

Recurrence of papillary or follicular thyroid cancer during the first year after initial surgery has a worse prognosis than occurs with later recurrence

Lin JD, Hsueh C, Chao TC. Early recurrence of papillary and follicular thyroid carcinoma predicts a worse outcome. *Thyroid* 2009;19:1053-9.

SUMMARY

BACKGROUND Recurrence of papillary and follicular thyroid cancer is a common problem that has been extensively studied. However, data concerning the timing of recurrence are relatively sparse and may be related to the long-term outcome of patients with recurrent tumors. This study was based on the hypothesis that an early recurrence of papillary or follicular thyroid cancer is associated with the response to therapy and, ultimately, to long-term outcome.

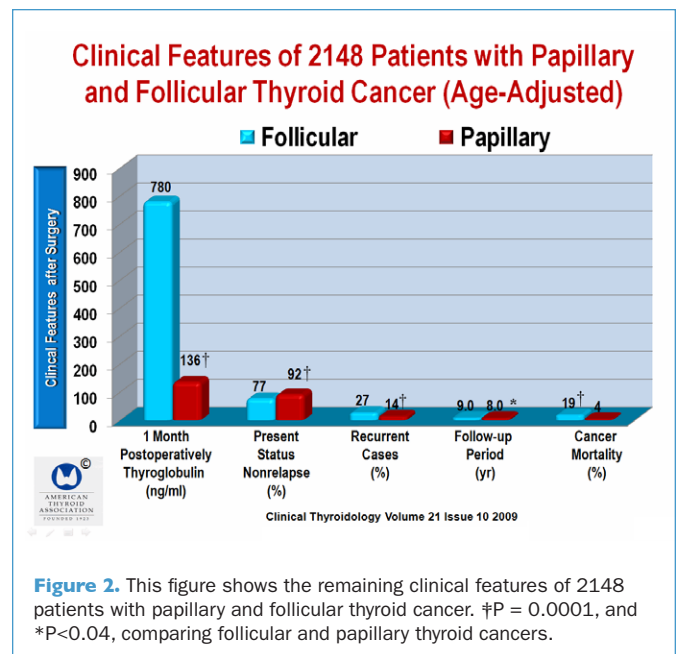
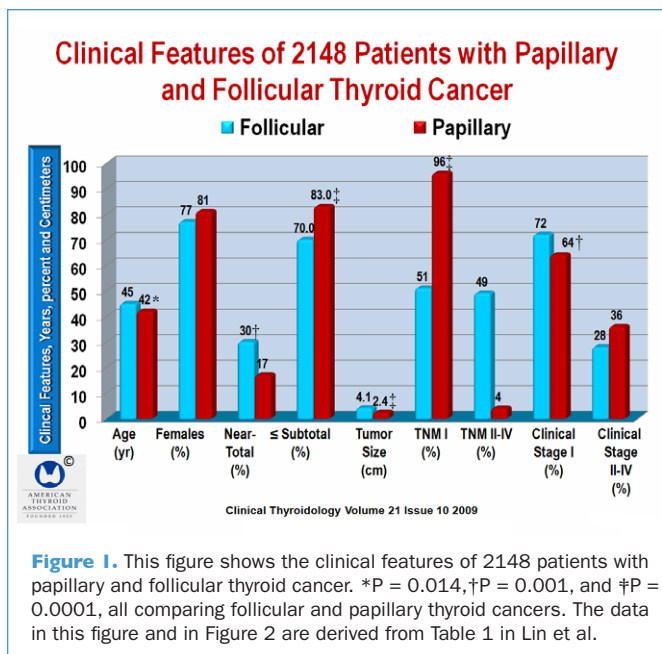
METHODS This is a retrospective study of 2148 patients, 1910 with papillary thyroid cancer and 238 with follicular thyroid cancer treated from 1977 through 2006 at the Chang Gung Memorial Hospital in Linkou, Taiwan. Tumors were staged according to the TNM (tumor–node–metastases) criteria (6th edition) and were categorized according to the Clinical Class criteria. All patients were treated postoperatively with thyroid hormone replacement or suppressive therapy. During follow-up, patients were evaluated with whole-body ¹³¹I scans (DxWBS), and chest x-ray examinations, and every 6 to 12 months had measurements of serum thyroglobulin (Tg) concentrations. Patients in whom tumor recurrence was suspected had neck ultrasonography with fine-needle aspiration biopsy (FNAB), computed tomography (CT) scans, and ¹⁸F-fluorodeoxyglucose positron-emission tomography (¹⁸F-FDG–PET) scans. Recurrences were stratified according to a cytologically or histologically diagnosed tumor (group A), a ¹³¹I-diagnosed tumor (group B), or other imaging study (group C). The patients were

further classified into an early or late recurrence group. The early group was defined as patients with tumor tissue that persisted after surgery or other adjuvant therapy, including distant metastases detected by a DxWBS within 1 year after thyroid surgery. The late recurrence group comprised patients with cancer recurring more than 1 year after initial thyroid surgery and ¹³¹I ablation therapy. At the end of the study period, lack of tumor relapse was defined as a negative ¹³¹I DxWBS and no local or distant metastases identifiable by a noninvasive examination.

RESULTS

Clinical Features of 2148 Patients with Papillary and Follicular Thyroid Carcinoma (Figures 1 and 2)

Of the 2148 patients, those with follicular cancer were older than patients with papillary cancer, but there was no sex difference between the two groups. Tumor was confined to the thyroid in 1390 of the 2148 patients (65%) with papillary or follicular thyroid cancer. The mean (±SD) tumor size was 2.6±0.04 cm for papillary and follicular tumors combined, 2.40±0.04 cm for papillary cancer, and 4.10±0.20 cm for follicular cancer (P<0.001). Cancer-specific mortality was higher with follicular cancer as compared with papillary thyroid cancer (19% vs. 4%). The clinical features of 2148 patients are shown in Figures 1 and 2. Over half the diagnoses (173 of 325; 53%) were confirmed by cytology or surgical histology, most of which were confirmed by locoregional neck surgery. Here and elsewhere, percentages are rounded to an integer.



Outcome with Early and Late Recurrence (Figures 3 to 5)

The mean time between the first thyroid surgery and detection of early recurrent cases was 55.0±0.4 years, as compared with 11.5 years in the group with late metastases. The early recurrence group as compared with the late recurrence was characterized by older age (51 vs. 44 yr), more males (40 vs. 28%), higher postoperative Tg value (2115 vs. 153 ng/ml), higher TNM stage (77 vs. 53%), more lymph-node and soft-tissue invasion (28 vs. 35%), and higher cancer mortality rates (40 vs. 22%) for early versus late recurrences.

Postoperative tumor recurrence was found in 352 of the 2148 cases (15%) of follicular and papillary thyroid carcinoma after a mean follow-up of 9.0±0.4 and 8.1±0.1 years, respectively.

Among the 352 patients with recurrence, 185 were in the early recurrence group (57%) and 140 were in the late recurrence group (43%). In the early recurrence group, 145 of 185 patients (78%) had distant metastases and 72 of 185 had local metastases (39%), whereas in the late recurrence group, 74 of 140 had distant metastases (53%) and 92 of 140 had local metastases (66%). In the early recurrence group, cancer death occurred in 6 of 40 patients with local metastases (15%) and 54 of 113 with distant metastases (48%). However, in the late recurrence group, 8 of 66 patients with local metastases died of disease (12%) and 23 of 74 died of distant metastases (31%).

Of the 325 patients with recurrence, 125 (38%) have survived without relapse. However, after a mean follow-up of 8.7±0.01

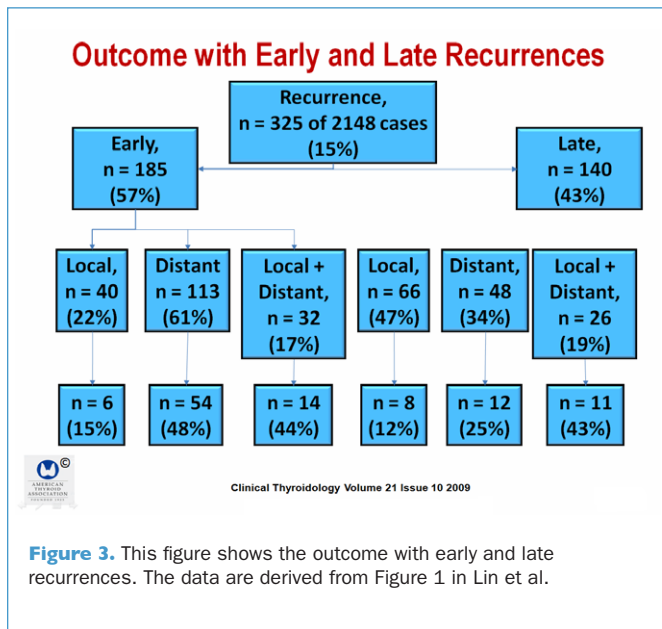


Figure 3. This figure shows the outcome with early and late recurrences. The data are derived from Figure 1 in Lin et al.

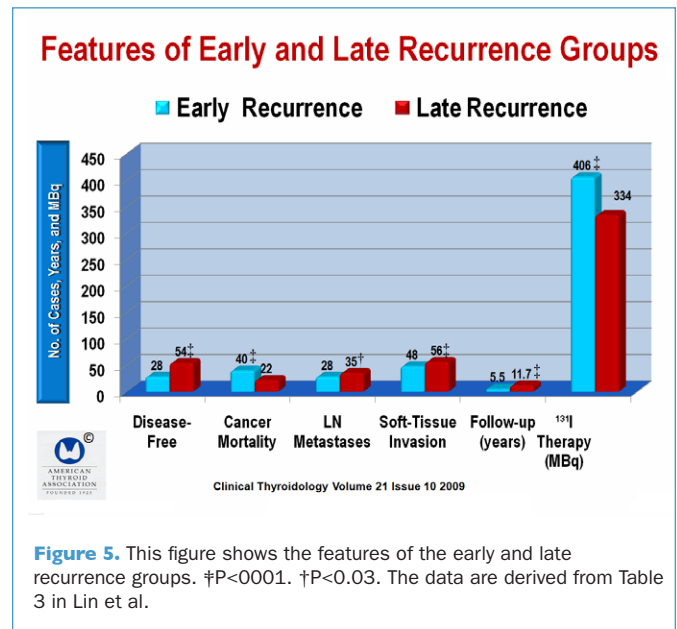


Figure 5. This figure shows the features of the early and late recurrence groups. †P<0.001. ‡P<0.03. The data are derived from Table 3 in Lin et al.

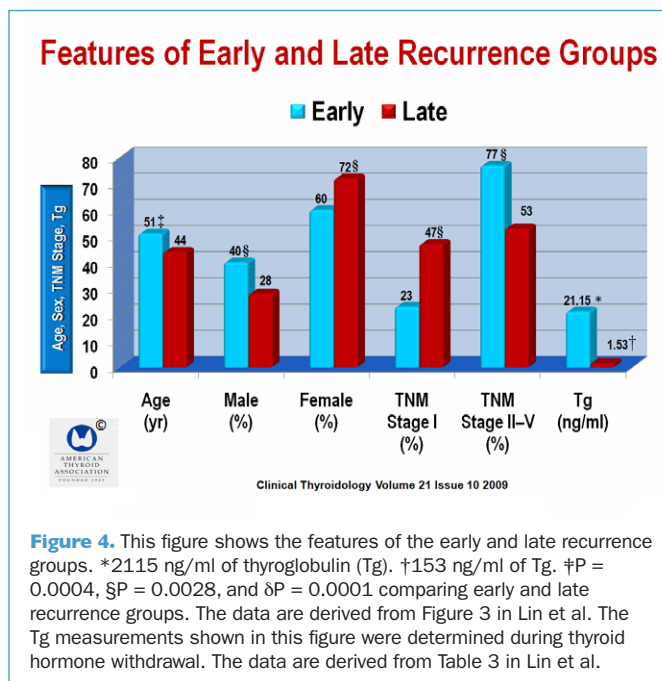


Figure 4. This figure shows the features of the early and late recurrence groups. *2115 ng/ml of thyroglobulin (Tg). †153 ng/ml of Tg. †P = 0.0004, §P = 0.0028, and δP = 0.0001 comparing early and late recurrence groups. The data are derived from Figure 3 in Lin et al. The Tg measurements shown in this figure were determined during thyroid hormone withdrawal. The data are derived from Table 3 in Lin et al.

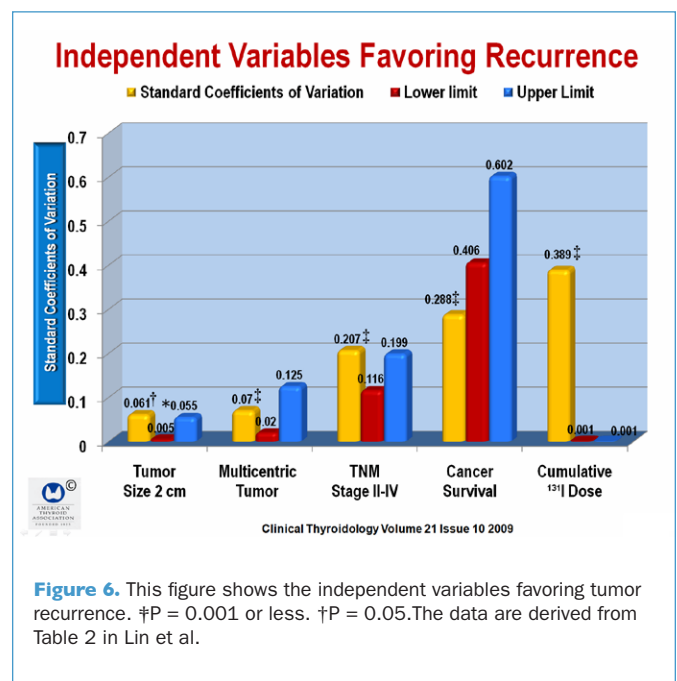


Figure 6. This figure shows the independent variables favoring tumor recurrence. †P = 0.001 or less. ‡P = 0.05. The data are derived from Table 2 in Lin et al.

years, 105 of the patients with recurrence died of disease (32%). Survival rates were significantly better with papillary cancer than with follicular cancer, with 5-, 10- and 20-year survival rates of 66%, 53%, and 35%, respectively, for the early recurrence group and 94.1%, 85.1%, and 60.2% for the late recurrence group. The survival rates with papillary and follicular cancer were greater in the late recurrence group than in the early recurrence group. Cancer-specific mortality was characterized by older age, male sex, larger tumor size, less aggressive surgery, and more treatment with external-beam radiotherapy. Cumulative ¹³¹I was not significantly different in the two groups.

COMMENTARY

Unlike the initial management of papillary and follicular thyroid cancer, the treatment of tumor recurrence is less consistent. This is especially important, since recurrence rates for these tumors may be as high as 50%, and the response rates to therapy depend on multiple variables, such as the location of persistent tumor, the patient’s age, and multiple factors including the response to initial therapy and the biologic characteristics of the tumor. Thus, reliable prognostic factors are seriously needed to manage differentiated thyroid cancer tumor recurrences and to devise robust treatment and follow-up schemes for patients with persistent or recurrent disease. Several studies provide insight into this problem. The 10-year survival rates of differentiated thyroid cancer range from 80 to 95% (1). Because age at the time of diagnosis varies widely, survival rates depend heavily on age at the time of diagnosis. In addition, tumor size is a well-recognized factor influencing the rate of tumor recurrence. However, Lin et al. found that patients with small primary tumors (≤2 cm) who do not have extrathyroidal invasion or a history of radiation or a family history of thyroid cancer are at very low risk for recurrence. Nevertheless, there is a small risk for recurrence.

For example, a study of 52,173 patients with papillary thyroid cancer, by Bilimoria et al. (2) found that the effect of tumor size on recurrent papillary thyroid cancer was dramatic. The mean 10-year recurrence rate was almost 5% for primary tumors <1 cm, 7% for tumors 1 to 1.9 cm, and almost 9% for tumors 2 to 3 cm, ranging up to nearly 25% in patients with primary tumors >8 cm.

Leboulleux et al. (3) performed a study aimed at evaluating the prognostic impact of lymph-node metastases and tumor extension beyond the thyroid capsule. The study subjects were 148 consecutive patients with papillary thyroid cancer who had lymph-node metastases with or without extrathyroidal tumor extension. All were initially treated with total thyroidectomy and central and ipsilateral lymph-node dissection followed by ¹³¹I ablation. Uptake of ¹³¹I outside the thyroid bed was found on the postablation whole-body scan (RxWBS) in 22% of the patients. After a mean follow-up of 8 years, 8 patients (7%) with a normal RxWBS experienced tumor recurrence. The 10-year disease-specific survival rate was 99% (95% confidence interval [CI], 97 to 100). The significant risk factors for persistent disease included the number of lymph-node metastases (>10) and lymph node metastases with extracapsular extension, tumor size >4 cm, and lymph-node metastases in the central neck. The significant risk factors for recurrent disease were

Independent Variables Favoring Recurrence (Figure 6)

Multiple-regression analysis identified the following five independent factors that portended recurrence: tumor size (2 cm), tumor multifocality, TNM stage, survival, and the amount of cumulative postoperative ¹³¹I.

CONCLUSION Recurrent papillary and follicular thyroid cancers are associated with high mortality rates and are difficult to eradicate. Recurrent cancer detected during the first year after initial surgery has a worse prognosis than that with late recurrences.

the number of lymph-node metastases (>10) and lymph-node metastases with extracapsular tumor extension, and a high Tg level on levothyroxine withdrawal 6 to 12 months after initial treatment.

Lin et al. found that survival rates were significantly better with papillary cancer than follicular cancer, and that survival rates were higher in the late recurrence group than in the early recurrence group. Cancer-specific mortality was characterized by older age, male sex, larger tumor size, less aggressive initial surgery, and more treatment with external-beam radiotherapy. However, cumulative ¹³¹I was not significantly different in the two groups. Still, multiple-regression analysis identified survival, 2-cm tumor size, TNM stage, tumor multifocality, and the amount of cumulative postoperative ¹³¹I to be independent risk factors influencing recurrence rates.

in a study of 203 patients with papillary microcarcinoma, Chow et al. (4) found that the lymph-node recurrence rate increased 6.2-fold when there were lymph-node metastases at presentation (95% CI, 1.3 to 23.4), which increased 5.6-fold when there were lymph-node metastases and multifocal tumor in the thyroidectomy specimen (95% CI, 1.3 to 23.5; P = 0.02). In addition, ¹³¹I ablation reduced the relative risk for lymph-node recurrence to 0.27 (95% CI, 1.30 to 100.00; P = 0.03). Radioiodine ablation reduced the relative risk for lymph-node recurrence to 0.27 (95% CI, 0.08 to 0.93; P = 0.04). The incidence of lymph-node metastases increased with the presence of multifocal disease in the primary thyroid tumors (34% vs. 20%; P = 0.034).

Another study, by Baudin et al. (4), found that multivariate analysis showed that two parameters significantly influenced papillary microcarcinoma recurrence—namely, the number of histologic foci (P<0.002) and the extent of initial thyroid surgery (P<0.01). Only 3.3% of patients with unifocal multifocal papillary microcarcinoma treated with lobectomy had tumor recurrence.

A unique study by Links et al. (6) analyzed the risk factors for survival, including the effects of therapy, after adjusting for the baseline mortality rate in the general population to elucidate the adverse effects of treatment on life expectancy. In this study, the initial treatment of 504 patients consisted of thyroidectomy and ¹³¹I ablation, and high-dose ¹³¹I treatments for patients with residual tumor. Patients who were in complete remission underwent

an annual physical examination and Tg measurements during thyrotropin suppression. Survival time was adjusted to standardized survival rates to account for the baseline mortality rate in the general population. After a median follow-up of 9 years, the 10-year overall survival rate was 83% and the disease-specific survival rate was 91%, and persistent disease was found in 75 patients (15%). Links et al. found that treatment including radioiodine is safe but unsuccessful in 20% of the patients. Moreover, age was not found to be a disease-specific risk factor. The authors thus suggested that age should not be used as an independent factor in treatment algorithms. Univariate analysis found that T4N1M1 status and Hürthle-cell tumors were harbingers of persistent and recurrent disease, and multivariate analysis found that age alone was not predictive of recurrent disease. Clearly, the two most important

findings in the Links study were that patients who were disease-free with thyroid cancer had a normal life span, whereas patients with persistent disease had a life expectancy that ranged widely, with a median survival that was reduced to 60%, and the second important finding was that, patient age was not an independent factor predictive of disease recurrence.


The study by Lin et al. adds an important prognostic facet to the management of tumor recurrence for patients with papillary or follicular thyroid cancer—prognosis is considerably worse when recurrence is found during the first year after initial surgery, whereas late tumor recurrence generally has a more favorable prognosis.

Ernest L. Mazzaferri, MD, MACP


References

1. Hundahl SA, Fleming ID, Fremgen AM, et al. A National Cancer Data Base report on 53,856 cases of thyroid carcinoma treated in the U.S., 1985-1995. *Cancer* 1998;83:2638-48.
2. Bilimoria KY, Bentrem DJ, Ko CY, et al. Extent of surgery affects survival for papillary thyroid cancer. *Ann Surg* 2007;246:375-84.
3. Leboulleux S, Rubino C, Baudin E et al. Prognostic factors for persistent or recurrent disease of papillary thyroid carcinoma with neck lymph node metastases and/or tumor extension beyond the thyroid capsule at initial diagnosis. *J Clin Endocrinol Metab* 2005;90:5723-9.
4. Chow SM, Law SC, Chan JK, et al. Papillary microcarcinoma of the thyroid—prognostic significance of lymph node metastasis and multifocality. *Cancer* 2003;98:31-40.
5. Baudin E, Travagli JP, Ropers J, et al. Microcarcinoma of the thyroid gland: the Gustave-Roussy Institute experience. *Cancer* 1998;83:553-9.
6. Links TP, Van Tol KM, Jager PL, et al. Life expectancy in differentiated thyroid cancer: a novel approach to survival analysis. *Endocr Relat Cancer* 2005;12:273-80.


DEDICATED TO SCIENTIFIC INQUIRY, CLINICAL EXCELLENCE, PUBLIC SERVICE, EDUCATION, AND COLLABORATION.




AMERICAN THYROID ASSOCIATION
FOUNDED 1923



ATA Publications



Public & Patients



Physicians & Professionals

ABOUT THE ATA
GIVE ONLINE
JOIN THE ATA
FELLOWS' CORNER
MEMBERS ONLY

JOIN THE AMERICAN THYROID ASSOCIATION

Are you intrigued by the study of the thyroid? **You belong in the ATA!**

ATA members are leaders in thyroidology who promote excellence and innovation in clinical care, research, education, and public policy.

Join us as we advance our understanding of the causes and improve the clinical management of thyroid diseases in this era of rapid pace biomedical discovery.

A close-knit, collegial group of physicians and scientists, the ATA is dedicated to the research and treatment of thyroid diseases. ATA's rich history dates back to 1923 and its members are respected worldwide as leaders in thyroidology.

The ATA encourages you to apply for membership. We want you to experience the wealth of knowledge and enjoy the benefits of being active in this highly specialized and regarded society. The ATA looks forward to having you as a member!

<http://www.thyroid.org/professionals/join/index.html>