion thyroidectomy, n = 28	0	1	13
Completion thyroidectomy in a second time, n = 4	1	1	4

Data are presented as number of patients.

daily lives, 20 because of the difficulty in finding the correct balance, 12 because of a significant weight gain since the introduction of hormonal supplementation, and five due to mood changes (Table II).

For the 180 patients who underwent total thyroidectomy, 20.4% were monitored by cervical ultrasound, with very random follow-up and rhythm, which ranged from once a year to once every 2 years. There was a monitored entire-body scintigraphy for 1.9% patients who had no additional radioactive iodine treatment. A second cancer was diagnosed for 21 patients (13 breast cancers).

DISCUSSION

Among patients presented during the multidisciplinary meeting for thyroid carcinoma, 16.2% were incidental papillary microcarcinomas, which are results comparable to data found in the literature (i.e., 20%).^{9,10} The incidence of papillary microcarcinomas has almost tripled in industrialized countries over the past 30 years. This evolution is explained by the growths of instrumental diagnosis (e.g., ultrasound, fine-needle aspiration) and the modernized techniques in sampling, conditioning, and reading for pathologists.^{9–11}

Our results illustrate this evolution with an average of seven new cases per year from 1996 to 2000, compared to 18 new cases per year from 2001 onward. The notion of overdiagnosis is mentioned in the literature. It is defined by establishing a diagnosis of a tumor that, untreated, will lead to neither symptoms nor death. Vaccarella et al. estimate that more than 470,000 women and 90,000 men have been overdiagnosed for thyroid cancer during the last 20 years in a study conducted in 12 industrialized countries (including France, Italy, South Korea, United States, and Australia).¹²

This trend is currently being pointed out by politicians to reduce healthcare spending (WHO press release no. 246 of August 18, 2016: "Over-diagnosis is a major driver of the thyroid cancer epidemic: up to 50%–90% of thyroid cancers in women in high-income countries), and also by surgeons and doctors more aware of the risk–benefit balance of the treatments proposed. The American Thyroid Association (ATA) recommends no fine-needle aspiration on nodules ≤ 10 mm regardless of their ultrasound.⁷

In our study, we investigated incidental thyroid papillary microcarcinoma with a risk of very low relapse (ATA 2015 Risk Stratification System With Proposed

Modifications) (i.e., intrathyroid, without locoregional or distant metastasis, focal or multifocal).^{6,13,14} Among them, we focused on those with optimal prognosis, as defined by Mazzaferri et al.: multifocals with an additional size of ≤ 10 mm.¹⁵ In the study by Sugitani et al.,¹⁶ out of 230 patients with asymptomatic thyroid papillary microcarcinoma not operated on, 1% developed a locoregional evolution over an average follow-up period of 5 years. Our work covered 225 surgically treated patients, interviewed with an average follow-up of 12 years and 3 months. None reported signs of recurrence at the thyroidectomy or cervical lymph node level, and none died due to their thyroid pathology.

These results are in line with the ATA, which describes an excellent prognosis of thyroid papillary microcarcinoma, with a mortality rate of $<1\%$, a locoregional relapse rate of 2% to 6%, and metastasis of 1% to 2%.⁷ All of these conclusions have been recently illustrated by two Japanese prospective studies,^{7,16} which concluded that survival between initial surgery and close surveillance of this type of lesion is identical. In 1,235 patients, Ito et al.¹³ observed a minority of patients (3.5%) who had progression of the disease over a 75-month follow-up period, and no deaths related to the thyroid pathology, making surveillance an alternative option for surgery.

Concerning the surgical attitude, the ATA advocates a less-invasive attitude by recommending lobectomy rather than total thyroidectomy, and the absence of radioactive iodine treatment for the management of thyroid papillary microcarcinomas of preoperative discovery. For tumors of perioperative discovery, the attitude should be the same as if the diagnosis of cancer had been made preoperatively.¹² The multidisciplinary meeting supports these recommendations by not proposing total thyroidectomy for partial thyroidectomy, and by never proposing radioactive iodine treatment since 1997.

Over the years, multiple tumor classification systems have been developed, always with the aim of predicting the risk of recurrence and death related to the disease.¹² The latest classification in thyroid cancer is the *TNM Classification of Malignant Tumours, Eighth Edition* (2017), classifying papillary carcinomas of <10 mm with minimal crossing of the thyroid capsule no longer in T3 but in T1a. However, Siddiqui et al. are not the first to demonstrate an increased risk of lymph node enlargement in patients with extrathyroid extension of microcarcinomas.^{6,10,17} Thus, particular attention must be paid to these lesions in the coming years to ensure that these are lesions with very low risk of recurrence.¹⁸ In all cases, cervical lymph node involvement, unchanged between the two classifications, seems to be the fundamental indicator in terms of prognosis, more than the size of the lesion itself or the minimal extrathyroid involvement.

Dysphonia occurring after thyroid surgery has been described in 51% to 87% of the patients,^{19,20} whereas the recurrent involvement is only objectified in 0.9%²¹ to 13% of the cases.²² The causes, in addition to recurrent paralysis, are numerous, some of which may be difficult to objectify and differentiate: adherence of laryngeal and paralaryngeal muscles, involvement of the external branch of the upper laryngeal nerve, secondary lesions to

intubation, and postoperative complications of a preoperative pathology.²³ These postoperative dysphonias may be persistent up to 6 months after surgery, and 14% of patients are impaired.²⁰ These numbers are close to our results, with 9.9% of our patients reporting a lack of projection, tiredness of the voice during the day, a lower and monotonous voice, and difficulty singing.

Calcium supplementation or vitamin D treatment was reported by 12 patients (5.7%), whereas post-thyroidectomy definitive hypocalcemia is described in the literature in 0.9%²¹ to approximately 6% of patients.²⁴ In our study, the population is predominantly female; our results may have been increased due to the confusion among telephone interviewees between post-thyroidectomy hypocalcemia and the prevention of osteoporosis. Furthermore, Conzo et al.²¹ had a transitory hypoparathyroidism number of 9.5% of patients who had thyroid surgery. Perhaps some of our patients had transitory hypoparathyroidism that required the introduction of supplementation that was not stopped.

Among the patients who had total thyroidectomy, 6.1% had long-term hypocalcemia and 10.6% had long-term dysphonia. When the patient underwent a lobo-isthmectomy, these numbers were lowered to 0% and 3.6%, respectively. These results are in line with the experts seeking to minimize surgical involvement to limit the risk of postoperative complications. With a rate of multifocal lesions of only 9.8%, we advocate for the same attitude. The authors are unanimous that to obtain optimal surgical results with the least possible morbidity, it is essential to be a trained, experienced surgeon who is regularly informed of the innovations and evolution of technical procedures and their indications.^{25,26} Of the patients treated with lobo-isthmectomy, 46.4% required hormonal supplementation with levothyroxine versus the 20% usually described.²⁷

Follow-up aims for early detection of persistence or recurrence of the disease, either in the thyroid or lymph nodes, to rapidly adopt a therapeutic strategy. This study proves that for very low-risk cancers, surgery alone cures them.¹⁶ Carcinology follow-up is unnecessary in terms of patients' survival and quality of life. Of the patients treated with total thyroidectomy, 22.2% were overly monitored. Follow-up has a cost. It comes mainly from the lack of information of general practitioners and patients, worried about the implications of the word cancer and then left on their own. Our goal is to remind them to minimize unnecessary health expenses.

For cancers with good prognosis or proven remission, there is no evidence that a suppressive dose of LT4 is useful or justified,¹⁶ which is why the multidisciplinary meeting does not recommend it. A second cancer was diagnosed in 21 patients (13 breast cancers). This correlation is mainly explained by epidemiological data, breast cancer being the most frequent cancer for women, who are more represented than men in thyroid pathology.

CONCLUSION

Our study shows that patients with incidental intrathyroid papillary microcarcinoma treated with partial or total thyroidectomy without additional treatment by

iodine-131 have identical survival compared to the general population at the same age. These data reinforce the current recommendations in favor of fewer interventions and less invasive management. They validate the absence of oncological follow-up and keep the quality of life of the patients a priority and limiting unnecessary healthcare costs.

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