Introduction

The prognostic significance of limited local lymph node metastases remains a controversial issue in patients with well-differentiated thyroid carcinomas (Tubiana et al. 1985, Mazzaferri 1991, Sellers et al. 1992). Increased risks of local tumor recurrence were found in several studies (Akslen & Myking 1992, Mizukami et al. 1992). In contrast, Coburn & Wanebo (1992) demonstrated that limited lymph node metastases were not significant prognostic variables. In prophylactic neck dissections, 27-82% of well-differentiated thyroid carcinoma patients had occult nodal metastases (Attie et al. 1972, Noguchi & Murakami 1987, Simpson et al. 1987). At present, neck dissections are recommended only for patients with palpable lymphadenopathy of well-differentiated thyroid carcinomas (Sellers et al. 1992). Under this policy of treatment, it is possible that there will be no recurrence in patients with occult nodal metastases, even in those who have not undergone nodal excision. To evaluate the
influence of limited lymph node metastases of well-differentiated thyroid carcinoma at the time of diagnosis and the prognostic variables of patients, 1013 thyroid cancer patients were retrospectively reviewed at our medical center.

Subjects and methods

From January 1977 through December 1995, 1013 thyroid carcinoma patients received primary treatment and were followed-up at Chang Gung Medical Center in Linkou, Taiwan. Of these patients, 910 had papillary or follicular thyroid carcinomas. Either near total thyroidectomy or modified radical neck thyroidectomy was performed on 689 patients after the tumors were found to be malignant by preoperative fine-needle aspiration or frozen sections. Two hundred and ten patients received either subtotal thyroidectomy or lobectomy only. Most of these patients received limited lymph node dissection in the anterior compartment of the neck only unless there were clinically detectable lymph node enlargements. One patient received biopsy only. Ten patients were referred from other hospitals without detailed records of the surgical methods used.

Four to six weeks after the operations, whole body ^131I image scans were performed after using 5 mCi ^131I for diagnostic scans. When 5 mCi ^131I scan was used for diagnosis, the patients were asked to return 24 h after using a single probe thyroid uptake system (AP 187-295; Atomic Product Corporation, Oak Ridge, TN, USA). If ^131I uptake of the neck was over 1% of the dose at 24 h, thyroid remnants were ablated with 30-100 mCi ^131I. If distant metastatic lesions were detected by the 5 mCi ^131I scan, 100-150 mCi ^131I was used for treatment. Hospitalization for isolation was arranged if the dose of ^131I was more than 30 mCi. The patients were discharged after the doctor confirmed that the whole body ^131I retention of the patients was below the regulatory limits. Whole body scans were carried out 2 weeks after the higher therapeutic doses (more than 30 mCi) of ^131I were used.

Long-term thyroxine (T\(_4\)) replacements were given after the therapeutic whole body imagings. The dose of the T\(_4\) replacement depended on the follow-up thyroid function test results. Serum thyrotropin (TSH) levels were kept at low normal levels during the replacement of T\(_4\). Most patients received the dose of T\(_4\) within 50 to 150 µg of the daily dose. To reduce the period of hypothyroidism, administration of tri-iodothyronine was permitted during the first 2 weeks of withdrawal from levothyroxine. Thyroid function tests including TSH, T\(_4\) and serum thyroglobulin (Tg) levels were determined 4-6 weeks after withdrawal from levothyroxine. The patients were asked to follow a low iodine diet for 1 week before the diagnostic scan and until the day after the administration of the ^131I therapy as previously described (Maxon et al. 1983). The same cancer investigation was performed on each patient 6 months to 1 year later. Treatments were continued until the ^131I uptake over the neck region was less than 1% and no evidence of distant metastasis was shown. The patients received follow-up examination 1 year after discontinuing treatment, and then again at 2 years after discontinuing treatment. If the follow-up scan was negative, further scans were obtained only at 5-year intervals unless clinical or other laboratory test results revealed recurrent thyroid carcinoma. For patients with ^131I uptake less than 1%, and serum Tg levels elevated, 75-100 mCi ^131I was used for the treatment of metastases that could not be detected by 5 mCi ^131I scan.

In this study, tumor staging was classified according to the clinical staging of DeGroot (1995). Stage 1 is a tumor with single or multiple intrathyroidal foci. Stage 2 is a tumor with limited cervical metastases only. Histopathologically proven cervical lymph node metastases were identified in all the patients. These were three categories of patients: namely, diagnosed preoperatively, diagnosed during operation, and diagnosed using final histopathologic examination results. Cervical lymph nodes were not grossly enlarged during the operations in the last group. The distribution of histologically proven metastatic cervical lymph node groups has been described in previous studies (DeJong et al. 1993). Stage 3 is a thyroid tumor with local cervical invasion or fixed cervical metastases. Stage 4 is a lesion metastasis outside the neck. The patients were categorized in two groups as no recurrence and local recurrence or 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, fine-needle aspiration cytological results, thyroid functions, results of thyroid scanning, histopathologic types, primary tumor size, methods of operation, operative findings, post-operative serum Tg levels, results of the post-operative 5 mCi ^131I cancer work-ups, accumulation of therapeutic ^131I dose, and the post-operative chest X-ray findings. Post-operative serum Tg levels were detected using 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 are presented as means±S.D. and two-tailed, unpaired nonparametric t-tests, chi-squared and ANOVA were used to evaluate the statistical significance of the data. Actuarial survival rates were calculated using the Kaplan-Meier method and differences in survival rates were examined using the test of Breslow and Mantel-Cox.
Table 2 Distribution of pathological proved cervical lymph nodes of 119 thyroid carcinoma patients

<table>
<thead>
<tr>
<th>Location of cervical nodes</th>
<th>Right</th>
<th>Left</th>
<th>Total</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilateral position</td>
<td>21 (26%)</td>
<td>49 (62%)</td>
<td>9 (12%)</td>
<td>0.0339</td>
</tr>
<tr>
<td>Mid jugular</td>
<td>20 (50%)</td>
<td>18 (45%)</td>
<td>2 (5%)</td>
<td>0.0310</td>
</tr>
<tr>
<td>Low jugular</td>
<td>26 (27%)</td>
<td>58 (61%)</td>
<td>11 (12%)</td>
<td>0.0310</td>
</tr>
<tr>
<td>Submandibular</td>
<td>15 (63%)</td>
<td>9 (37%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Supraclavicular</td>
<td>22 (26%)</td>
<td>52 (83%)</td>
<td>9 (11%)</td>
<td>0.0224</td>
</tr>
<tr>
<td>Posterior triangle</td>
<td>11 (89%)</td>
<td>5 (31%)</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Table 1 Distribution of pathological proved cervical lymph nodes of 119 thyroid carcinoma patients

<table>
<thead>
<tr>
<th>Location of cervical nodes</th>
<th>Right</th>
<th>Left</th>
<th>Total</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>High jugular</td>
<td>23</td>
<td>18</td>
<td>41</td>
<td>25</td>
</tr>
<tr>
<td>Mid jugular</td>
<td>42</td>
<td>20</td>
<td>62</td>
<td>37</td>
</tr>
<tr>
<td>Low jugular</td>
<td>21</td>
<td>11</td>
<td>32</td>
<td>19</td>
</tr>
<tr>
<td>Submandibular</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Supraclavicular</td>
<td>12</td>
<td>10</td>
<td>22</td>
<td>13</td>
</tr>
<tr>
<td>Posterior triangle</td>
<td>5</td>
<td>2</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>106</td>
<td>61</td>
<td>167</td>
<td>100</td>
</tr>
</tbody>
</table>

**Results**

Of the 910 papillary or follicular thyroid carcinoma patients, 565, 134, 120 and 91 patients were categorized, respectively, as clinical stages 1, 2, 3 and 4 at the time of diagnosis. Of the 134 clinical stage 2 patients, 15 who did not have complete information and regular follow-ups were excluded from this study. Of the remaining 119 stage 2 patients, 92 were female with a mean age of 35.3±14.7 years and 27 were male with a mean age of 43.4±13.2 years. Histopathologic findings included 111 papillary thyroid carcinomas and eight follicular carcinomas. These clinical stage 2 patients included 15.0% and 4.7% of the papillary (741 patients) and follicular (169 patients) thyroid carcinoma patients, respectively, in this series. Of the 119 patients, 114 patients received $^{131}$I treatment for remnant ablation or distant metastases. The mean accumulative $^{131}$I dose was 144±10 mCi (range 30-550 mCi). During the follow-up period, 18 patients received external radiotherapy on the neck and upper mediastinum area either because the lymph node metastases recurred or the tumor tissues could not be removed during surgery. After the treatments, 93 patients remained disease-free and 26 had local recurrence or distant metastasis. Twenty-six patients (21.8%) did not improve during the follow-up period. Ten patients remained in stage 2. Five and eleven patients progressed to stage 3 and 4 respectively. Among the eleven patients in stage 4, five had mediastinum metastases, three had bone, two had lung and one had lung and mediastinum metastases. Of the 565 clinical stage 1 patients, 4.1% (23 patients) aggravated to stages 2 to 4 during the restaging period.

Table 1 shows details of the lymph node metastases of the 119 patients in clinical stage 2. Most of the patients presented with high or middle jugular lymph node metastases.
Lin et al.: Thyroid carcinoma with lymph node metastases

metastases; and the incidence of the right side lymph node metastases was higher than that of the left side (Table 2). Most of the patients in this study presented with a single group of lymph node metastases (79.8%). Among the single group of the lymph node metastases, 12% were without grossly enlarged lymph node, which could be detected only by using histopathological examination. In our study, lymph node involvement was an important predictor of tumor recurrence, but it was not important in influencing patients' survival (Table 2).

Table 3 shows the clinical information of these two groups, improved or not improved, in clinical stage 2 to 4 patients. Age, first post-operative 5 mCi $^{131}$I uptake percentage, 1-month post-operative serum Tg levels and the survival rate were significantly different between these two groups ($P<0.05$). Otherwise, gender, tumor size, thyroid function, sonographic finding, and histopathological types were without statistical differences. When the multivariate analysis was examined in these patients there was no independent prognostic factor presenting significance.

Median follow-up period of these patients was 5.4 years. During this follow-up period, five patients died. Three died of thyroid cancer while two died of intercurrent diseases. Figure 1 illustrates the Kaplan-Meier survival curves of the patients in clinical stage 1 and 2. The 1-, 5- and 10-year survival rates of the clinical stage 2 patients were 1.000, 0.945 and 0.921 respectively.

**Discussion**

In our previous studies, age, histopathological types, tumor size, post-operative Tg levels, clinical staging, and post-operative X-ray results were the significant prognostic factors in this area (Lin et al. 1994, 1996a). The data were further investigated to obtain the prognostic variable for the clinical stage 2 patients of this study. Earlier reports from Cady *et al.* (1976) revealed that those with cervical lymph node metastases had a lower mortality rate than those without nodal metastases. In contrast, Mazzaferri & Jhiang (1994) demonstrated that both cervical or mediastinal lymph node metastases had higher recurrence and cancer mortality rates. Subsequent studies concluded that the adverse effect of cervical lymph node involvement could be masked if the patients analyzed included relatively few elderly patients (Harwood *et al.* 1978, Cady *et al.* 1979). Our data confirmed the prognostic significance of age in papillary and follicular thyroid carcinoma patients with lymph node metastases. As in previous studies, papillary thyroid carcinoma had been known to be more commonly found with cervical lymph node metastases than follicular carcinoma (Coburn &
Wanebo 1992, Sellers et al. 1992). From 63 to 80% of papillary thyroid carcinoma patients had micrometastases (Noguchi et al. 1970, Attie et al. 1972). Most of these micrometastases were clinically insignificant (Sellers et al. 1992). More data are needed to determine the clinical significance of palpable cervical lymph nodes in the patients with papillary and follicular thyroid carcinomas.

After the operations, most of our patients remained disease-free. Only 21.8% (26/119 cases) remained in stage 2 or progressed to stage 3 or 4. This ratio was higher than stage 1 patients (4.1%). Our study, corroborated that of Simpson et al. (1987): that is, nodal involvement was a potent predictor of tumor recurrence but unimportant for survival. This suggests that the management of nodal involvement is very significant, especially for patients with papillary thyroid cancers (Simpson et al. 1987). Although only three patients died of thyroid cancer in our study, studies showed that once patients progressed to advance clinical stages, poor prognoses are expected (Samaan et al. 1983, Carcangiu et al. 1985, Simpson et al. 1987). Age was the most important prognostic factor in clinical stage 2 patients (Rossi et al. 1986, Coburn & Wanebo 1992, Sellers et al. 1992). Unlike Coburn & Wanebo (1992), gender was not a significant prognostic factor in our study. Tg levels can be used as tumor markers for follow-up of well-differentiated thyroid cancer patients (Ashcraft & van Herle 1981). Although serum Tg levels had been used to detect tumor recurrence following surgery (Harvey et al. 1990, Ozata et al. 1994), there is limited information about the use of the serum Tg level as a prognostic factor in well-differentiated thyroid cancer patients with lymph node metastases. In our studies and those of others, serum Tg levels could be used as a prognostic factor in papillary, follicular and occult thyroid carcinoma patients (DeGroot 1995, Lin et al. 1996b).

Post-operative high Tg levels imply that residual cancer cells presented in the body which may not be detected by $^{131}$I or other conventional examinations. In our study,
post-operative Tg levels were still a useful prognostic factor in clinical stage 2 patients. Mean Tg levels were much higher in the patient groups that progressed to higher stages (121.0±27.5 vs 24.8±5.5 ng/dl) (P=0.001). A higher percentage of the first post-operative 5 mCi diagnostic scan revealed a poor response after the treatment. This result demonstrated more thyroid remnants after the operation and poorer prognosis after the treatment. A lesser degree of initial surgery cannot be excluded because of the higher percentage of the first post-operative 5 mCi diagnostic scan and elevated post-operative serum Tg levels that remained in stage 2 or that progressed to stage 3 or 4.

In conclusion, patients with papillary thyroid carcinoma revealed a high percentage of lymph node metastases. Although lymph node metastases did not influence survival rate, older age, high post-operative serum Tg levels, and larger remnant thyroid tissues demonstrated poor patient prognosis after treatment.

References
DeJong SA, Demeter JG, Jarosz H, Lawrence AM & Paloyan E 1993 Primary papillary thyroid carcinoma presenting as cervical lymphadenopathy: the operative approach to the 'lateral aberrant thyroid'. American Surgeon 59: 172-177.
Lin JD, Chao TC, Weng HF, Huang HS & Ho YS 1996b Clinical presentations and results of treatment of 74 occult thyroid carcinoma patients in Northern Taiwan. American Journal of Clinical Oncology 19: 504-508.
Mazzaferrari EL & Jhiang SM 1994 Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. American Journal of Medicine 97: 418-428.