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Prognostic Variables of Papillary Thyroid Carcinomas with Local Invasion

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Abstract. To evaluate the significance of the extrathyroid extension (ETE) of papillary thyroid carcinoma at the time of diagnosis and the prognostic variables of patients, we retrospectively reviewed 1,013 thyroid cancer patients. Of the 741 papillary thyroid cancer patients, 466 (62.9%) were categorized in clinical stage I and 114 (15.4%) were categorized in clinical stage III. Of the 114 patients in clinical stage III, 81 were female (mean age 44.4 ± 15.7 years) and 33 were male (mean age 46.9 ± 18.1 years). Of the clinical stage III patients, 104 patients received post-operative radioactive iodide (^{131}I) therapy while 22 patients received external radiotherapy in the neck and upper mediastinum area post-operatively. In the study, age, gender, ^{131}I accumulated dose, post-operative serum thyroglobulin (Tg) levels, and survival rate were demonstrated to be statistically significant in the groups with no recurrence and recurrence after treatment. The average follow-up period of these patients was 6.0 years. During this follow-up period, 11 patients expired. Eight died of thyroid cancer (7.0%) and 3 died of intercurrent diseases including asthma, renal cell carcinoma and propranolol overdose. Four of the 8 patients (50%) died of airway obstruction due to cancer cell invasion. Another 4 died of distant metastases, including 2 patients with skull metastases and brain invasion. The 5- and 10-year survival rates were 0.981 and 0.956 in clinical stage I and 0.923 and 0.843 in clinical stage III, respectively. In conclusion, the survival rate of the ETE of papillary thyroid cancer was lower when compared with stage I, especially in older male patients with higher post-operative serum Tg levels.

Key words: Radioactive iodide, External radiotherapy, Thyroglobulin

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ALTHOUGH well differentiated thyroid carcinoma had been known as a rather indolent malignancy, most studies revealed poor prognosis for papillary thyroid carcinoma with extrathyroid extension (ETE) at the time of operation when they were compared with patients without ETE [1–4]. There is little information, however, about the prognostic variables for papillary thyroid carcinoma with ETE at the time of diagnosis. To evaluate the significance of ETE of papillary thyroid carcinoma in terms of survival and tumor recurrence, and to determine the prognostic variables of patients, we retrospectively reviewed and analyzed 1,013 thyroid cancer patients.

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Subjects and Methods

From January, 1977 to December, 1995, 1,013 thyroid carcinoma patients received their treatment and were followed up at the Chang Gung Medical Center in Linkou, Taiwan. Of these patients, 910 cases of papillary or follicular thyroid carcinoma including 741 papillary thyroid carcinoma patients were diagnosed. In this medical center near total

thyroidectomy or modified radical neck thyroidectomy were conducted on the papillary thyroid cancer patients with local invasion. Whole body ^{131}I images were performed 4 to 6 weeks after the operations after using 5 mCi of ^{131}I for diagnostic scans. If ^{131}I uptake of the neck was over 1% of the dose at 24 h, the thyroid remnant was ablated with 30 to 100 mCi of ^{131}I. If distant metastatic lesions were detected by the 5 mCi ^{131}I scan, 100 to 150 mCi ^{131}I was used for treatment. Hospitalization for isolation was arranged if the dose of ^{131}I was over 30 mCi. Whole body scans were carried out 2 weeks after the higher therapeutic dose (over 30 mCi) of ^{131}I was given. Long term thyroxine replacements were given after the therapeutic whole body imagings. The patients were asked to follow a low iodine diet beginning at the week before the diagnostic scan until the day after the administration of the ^{131}I therapy as previously described [5]. Repeat cancer investigation including chest x-ray, 5 mCi ^{131}I scan and the serum thyroglobulin (Tg) level was performed a half to one year later 4 to 6 weeks after thyroxine replacement was stopped. Treatment was continued until the ^{131}I uptake over the neck region was less than 1% and no distant metastasis was evident. The patients received follow-up after one year, and then 2 years thereafter. If the follow-up scan was negative, then further scans were obtained only at 5-year intervals unless clinical or other laboratory data revealed recurrent thyroid carcinoma.

External radiotherapy to both sides of the neck, from the thyroid to the supraclavicular fossae and extending down to the superior mediastinum, was performed on patients with residual tumor that could not be removed by surgery. Most patients received total tumor doses of 60 Gy in 30 days. Treatment in 2 Gy fractions to both fields was continued daily for 6 weeks.

In this study, tumor staging was classified according to the clinical staging as described by DeGroot [6]. Stage I is a tumor with one or more intrathyroidal foci. Stage II is a tumor with cervical metastases. Stage III is a thyroid tumor with ETE including fixed cervical metastases. Stage IV is metastatic lesions outside of the neck. All the patients were categorized in groups with no recurrence or recurrence including lymph node metastasis, local recurrence and distant metastasis, at the end of 1995 after the treatment. Hospital records were reviewed and the following data were stored in the computer: age, gender, histopathological type, primary tumor size, method of operation, operative findings, post-operative serum Tg level, results of the post-operative 5 mCi of ^{131}I cancer work ups, accumulation of therapeutic ^{131}I doses, and the post-operative chest x-ray findings. The post-operative serum Tg level was detected with a Tg kit (CIS bio international, France). The detection limit of the Tg kit was 0.5 ng/mL. Interassay coefficient of variation was 8% at a Tg level of 4.9 ng/mL, 6.9% at 223.2 ng/mL, and 5.1% at 312.9 ng/mL.

Data were presented as the mean ± SD, and univariate and multivariate statistical analyses of the significance of the various factors were performed by the Kaplan-Meier method and the log-rank test [7]. Statistical significance was regarded as corresponding to a P value less than or equal to 0.05. Actuarial survival rates were calculated by the Kaplan-Meier method and differences in survival rates were examined by means of the Breslow and Mantel-Cox tests.

Results

Of the 741 papillary thyroid carcinoma patients, 466 (62.9%), 126 (17.0%), 114 (15.4%), and 35 (4.7%) patients were categorized as clinical stage I, II, III, and IV, respectively, at the time of diagnosis. Table 1 shows the clinical presentations and results of the treatment of stage I and III patients. The patients with papillary thyroid carcinoma with ETE were older, had a higher male ratio, bigger tumor size and higher post-operative serum Tg level. There were fewer stage III patients who were disease-free and surviving during the follow-up period. These differences between the two groups were statistically significant ($P<0.05$).

Of the 114 patients in clinical stage III at the time of diagnosis, 81 were female with a mean age of 44.4 ± 15.7 years, and 33 were male with a mean age of 46.9 ± 18.1 years. The differences in age in both genders were not statistically significant ($P=0.46$). The invasive cancer tissue of 29 patients (25.4%) could not be removed completely by a surgical procedure. Eight-five patients (74.6%) presented with local invasion, which could be resected by a surgical procedure (Table 2). Patients with invasive cancer tissue that could not be

Table 1. Clinical presentations of papillary thyroid cancer patients in clinical stages I and III

Factor	Stage at diagnosis		
	Stage I (n=466)	Stage III (n=114)	*P* value
Age (yrs)			
≤ 45 yrs />45 yrs	330/136	55/59	0.0004
Gender			
F/M	386/80	81/33	0.0066
Operative method			
Total/Subtotal/Lob*†	352/89/24	94/16/3	0.2097
Tumors size			
≤ 2.5 cm/>2.5 cm	272/165	41/63	0.0001
Post-operative ^{131}I uptake			
≤ 1%/> 1%	40/254	11/53	0.5853
Tg level			
≤ 3 (ng/ml)/> 3 (ng/ml)	142/268	23/77	0.0348
^{131}I accumulative dose			
≤ 30 mCi/> 30 mCi	119/262	34/70	0.8692
Present status			
No recurrence/Recurrence	451/15	83/31	0.0001
Survival			
Y/N	457/9	103/11	0.0002

*: Total thyroidectomy/Subtotal thyroidectomy/Lobectomy.
†: including one patient who received biopsy only when in stage III.

Table 2. Clinical presentation of the two groups with different operative findings and surgical results in well differentiated thyroid cancer in clinical stage III at time of diagnosis

Factors	Surgical findings		
	Complete resection (n=85)	Incomplete resection (n=29)	*P* value
Age at diagnosis			
≤ 45 yrs/>45 yrs	43/42	12/17	0.5210
Gender			
F/M	67/18	14/15	0.0038
Operative method			
Lob/Subtot / Tot*	2/10/73	1/6/21	0.4052
Tumor size			
≤ 2.5 cm/>2.5 cm	32/49	9/14	0.8343
Clinical presentation			
Neck nodule/Lymph node/Others	79/5/1	27/1/0	0.7526
Post-operative ^{131}I uptake			
≤ 1%/>1%	7/40	4/13	0.6645
Post-operative thyroglobulin			
≤ 3 ng/ml/>3 ng/ml	22/54	1/23	0.0253
^{131}I therapy accumulative dose (mCi)			
≤30 mCi/>30 mCi	28/50	6/20	0.3343
Present status#			
No recurrence / Recurrence	75/10	8/21	0.0001
Survival			
Yes/No	81/4	22/7	0.0070

*: Lobectomy/Subtotal thyroidectomy/Total thyroidectomy. #: Status at the end of 1995.

removed completely had a higher male ratio, higher Tg level, advanced follow up stage, and lower survival rate. One hundred and four out of the 114 patients received post-operative ^{131}I therapy with a mean dose of 135.0 ± 13.3 mCi (range 30 to 650 mCi). Of the 104 patients who received ^{131}I therapy, 72 patients were without recurrence at the end of 1995. Otherwise, 10 and 11 patients had local recurrence and distant metastases, respectively, at the end of 1995. One patient in clinical stage III and 2 in clinical stage IV died of cancer during this period. On the other hand, 2 patients in clinical stage I died due to non-cancer causes. Ninety-three patients had a Tg level before and after the ^{131}I therapy. In seventy-seven of the 93 (82.8%) patients, the serum Tg level decreased. The mean Tg level before and after treatment were 43.2 ± 12.2 to 18.8 ±7.6 ng/mL. Twenty-two patients received external radiotherapy in the neck and upper mediastinum area postoperatively. Of these patients, one received external radiotherapy over the brain after skull metastases, which were detected during the follow-up period. Table 3 shows the clinical information of these 114 patients in 2 groups, one with improvement, those in no recurrence at the end of 1995, and other recurrence or distant metastases during the follow-up period. Age, gender, the one month post-operative serum Tg level, ^{131}I accumulated dose, and survival rate of these two groups were significantly different ($P<0.05$). On the other hand, operative methods, and tumor size in these two groups were not statistically different. Multivariate statistical analysis of the significance of various factors showed that age and gender were independent factors in the prognosis of these patients. Relative risk for patients older than 45 years old and male was 11.5 and 12.1, respectively (Table 4).

The average follow-up period for the patients in our study was 6.0 years. Eleven patients expired during this follow-up period, 8 from thyroid cancer (7.0%) and 3 from intercurrent diseases: asthma, renal cell carcinoma and propranolol overdose. Fig. 1 shows the Kaplan-Meier survival curve of these patients. The 5-, and 10-year survival rates were 0.981, and 0.956 in clinical stage I and 0.923, and 0.843 in clinical stage III, respectively. Of the 8 patients died of papillary thyroid cancer, 5 received external radiotherapy on the neck and upper mediastinum for residual tumor. One received external radiotherapy of the brain 5 years after the operation. Five of these 8 patients received ^{131}I treatment with accumulated doses ranging from 100 mCi to 560 mCi. Four patients (50%) died of

Table 3. Clinical presentations of papillary thyroid carcinoma with extrathyroid extension in groups with no recurrence and recurrence during the follow-up period

Factor	Present status: No recurrence (n=83)	Present status: Recurrence (n=31)	*P* value	Relative risk	95% confidence interval
Age (yrs)					
≤ 45 yrs/>45 yrs	45/38	10/21	0.0033	2.457	1.05–5.73
Gender					
F/M	68/15	13/18	0.0001	6.277	2.65–14.88
Operative method					
Total/Subtotal/Lob*†	71/10/2	23/6/1	0.5317	–	–
Tumors size (cm)					
≤ 2.5 cm/>2.5 cm	34/44	7/19	0.2025	2.097	0.80–5.52
Post-operative ^{131}I uptake					
≤ 1%/> 1%	7/40	4/13	0.6645	0.569	0.14–2.25
Tg level (ng/ml)					
≤ 3 (ng/ml)/> 3 (ng/ml)	22/54	1/23	0.0253	9.370	1.62–54.03
^{131}I accumulative dose					
≤ 30 mCi/> 30 mCi	30/47	4/23	0.0391	3.670	1.21–11.16
Survival					
Y/N	81/2	22/9	0.0001	16.568	4.55–60.28

*: Total thyroidectomy / Subtotal thyroidectomy / Lobectomy. †: including one patient who received biopsy only on recurrence.

Table 4. Multiple logistic regression model predicting progression to clinical presentations of papillary thyroid carcinoma with extrathyroid extension in no recurrence and recurrence groups during the follow-up period

Factor	*P* value	Relative risk	95% confidence interval
Age (≤ 45 yrs/>45 yrs)	0.0133	11.5	1.66–79.89
Gender (M/F)	0.0052	12.1	2.10–68.87

Dependent variable: clinical presentations of papillary thyroid carcinoma with extrathyroid extension in recurrence and no recurrence. Independent variables: age, gender, operative method, tumor size, post-operative ^{131}I uptake, thyroglobulin level.

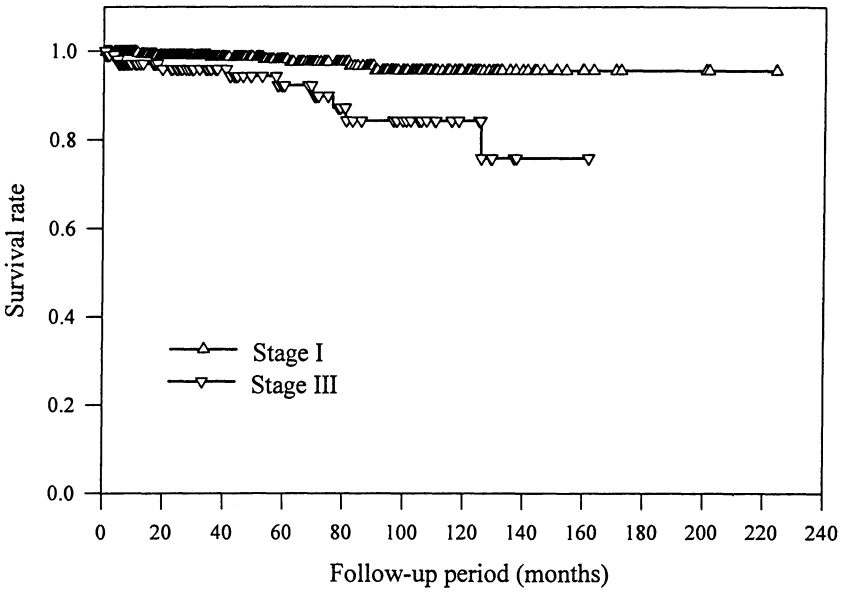

Fig. 1. Kaplan-Meier survival curve of papillary thyroid carcinomas in clinical stage I and III patients.

airway obstruction from cancer cell invasion. Four patients died of distant metastases including 2 skull metastases and brain invasion.

Discussion

Previous studies have indicated that age, histopathological type, tumor size, post-operative Tg level, clinical staging, and post-operative x-ray results were the significant prognostic factors for papillary and follicular thyroid carcinomas in this area [3, 8]. Further investigation with these data was performed to determine the prognostic variable for clinical stage III papillary thyroid carcinoma patients. Papillary thyroid carcinoma had been known to be more common with cervical lymph node metastases than follicular carcinoma [9, 10]. As our study showed, about half of the mortality in the papillary thyroid cancer patients was due to local tumor invasion [11–13]. Although most of the patients in our study received treatment that included nearly total thyroidectomy with lymph node dissection, post-operative ^{131}I treatment and one-fifth of these patients received external radiotherapy, 7% of the patients still died of thyroid cancer. The ratio of papillary thyroid cancer with ETE and the mortality rate of patients with ETE in our study was close to that in the series from Mayo Clinic [14] and Mazzaferri *et al.* [11]. This ratio of

papillary thyroid cancer with ETE is higher than in the whole series of thyroid carcinoma from Mellière *et al.* [12].

Female patients dominate well-differentiated thyroid cancer patients. In previous studies, gender was not shown to affect the outcome of treatment in well-differentiated thyroid cancer patients [1, 3, 4, 11] but in this study, once ETE of papillary thyroid carcinoma was present at the time of operation, male patients demonstrated a poorer prognosis than females. Our results were in accordance with the large series studies by McConahey *et al.* [14], Simpson *et al.* [15], and a long term follow-up study by Schindler *et al.* [16]. There is a need to further investigate the reasons for the poorer prognosis of male patients. More aggressive surgical procedures for male patients with ETE of papillary thyroid cancer are also advocated. The data from the Memorial Sloan-Kettering Cancer Center on 1,012 differentiated thyroid carcinomas, however, did not show that gender affected survival in patients with ETE [17].

Serum Tg levels have been used as a tumor marker in the follow-up of well-differentiated thyroid cancer patients [18–21]; and it was previously reported that the post-operative serum Tg level can be used as a prognostic factor in these patients [8]. In a recent study by DeGroot *et al.*, patients who had a serum Tg level below 2 ng/mL and underwent thyroid hormone replacement therapy or who had a serum Tg level below 3 ng/mL and did not undergo thyroid hormone replacement, rarely experienced tumor recurrence [22]. A high serum Tg level in the poorer prognostic patient group may reveal either residual tumor tissues that were not removed by surgery or distant metastases that could not be detected by ^{131}I or other non-invasive examinations in the study. High one month post-operative serum Tg levels could be regarded as an ominous sign of papillary thyroid carcinoma with ETE.

In the analysis of 79 differentiated thyroid carcinomas with ETE from the Memorial Sloan-Kettering Cancer Center, Andersen *et al.* [17] concluded that survival of patients was adversely affected by nonpapillary histology, distant metastasis, age >45, tumor size >4 cm, and incomplete excision. The presence of thyroid carcinoma adherences to the trachea, esophagus or soft tissues were not necessarily associated with poor prognosis [12, 23]. Although an aggressive surgical procedure including total resection was advocated for thyroid carcinoma with trachea or esophagus invasion [12], whether the resection should be performed with acceptable morbidity of the papillary thyroid carcinoma needs further investigation. The data from the Mayo Clinic series of 48 patients with well differentiated thyroid cancer invading the upper aerodigestive tract showed that an aggressive radical surgical procedure did not improve the survival of the patients [24]. In the current study, most of our patients received conservative surgical treatment; if the trachea or esophagus invasion could be completely eliminated, the patient received post-operative ^{131}I treatment and external radiotherapy. During this limited follow-up study, the 5- and 10-year survival rates were comparable with those in previous studies [24].

The role of adjuvant external radiotherapy for the post-operative treatment of well differentiated human thyroid cancer is still a controversial issue [25, 26], although its use has been reported in patients with well-differentiated thyroid cancer with post-operative residual disease, local recurrence, or in ^{131}I treatment refractory patients [27, 28]. In a recent study with a limited follow-up, Lin *et al.* [29] found that external radiotherapy did not improve the survival of patients with well-differentiated thyroid cancer at an advanced clinical stage. Although survival was not improved, the reduction of residual tumor size and improvement in the quality of life were expected in the patients who received external radiotherapy. To enhance the effect of external radiotherapy, a combination of doxorubicin and radiation therapy was advocated for local advanced thyroid carcinomas [30]. The median survival time was 4 years with better quality of life obtained for the well differentiated papillary, follicular or mixed type tumor.

In conclusion, papillary carcinoma patients with ETE seemed to have a poor prognosis when they were compared with intrathyroid papillary carcinoma patients, especially older patients, male patients and those with a higher post-operative serum Tg level.

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