The need for radioiodine ablation and follow-up for patients with papillary thyroid microcarcinoma should be based on patient- and tumor-related prognostic variables

Lombardi CP, Bellantone R, De Crea C, Paladino NC, Fadda G, Salvatori M, Raffaelli M. Papillary thyroid microcarcinoma: extrathyroidal extension, lymph node metastases, and risk factors for recurrence in a high prevalence of goiter area. World J Surg 2010. 10.1007/s00268-009-0375-x [doi]

SUMMARY

BACKGROUND

The optimal therapy for papillary thyroid microcarcinoma (PTMC) and the follow-up for these small tumors remain controversial despite the fact that they comprise a large group of tumors that are commonly diagnosed with ultrasound-guided fine-needle aspiration biopsy. This retrospective study of PTMC was aimed at determining the risk factors for tumor recurrence in an area with a high prevalence of goiter.

METHODS

This is a study from the Division of Endocrine Surgery, in the, Università, Policlinico, Rome, Italy, in which medical records from October 2002 through June 2007 were searched for patients who had thyroidectomy with a final pathology report of PTMC. The retrieved data were as follows: patient age, sex, type of diagnosis, including incidental or nonincidental tumors, autoimmune thyroid disorders, including Graves' disease and thyroiditis, the extent of thyroid resection, type of lymph-node dissection, thyroid weight, tumor size, tumor multifocality, extrathyroidal tumor extension and tumor–node–metastases (TNM) staging, and follow-up results. Patients who completed the follow-up evaluation were included in the study.

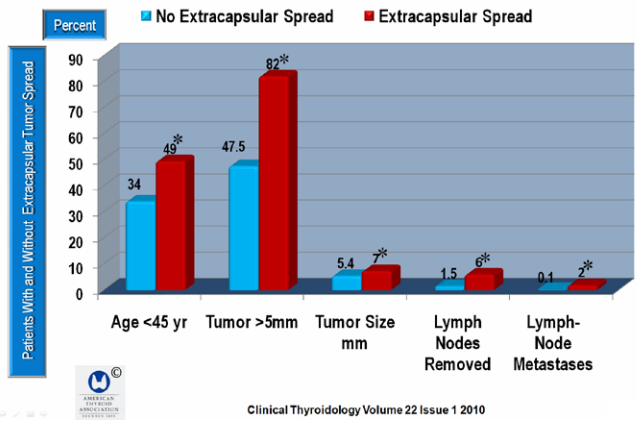

Figure 1. This figure shows the univariate analysis results of factors associated with and without extracapsular tumor spread (ECS), including age, tumor size, and lymph-node metastases at first surgery. *P<0.001 for age <45 yr for patients with versus those without extracapsular tumor spread.

PTMC was defined as incidental when it was found on the surgical histology specimens from patients who had thyroid surgery for non-malignant thyroid disorders and was described as nonincidental when the tumor was diagnosed preoperatively on the basis of fine-needle aspiration biopsy, or the patient was preoperatively proven or suspected of having cervical lymph-node metastases or distant metastases. Hemithyroidectomy was defined as complete extracapsular resection of a thyroid lobe containing more than half of the isthmus including the pyramidal lobe. Total thyroidectomy was defined as total bilateral extracapsular thyroidectomy. Completion thyroidectomy was defined as resection of all residual thyroid tissue after previous partial thyroidectomy performed within 6 months after hemithyroidectomy or other partial resection, which was considered as a one-step thyroidectomy. Completion thyroidectomy performed more than 6 months after partial thyroid resection was considered surgery for a local recurrence.

The term node picking was defined as the selected removal of enlarged or suspicious lymph nodes in the central (level VI) or lateral (level II to V) neck compartments, in which case, the lymph nodes were usually sent for frozen-section analysis. When metastases were identified intraoperatively, systematic compartment-oriented lymph-node dissection was performed. Central compartment lymph-node dissection is defined by complete level VI dissection, and lateral neck lymph-node dissection is a level II to level V dissection. The need for any lymph-node dissection was established on the basis of the preoperative or intraoperative evidence of enlarged, suspicious, or malignant nodes. Tumors were defined as multifocal if two or more tumor foci were found in one (unilateral) or both (bilateral) thyroid lobes, and the largest tumor dimension was used for statistical analysis.

The criteria for successful ^{131}I thyroid remnant ablation were defined as the disappearance of any visible area of radioiodine uptake in the thyroid bed, and a radioiodine neck uptake<1%, and undetectable serum thyroglobulin off levothyroxine and a serum thyrotropin (TSH)≥30 IU/ml)

RESULTS

Comparative Analysis of Patients with and without Extracapsular Tumor Spread (Figure 1)

During the study period, a total of 5355 patients had thyroidectomy, 2220 of whom (41%) had thyroid malignancy and 933 of whom had PTMC (17%). Of the patients with PTMC, 197 were men (21%) and 736 were women (79%), with a mean (±SD) age of 49.4±1.3 years (range, 9 to 81). The diagnosis was incidental in 704 patients (75.5%) and nonincidental in 229 (24.5%). Among

the nonincidental group, 225 patients (88%) had a preoperative fine-needle aspiration biopsy (FNAB) that was suspicious for or diagnostic of a malignant thyroid nodule, and the remaining 4 had lateral lymph-node metastases. The indications for thyroidectomy in patients with an incidental diagnosis were compressive goiter symptoms in 458 of 704 (65%) and toxic goiter in 246 (35%).

Univariate analysis showed that patients with extracapsular tumor spread (ECS) were significantly younger than those without ECS (44.6±13.8 vs. 49.9±12.9 yr, P<0.001), had larger tumors (7.7±2.3 vs. 5.2±3.0 mm, P<0.001), had a greater number of lymph nodes removed(5.9±11.7 vs. 1.5±4.9, P<0.001), and had a greater number of metastases at first surgery (1.8±6.3 vs. 0.1±1.4, P<0.001).

Multivariate analysis showed that the independent variables for ECS were tumor size, diagnosis of nonincidental PTMC, and cervical lymph-node metastases at the time of diagnosis.

Comparative Analysis of Patients with and without Lymph-Node Metastases (Figure 2)

Univariate analysis showed that patients who had lymph-node metastases at the time of diagnosis (pN1) or within 6 months after initial surgery were significantly younger (42.3±16.4 vs. 49.9±12.6 yr, P<0.001), had larger tumors (7.3±2.4 vs. 5.4±3.1 mm, P<0.001), and had a larger number of lymph nodes removed at first surgery (15.1±16.9 vs 1.0±2.5, P<0.001).

Multivariate analysis showed that nonincidental diagnosis, ECS, multifocal disease, and the number of excised lymph nodes were independent risk factors for lymph-node metastases at the time of diagnosis.

Comparative Analysis of Patients with and without Tumor Recurrence (Figure 3)

Follow-up evaluation was completed in 287 of all patients with PTMC (30.8%), comprising 52 men and 235 women with a mean age of 49±13.9 years (range, 11 to 81); 105 of the 287 patients (36.6%) had ^{131}I therapy, and successful ablation was achieved after the first ^{131}I treatment in 91 (86.7%). Nine of the 287 patients had a tumor recurrence (3.1%), 7 in regional lymph nodes, 1 in regional lymph nodes and multiple bone metastases, and 1 with lung metastases. The mean time between the first operation and diagnosis of recurrence was 17.1±15.7 months (range, 7 to 51). After a mean follow-up of 35.5 months, all of the patients were alive, 4 with (1.4%) recurrent disease in lateral neck lymph-node metastases, 2 in lung, and 1 in bone.

Univariate analysis showed that risk factors for recurrence were multifocal disease (P<0.05), ECS (P<0.01), lymph-node metastases at the time of diagnosis (P<0.001), and the number of removed and metastasized lymph nodes (P<0.05 and P<0.001, respectively). Patients who required lymph-node dissection at first surgery frequently had recurrence (P<0.005). Also, follow-up was significantly longer in patients in whom a recurrence developed (48.9±24.7 vs. 34.9 ± 20.0 months, P<0.05). The mean tumor size did not differ significantly different among patients who experienced a recurrence and those who did not.

Multivariate analysis showed that the independent risk factors for recurrent disease were the number of removed and metastasized nodes at first operation and the length of the follow-up (time elapsed from the first surgery).

CONCLUSION

The need for radioiodine ablation and the follow-up protocol for patients with PTMC should be based on patient- and tumor-related prognostic variables, similar to that in patients with larger papillary thyroid cancers.

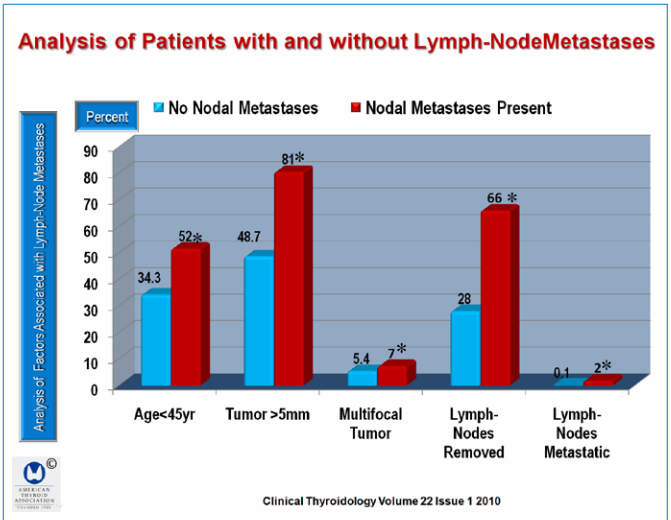

Figure 2. This figure shows the factors associated with pN1 lymph-node metastases at the time of diagnosis *P<0.001 comparing patients with versus those without lymph-node metastases, and P<0.001 comparing patients who did and did not require lymph-node dissection at initial surgery.

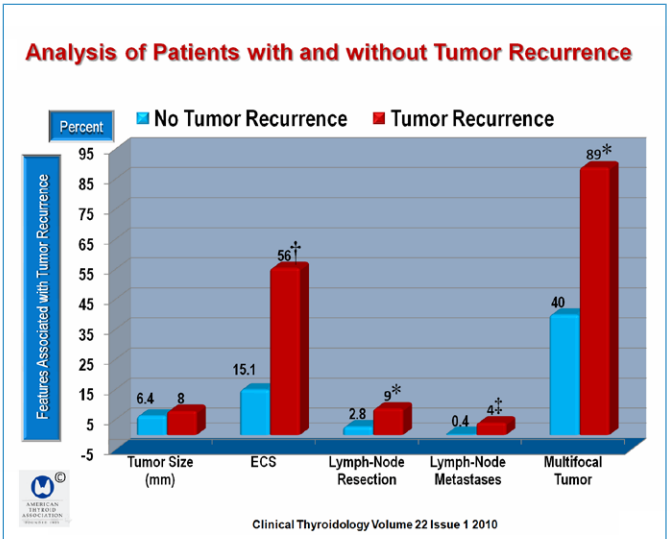

Figure 3. This figure shows that risk factors for recurrence were multifocal disease (*P<0.05), extracapsular spread (ECS) (†P<0.01), lymph-node metastases at the time of diagnosis (P<0.001), and the number of removed and metastasized lymph nodes (*P<0.05 and †P<0.001, respectively). Patients who required lymph-node dissection at first surgery frequently had recurrence (*P<0.005). Not shown is that follow-up was significantly longer in patients in whom recurrence developed (P<0.05).

COMMENTARY

Although it is widely recognized that the incidence of PTMC has more than doubled worldwide over the past three decades, its management has been a matter for global debate. The reason for this rests solely on the fact that at the time of diagnosis we cannot clearly determine whether a patient's PTMC is a potentially aggressive tumor or a biologically benign tumor that requires little or no management. As a direct consequence, at one end of the spectrum, management protocols range from simply performing extended follow-up without therapy to protocols that are essentially the same as those for the treatment of larger papillary thyroid cancers. Nonetheless, it is clear that some patients with PTMC die from this tumor, while others go without therapy for decades without consequences. Lombardi et al. make the point that this problem is clearly reflected in the large number of recently published reviews, guidelines, and meta-analyses that have failed to find any compelling evidence on which to base management protocols for PTMC (1-5).

The aim of the study by Lombardi et al. was to determine the best therapeutic option based on risk factors in a cohort with a high prevalence of goiter. The majority of tumors (75%) were incidental findings in patients who had surgery for goiters causing suppression (65%) or thyrotoxic goiters (35%). Multivariate analysis showed that tumor size, nonincidental diagnosis, and cervical lymph-node metastases at the time of diagnosis were independent risk factors for ECS, whereas ECS, multifocal disease, and the number of resected lymph nodes were independent factors for lymph-node metastases at the time of diagnosis. Lastly, multivariate analysis showed that the independent risk factors for recurrent disease were the number of removed and metastasized nodes at first operation and the length of follow-up (time elapsed from the first surgery). Diagnosis of tumor was incidental in 704 cases (75.5%) and nonincidental in the remaining 229 patients (24.5%). Among the nonincidental cases, 225 had a preoperative FNAB consistent with a suspicious or malignant thyroid nodule and the remaining 4 had a preoperative diagnosis of lateral neck node metastases Contrary to other studies, patients with lymph-node metastases and ECS were younger than those with PTMC confined to the thyroid. In short, these findings show that patients with clinically evident tumors have a more advanced stage of disease that requires more aggressive therapy than incidentally diagnosed tumors.

The authors point out that the study has several limitations; namely, follow-up was completed in only about one third of the patients, and mean follow-up was only about 3 years, with the longest being 7 years. This is a relatively short follow-up considering that it may take several decades to identify residual tumor (6). Nonetheless, in spite of these limitations the recurrence rates are in keeping with most published reports and reviews (7).

In conclusion, although other factors likely impact recurrence of PTMC, this carefully crafted study provides information that is unique and likely to influence future protocols for the management of PTMC.

— Ernest L. Mazzaferri, MD, MACP

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