

Disease-free and cancer-specific survival is similar in familial and sporadic papillary thyroid cancer in Japanese patients

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SUMMARY

BACKGROUND The risk for familial nonmedullary thyroid cancer (FNMTC) is elevated among individuals with first-degree relatives who have the same type of tumors. However, there is debate concerning the biologic characteristics of FNMTC. This is a study of the prevalence and biologic behavior of this familial disorder.

METHODS From 1987 through 2004, 6015 patients had initial surgical treatment of papillary thyroid carcinoma at Kuma Hospital in Japan. Among this group, 273 (4.5%) were classified as having familial nonmedullary thyroid cancer on the basis of two or more first-degree relatives with papillary cancer, including the index patient, none of whom had other familial thyroid cancer syndromes or prior exposure to radiation. The extent of thyroidectomy was based on preoperative neck ultrasound findings. Cervical lymph-node central compartment dissection was performed systematically (prophylactically) in 5706 (95%) patients with tumors larger than 1 cm without preoperatively identified lymph-node metastases, and was done therapeutically in patients with known cervical lymph-node metastases. Thereafter, patients had a once-yearly follow-up with ultrasonography and either chest roentgenography or computed tomography.

RESULTS In all, 273 of 255 patients (93.4%) were members of families with 2 affected individuals, including the patient under study, and 18 (6.6%) had 3 or more affected family members. Total or near-total thyroidectomy was performed in 177 of 273 (69%) with familial tumor and 2894 of 5742 (50%) patients with sporadic tumors, and lobectomy or less was performed in 72 of 273 (26%) with familial tumors and 2308 of 5742 (40%) with sporadic tumors (Figure 1). Among the patients with familial tumors, lymph-node compartment dissection was bilateral in 27 (10%), unilateral in 174 (64%) and limited to the central neck compartment in 62 (22%) or was not performed in 10 (3%) patients. Among the 5742 patients with sporadic disease, lymph-node compartment dissection was bilateral in 537 (9%), unilateral in 3800 (66%) and confined to the central neck compartment in 1106 (19%) and was not performed in 299 (6%) patients (Figure 1). Only 127 patients (2%) had postoperative ¹³¹I remnant ablation. Tumor recurrence was based on the results of imaging studies. The positive predictive value of identifying tumor multicentricity on preoperative ultrasound was 80%, the negative predictive value 78%, the sensitivity 60%, and the specificity 90% (Figure 2). Multicentric tumors were detected by preoperative ultrasonography in 104 of 273 patients (38%) with familial tumors and in 1618 of 5742 (28%) with sporadic tumors (P<0.006, comparing sporadic tumor with familial tumor) (Figure 3). Multicentric tumors were confirmed by the surgical pathology in 127 of 273 patients (46%) with familial tumors and 2201 of 5742 (38%) with sporadic tumors (P = 0.008)

In all, tumor recurred in 463 of 5931 patients (7.8%) who underwent locally curative surgery, 21 (0.4%) with familial tumor and 442 (7.5%) with sporadic tumor (P = 0.004). Of patients that had less than near-total thyroidectomy, tumor growth appeared in remnant thyroid tissue in 4 of 85 (5%) with familial tumor, and 33 of 2844 (1%) with sporadic tumor (P<0.004). Recurrences among the 6051 patients were found in other organs in 342

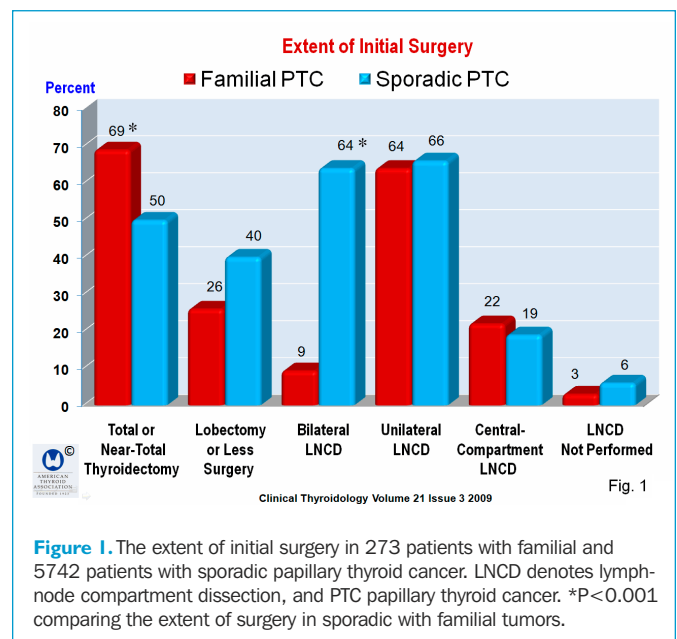


Figure 1. The extent of initial surgery in 273 patients with familial and 5742 patients with sporadic papillary thyroid cancer. LNCD denotes lymph-node compartment dissection, and PTC papillary thyroid cancer. *P<0.001 comparing the extent of surgery in sporadic with familial tumors.

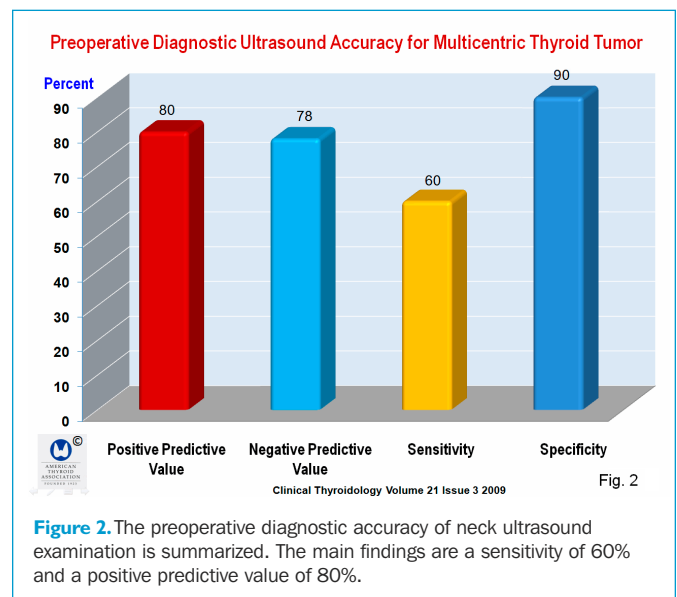
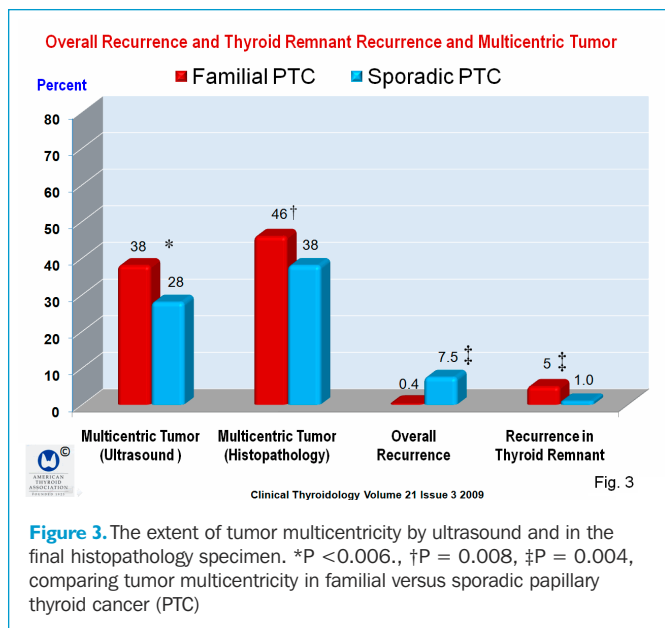


Figure 2. The preoperative diagnostic accuracy of neck ultrasound examination is summarized. The main findings are a sensitivity of 60% and a positive predictive value of 80%.



patients (5.7%), but there were no significant differences among patients with sporadic or familial tumors. There was no significant difference in disease-free survival and cancer-specific mortality rates among patients with familial or sporadic tumor.

Multivariate analysis found that the following variables influenced disease-free survival: tumor larger than 4 cm (P < 0.001), tumor stage pT₄ (tumor of any size extending beyond the thyroid (P < 0.0001), age 55 or older (P < 0.001), male sex (P = 0.003), and stage N1b (bilateral, midline, or contralateral cervical or mediastinal lymph-node metastases, P < 0.0001). In addition to distant metastases, multivariate analysis of disease-free survival found the same independent variables as found in the multivariate analysis of disease-free survival. Tumor multicentricity was not recognized as an independent variable in either multivariate analysis.

CONCLUSION Disease-free survival and cancer-specific mortality rates are similar in Japanese patients with sporadic and familial papillary thyroid cancer.

COMMENTARY

About 5% of papillary thyroid cancers are inherited as a familial tumor without other associated pathology, which is usually referred to as familial nonmedullary thyroid cancer (1). Although the causative gene(s) is yet to be identified, one family in Tasmania was found to have a mutation in chromosome 2q21 (2). A more recent study found that the polymorphic mature microRNAs from the passenger strand of pre-miR-146a contribute to familial thyroid cancer (3). How this will translate into clinically identifying patients with familial nonmedullary thyroid cancer awaits further study. Nonetheless, FNMTc is recognized as a distinct clinical entity in which almost all of the tumors are papillary thyroid cancers (4). Still, sporadic papillary cancer is so prevalent that up to 69% of two-hit families actually have sporadic, not familial, tumor (5). An estimated 1 of 338 persons with thyroid cancer (~3%) carries the genetic trait for familial papillary thyroid cancer, and its presence is most certain in families with 3 to 5 affected members, in which case there is a 96% likelihood it is an affected kindred (5).

It has been suggested that familial papillary thyroid cancer seems to have a less favorable prognosis as compared with sporadic tumors (1). Some studies find that familial papillary cancer is characterized by an earlier age at onset and a more aggressive phenotype than sporadic tumors (6). A study of 258 cases found that although sex, age, and tumor histology were similar to that with sporadic papillary cancer, familial tumors were more likely to have intrathyroidal dissemination (41% vs. 29%) and higher recurrence rates (16% vs. 10%) as compared with


sporadic tumors, without displaying significant differences in size, local invasion, or macroscopic metastasis (7). A meta-analysis found that individuals with familial papillary cancers have an increased risk of multifocal disease, local invasion, and lymph-node metastases and that these aggressive features appear to contribute to the higher recurrence rate and decreased disease-free survival rates in familial papillary thyroid cancer as compared with sporadic thyroid cancer (1).

The study by Ito et al. finds a somewhat different outcome than that reported by many others. Since this is a genetic disorder, familial papillary thyroid cancer in Japanese patients may be genetically predisposed to a less aggressive course. It also is important to note that the majority of sporadic cases in the Ito study had only 2 family members with familial tumors, and the presence of this disease is much more certain when there are 3 to 5 affected kindred. Also, it is difficult to know the outcome of patients with familial tumors as compared with sporadic cases, as many patients in this series had less than total thyroidectomy without radioiodine ablation. Furthermore, neck ultrasonography had a sensitivity of less than 60%. Still, more patients with familial tumors in the Ito study had significantly greater rate of multifocal tumor as compared with patients who had sporadic disease, although this was not an independent variable in multivariate analysis. This is a complex problem that spans genetics, clinical diagnosis, and therapy, any of which can alter prognosis, thus altering the apparent behavior of a tumor.

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