INTRODUCTION

The behaviour of the differentiated thyroid cancers in endemic areas is reported to be different from that in non-endemic areas. In endemic areas not only is there a preponderance of the follicular and anaplastic cancers, both recognized for their virulent nature, even the papillary cancers are reported to pursue a more aggressive behaviour. (1,2) From amongst 289 thyroid cancers from an endemic goitrous area, we conducted a retrospective analysis in an effort to identify the various prognostic factors in patients with differentiated thyroid cancers in an endemic goitrous area.

MATERIALS AND METHODS

Of the 289 thyroid cancers analyzed, there were 215 differentiated thyroid cancers which histologically classified according to the WHO classification. (1) Thus, there were 132 papillary and 83 follicular cancers; both histologic types occurred at an earlier age with a male to female ratio of 1:1.1. There was a significant difference in the size of the primary tumours; 60/132 of papillary and 30/83 of follicular cancers were early TO-2 lesions and 20 papillary and 24 follicular cancers were advanced T3 lesions. Age did not affect the size of the primary tumour. Regional lymph node and pulmonary metastasis was common in both types of cancer while distant metastases occurred more frequently in follicular cancers (P<0.005). Following surgery, contralateral lobe recurrence in the remaining lobe was more common in follicular cancers while loco-regional recurrence after near-total thyroidectomy was more frequent in the papillary cancer group (P>0.05). Mortality in 26/132 papillary and 28/83 follicular cancer patients was high in both groups but significantly higher in follicular cancers (P<0.005). Although amongst papillary cancers mortality was higher in patients above 40 years of age (P<0.05), age did not affect survival in patients with follicular cancers. Sex did not affect survival in either group. The extent of the disease at presentation was found to be the most important determinant of survival with mortality significantly higher in T3N3M1 lesions (P<0.001). (Korean J Endocrine Surg 2002;2:37-41)

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60 papillary cancers with $T_0N_0M_0$ of which 38 patients were < 40 years of age. There were 30 cases of follicular cancers who presented with this early stage of the disease with 17 of them being < 40 years of age. There were 34 papillary and eight follicular cancers with $T_0N_1M_1$ of which 24 papillary and 3 follicular cancers were below 40 years of age. Advanced $T_1N_1M_1$ were encountered in 38 papillary and 45 follicular cancers of which 16 amongst papillary and 14 of follicular cancers occurred in patients < 40 years of age.

Distant metastasis at presentation were found in 17 papillary and 29 follicular cancers. Patients with pulmonary metastasis were typically asymptomatic at the time of detection of the lung of involvement. Pulmonary involvement was found in eleven papillary and sixteen follicular cancers. Skeletal metastases were usually associated with bony pain and/or pathological fracture and occurred in 5 papillary and 26 follicular cancers.

Surgery for the primary tumour aimed at near-total thyroidectomy while a hemithyroidectomy was performed in patients who did not have a definite preoperative diagnosis and who refused a completion thyroidectomy at a second stage (Fig. 2). The patients' follow-up ranged from 3 ~ 20 years (average 12.6 years). All patients were treated with suppressive doses of thyroid hormone. In patients with complete remission after the initial treatment of the tumour, clinical examination, chest x-ray, and serum TSH and thyroglobulin estimations were performed at 6, 12, 18 and 24 months and then annually. Whole body $^{131}$I scan was performed 3 ~ 6 weeks after near-total thyroidectomy to detect and treat any residual and/or metastatic disease, followed six months later by a repeat whole body scan to ensure total ablation of the disease. Recurrences were defined as a separate appearance of the disease after apparent previous control, regression, or removal. Progressive disease course without remission or disease-free interval was not classified as a recurrence. Thus, a contralateral lobe recurrence after hemithyroidectomy occurred in 5/30 papillary and 3/13 follicular cancers. Loco-regional recurrence, which was categorized as a recurrence in the thyroid bed, residual thyroid tissue, ipsilateral or contralateral lymph nodes or lymph nodes of the upper mediastinum, or recurrence in the other cervical structures, was seen in 32/99 papillary and 13/65 follicular cancers undergoing near-total or sub-total thyroidectomy. Mortality due to thyroid cancer occurred in 26 papillary and 28 follicular cancers.

Significance of the various parameters was calculated using the chi-square test.
RESULTS

Although papillary cancer was the predominant tumour in the patients under study occurring in 46% of the patients, follicular cancer in 29% and anaplastic and squamous cell cancers in 13% constituted a large percentage. Papillary cancers occurred at all ages, with the majority seen in the 3rd, 4th and 5th decades of life (53.8% in patients <40 years of age). However, of interest was the occurrence of follicular cancers in the younger age groups (33.7% in patients <40 years and nearly 7% in patients <19 years of age). Females predominated with 52.3% papillary and 57.8% follicular cancers seen in females.

The striking features, therefore, and which ignore the particular cell type, were the occurrence of tumours at an earlier age, higher percentage of follicular cancers in younger patients, and the male to female parity.

The commonest presentation of both histologic types was as overt lesions (P > 0.05). There was a significant difference in the size of the primary tumour at presentation. There was no relationship to the age and sex of the patient. Lymph node involvement was present in 52 papillary and 33 follicular cancers (P > 0.1). Nodal involvement was not affected by the age and sex of the patient. Distant metastases were more common in follicular cancers (P < 0.001), were significantly higher in the older age group in both cancers, and were not affected by the sex of the patient. Although there was a significantly higher prevalence of skeletal metastases in follicular cancers, there was no difference in the metastases to the lungs (P > 0.1).

If T0-2N0M0 is taken as an early stage of the disease, 45.5% papillary and 36.1% follicular cancers were early cancers (P > 0.5). Advanced T3N2M1 lesions occurred in 28.8% papillary and 54.2% follicular cancers (P < 0.001). Although a significantly higher number of papillary cancers occurred as early lesions, there was no statistical difference in the occurrence of follicular cancers amongst the various stages of the disease.

There was no significant difference in the development of contra-lateral lobe recurrence following hemithyroidectomy or the development of loco-regional recurrence following subtotal or near-total thyroidectomy between the papillary and follicular cancers (P > 0.5).

Mortality was high in both the histologic types but significantly higher in follicular carcinomas (P < 0.05). Although mortality was significantly higher in patients >40 years with papillary cancers (P < 0.05), age did not affect the survival of patients with follicular cancers (Table 1). Sex of the patient also did not reflect on the mortality in both types of tumours. Mortality was significantly higher in both the groups if the cancers at presentation were advanced T3N2M1 lesions (P < 0.05); there was no difference in the mortality of early T0-2N0M0 lesions. Only two patients with the early T0-2 size of the primary tumour but N1 lymph node status died of the disease, probably emphasizing the better prognosis for patients with small tumours if they are metastatic to the regional lymph nodes.

Death due to local recurrence of the tumour occurred in 50% papillary and 69% follicular cancers; thus, 55% of differentiated thyroid cancers with loco-regional recurrence died of the disease. Distant metastases at presentation signified a poor prognosis with 34% papillary and 48% follicular cancers succumbing to the metastatic disease. Metastases to the lungs and the skeletal system resulted in death in 31% and 27% of the patients respectively; all patients with metastasis to the brain, vertebral column, and liver died.

Table 1. Mortality in WDTC : Prognostic factors

<table>
<thead>
<tr>
<th>Histologic type</th>
<th>Papillary</th>
<th>Follicular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 40 y</td>
<td>26 (132)</td>
<td>28 (83)</td>
</tr>
<tr>
<td>&gt; 40 y</td>
<td>9 (71)</td>
<td>11 (28)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>9 (63)</td>
<td>13 (35)</td>
</tr>
<tr>
<td>Females</td>
<td>17 (69)</td>
<td>15 (48)</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T0-2N0M0</td>
<td>5 (60)</td>
<td>3 (30)</td>
</tr>
<tr>
<td>T0-2N1-2M0</td>
<td>1 (34)</td>
<td>1 (8)</td>
</tr>
<tr>
<td>T3N3M1</td>
<td>20 (38)</td>
<td>24 (45)</td>
</tr>
<tr>
<td>Distant metastases</td>
<td>9 (17)</td>
<td>13 (29)</td>
</tr>
</tbody>
</table>

DISCUSSION

The patients under study were from a geographic area of endemic goitre where there is a relatively high proportion of follicular cancers which generally imply a worse prognosis, with patients in the older age group, with larger size of the primary tumour, and fewer lymph node metastases. (3,4) Papillary cancers of the thyroid, on the other hand, have been recognized for a more favourable prognosis and the greater incidence of lymph node involvement. However, these observations were not confirmed by our study in which there was no distinction between the two histologic types, and the disease had a short duration of symptoms at presentation and displayed an aggressive biological behaviour irrespective of the histology, comparable to reports from other endemic goitrous areas. (2)

Follicular cancers had a higher mortality than papillary
carcinomas \((P < 0.05)\), although mortality was high in both groups. Besides the histology of the tumour, extent of the disease and distant metastases at presentation were considered in the univariate analysis of factors affecting survival in our patients. These results are similar to other reports stating that survival rates with papillary and follicular carcinomas are similar among patients of comparable age and disease stage. \((18,19)\)

The age of the patient at the time of diagnosis is an important consideration as it influences outcome of the disease. \((6,8,13,14,15,17,18)\) Follicular cancers have generally been reported to occur in the older patients with a median age at diagnosis typically in the 6th decade of life \((6)\), while the mean age of patients with papillary cancers has been reported to be in the 5th decade \((5)\). Our patients in both groups presented a decade earlier than reported. However, except amongst papillary cancers, where the prognosis was significantly better in patients below 40 years, age did not affect survival in patients with follicular cancers.

Sex as a prognostic factor is being debated \((5,7,8,9,18)\) some authors claim the importance of sex as one of the major determinants of survival in differentiated thyroid cancers with males having a poorer prognosis. \((3,5,7)\) However, we could not confirm this finding since survival in our patients was not found to be different between the two sexes, a finding which is confirmed by other authors. \((5,10,18)\)

The extent of the disease also contributes to prognosis; advanced lesions all confer a worse prognosis. \((3,5,6,7,11,12,18)\)

A study of 157 differentiated thyroid cancers included in the multicentric EORTC trial, places tumour stage in first place as a prognostic factor. \((13)\) Our findings of the extent of the disease as a predictor of death is in agreement with these reports. However, as mentioned earlier, the presence of lymphadenopathy did not have an unfavourable effect on the prognosis of the disease in the current study as has also been noted by several other authors. \((3,5,9,18,20)\)

Finally, distant metastasis at presentation was also found to be an important prognostic variable. Distant metastasis at presentation in 21% of our patients occurred more frequently than reports in literature. \((14,15,18)\) Of the patients thus affected, 47% died confirming the findings of other authors. \((3,5,15,16)\)

Near total or total thyroidectomy is the surgical treatment of choice for thyroid carcinoma. \((1,18)\) The extent of surgery is a prognostic factor. The extent of surgery is a prognostic factor. \((3,5,9,18,20)\) Near total or total thyroidectomy is the surgical treatment of choice for thyroid carcinoma. \((1,18)\) The extent of surgery is a good indicator of the outcome. In the present study 32/99 \((32.3\%)\) papillary and 13/65 \((20\%)\) follicular cancer patients who underwent near total thyroidectomy developed loco-regional recurrence during the 3 year follow up period \((P > 0.05)\). Death due to local recurrence of the tumour occurred in 50% papillary and 69% follicular cancers; thus, 55% of differentiated thyroid cancers with loco-regional recurrence died of the disease.

Thus, in our study, the extent of the disease, especially the presence of distant metastases at presentation, was found to be the most important determinant of survival followed by histology of tumour and age which was prognostically significant only in cases of papillary cancers.

**REFERENCES**