

Papillary and follicular thyroid carcinoma: the treatment results of 357 patients at the National Kyushu Cancer Centre of Japan

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Abstract

During the period from April 1974 to March 1993, 357 patients received surgical treatment for papillary and follicular carcinoma of the thyroid gland at the Department of Head and Neck Surgery of National Kyushu Cancer Centre, Japan. In this paper, we review the various clinico-pathological features of these patients and analyse their influence on patient survival. While the majority of the patients' ages ranged from the third through seventh decade, only the patients older than 40 years old died. In papillary carcinomas, there was a statistically significant difference in the survival rate between younger (less than 45 years old) and older (45 years of age or older) patients. The rate of patients who died of thyroid cancer also increased in the cases with extra-thyroidal tumour invasion, and metastasis to distant organs. A multivariate analysis also showed that the age, extrathyroidal invasion and distant metastasis are significant prognostic factors. However, sex, histology and lymph node metastasis were not prognostic factors for survival.

Key words: Thyroid neoplasms; Carcinoma, papillary; Carcinoma, follicular; Prognosis

Introduction

Carcinoma of the thyroid gland is the most common endocrine malignancy managed by head and neck surgeons. The majority of thyroid tumours are well differentiated-type tumours such as papillary and follicular carcinoma and which account for approximately 80 per cent of all cases (Mazzaferrri and Young, 1981). In general, these well differentiated thyroid carcinomas are of low grade malignancy with a good prognosis and the factors that influence prognosis have been described as the age at the initial diagnosis, sex, extent of tumour, regional and distant metastasis, histology and treatment (Crile *et al.*, 1985).

Although controversy still remains regarding the treatment of thyroid cancer, the generally accepted initial therapy is a surgical removal of the primary lesion and the metastatic lymph nodes, followed by post-operative radioactive iodine treatment or suppressive doses of thyroid hormone (Ward, 1986; Harley *et al.*, 1988; McCaffrey *et al.*, 1994).

The purpose of this report is to review our experience of 357 thyroid cancer patients treated at the National Kyushu Cancer Centre from April 1974 through March 1993. In this retrospective study, we

also evaluated the influence of clinical and pathological findings on the prognosis of patients.

Patients and methods

Study subjects

From April 1974 to March 1993, 357 patients (276 females, 81 males) received primary treatment for thyroid carcinoma of the Department of Head and Neck Surgery, National Kyushu Cancer Centre Hospital, Fukuoka, Japan. The age of the patients ranged from eight to 84 (mean age 52.3) years old.

The patients underwent a surgical removal of the

TABLE I
AGE AND SEX DISTRIBUTION OF THYROID CANCER PATIENTS

Age group	Female	Male	Total
0-19	4	3	7
20-29	17	4	21
30-39	40	8	48
40-49	69	15	84
50-59	60	18	78
60-69	48	21	70
70-79	33	12	45
80-	3	0	4
Total	276	81	357

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TABLE II
PROGNOSIS OF PATIENTS ACCORDING TO SEX AND AGE

	Death from		Alive	Total
	thyroid ca.	other diseases		
(a) Sex		(%)		(%)
male	8	(9.9)	67	81 (100)
female	20	(7.2)	248	276 (100)
(b) Age				
<20	0		7	7
20-29	0		20	21
30-39	0		47	48
40-49	2	(2.4)	82	84 (100)
50-59	6	(7.7)	68	78 (100)
60-69	10	(14.5)	56	69 (100)
70-79	9	(20.0)	33	45 (100)
80≤	1	(20.0)	4	5 (100)
Total	28	(7.8)	315	357 (100)

thyroid tumour either with, or without, a dissection of the neck lymph nodes as described below. The surgical procedures were classified as a total thyroidectomy, subtotal thyroidectomy, lobectomy or less and others. 'Lobectomy or less' included a lobectomy and any surgical procedure less than an excision of an entire lobe (Beenken *et al.*, 1989). Basically, ipsilateral paratracheal lymph node dissection was routinely performed with a subtotal thyroidectomy. In cases with a total thyroidectomy, a paratracheal dissection was performed bilaterally. In patients who were diagnosed as positive for neck lymph nodes before surgery, either a radical or functional neck dissection was performed. The extent of the tumour was recorded whether or not an extrathyroidal tumour growth (in the trachea, nerves, vessels or lymphoid tissue) was determined histologically. All patients had been advised to take suppressive doses of thyroid hormone after the initial surgery. Post-operative iodine ¹³¹I therapy was not performed routinely, with only 15 patients being treated with iodine.

All histological specimens were diagnosed by the same pathologist. Age, sex, histological type, tumour extent as well as regional or distant metastasis were evaluated as risk factors in relation to prognosis retrospectively. The clinical follow-up ranged from one to 20 years. The survival data are based on cause-specific death, i.e. death from thyroid cancer.

Statistics

The survival curve was calculated by the Kaplan-Meier life table method and the survival rate between each group was compared using the generalised Wilcoxon test. To examine the influence on each variable on survival, simultaneously, the Cox regression analysis (Cox, 1972) was used. The difference was considered to be statistically significant when the *p* value was less than 0.5.

Results

The majority of patients were in ages ranging from the third through the seventh decades, but the peak age of patients was in the fourth decade for females and the sixth decade for males (Table I). The female to male ratio was 3.4:1. Histologically, 270 (75.6 per cent) patients had papillary carcinoma and 87 (24.4 per cent) had follicular carcinoma. Metastasis to the regional neck lymph nodes was observed in 168 patients (47.1 per cent), and 11 patients (3.1 per cent) had distant metastases (10 lung, one brain). Of 357 cases in our study population, 28 (7.8 per cent) died of thyroid cancer and 14 (3.9 per cent) died because of other causes (Table II).

A comparison of the number of patients who died of disease according to sex, age group and clinico-pathological findings are summarised in Tables II

TABLE III
PROGNOSIS OF PATIENTS ACCORDING TO TREATMENT AND NECK DISSECTION

	Death from		Alive	Total
	thyroid ca.	other dis.		
(a) Surgery		(%)		(%)
total thyroidectomy	6	(8.2)	64	73 (100)
subtotal thyroidectomy	4	(6.6)	55	61 (100)
lobectomy or less	16	(7.5)	190	213 (100)
others	4	(40.0)	6	10 (100)
(b) Neck dissection				
radical or functional				
neck dissection	16	(15.2)	85	105 (100)
paratracheal				
neck dissection	14	(7.4)	172	190 (100)
none	0	(0)	58	62 (100)
Total	30	(8.4)	315	357 (100)

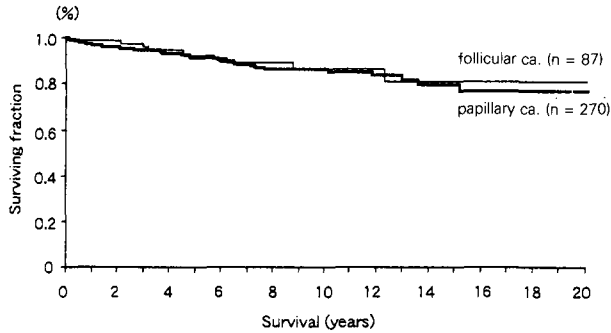


FIG. 1

Total survival curves of papillary (n = 270) and follicular (n = 87) carcinoma of the thyroid gland.

and III. While the majority of patients were from the third to seventh decade, only the patients in the age group older than the fourth decade died of thyroid cancer. Twenty (7.2 per cent) of 276 female patients and eight (9.9 per cent) of 81 male patients died. The average 10-year survival rates were 88.8 per cent for females and 78 per cent for males, and there was no statistically significant difference between them. Histologically, the average 10-year survival rate was 86.3 per cent for papillary carcinoma and 86.8 per cent for follicular carcinoma without any significant difference between them (Figure 1). Although no statistical difference was observed, there was a tendency that the survival rate of female patients was better in papillary carcinoma but worse in follicular carcinoma (Figure 2).

The ratio of patients who died of thyroid cancer increased in the older age group. When the patients

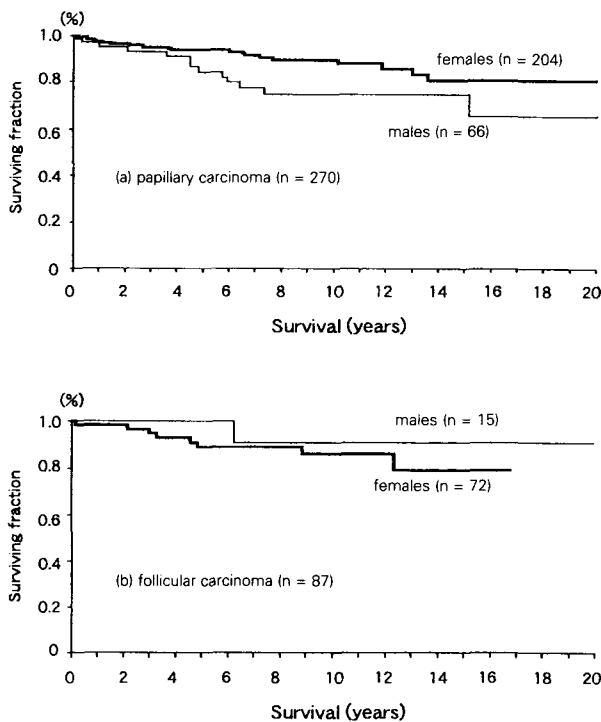


FIG. 2

Survival curves of female (n = 276) and male (n = 81) thyroid cancer patients according to histological type.

were divided into younger (less than 45 years old) and older (45 years or older) age groups, the younger age group showed a better survival curve. In papillary carcinomas, a statistically significant difference ($p = 0.0055$) in the survival curve between the older and younger age group was detected (Figure 3a).

Three hundred and forty-seven (97.2 per cent) patients received either a total-, subtotal thyroidectomy or lobectomy as summarised in Table III. The ratio of those dying from thyroid cancer was almost equal between each surgery group. Four of 10 patients, whose treatment was classified as 'others' in Table IIIa, died mainly because of inoperability due to tumour extension to either the skin or lung. In 105 patients who received a radical or functional neck dissection, 16 (15.2 per cent) died of their disease. In 190 patients who received a paratracheal lymph node dissection alone, 14 (7.4 per cent) died (Table IIIb).

There was also a tendency for the ratio of patients who died of thyroid cancer to increase in cases with extrathyroidal invasion and metastasis to either the lymph nodes or distant organs. Extrathyroidal tumour invasion was found in 145 cases (40.6 per cent). Metastasis to the regional lymph nodes was found in 168 cases (47.1 per cent). Distant metastasis was found in 11 patients, and five of 11 died (Table IV). The correlation of lymph node metastasis and tumour extent is analysed in Table V. There was a tendency that the neck lymph node positive cases increased in the cases with advanced tumour extension, but no statistical difference was seen between

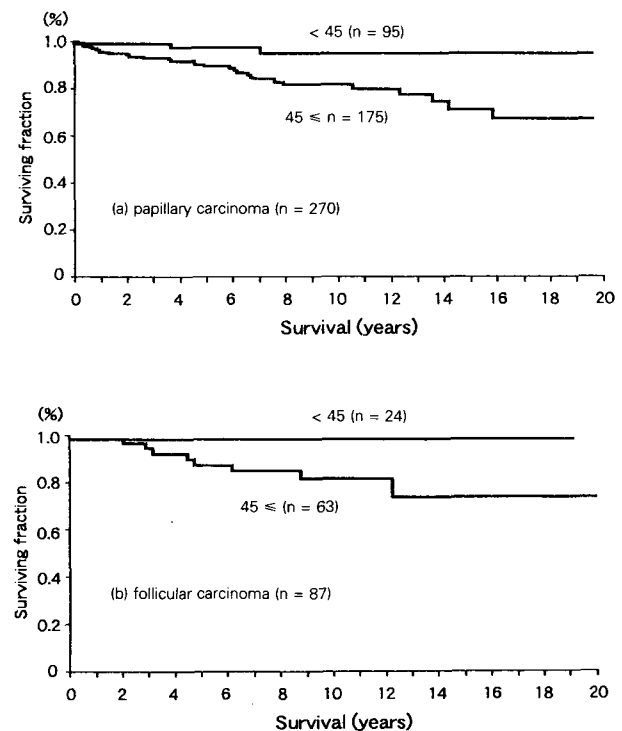


FIG. 3

Survival curves of thyroid cancer patients younger than 45 years (n = 119) and 45 years of age or older (n = 238) according to histological type.

TABLE IV
PROGNOSIS OF PATIENTS ACCORDING TO HISTOLOGY, TUMOUR EXTENT, LYMPH NODE AND DISTANT METASTASIS

	Death from		Alive	Total
	thyroid ca.	other dis.		
(a) Histology				
papillary c.	22 (8.1)	11	237	270 (100)
follicular c.	6 (6.9)	3	78	87 (100)
(b) Extrathyroidal invasion				
(-)	8 (3.8)	7	197	212 (100)
(+)	20 (14.0)	7	118	145 (100)
(c) Lymphnode metastasis				
(-)	10 (5.3)	6	173	189 (100)
(+)	18 (10.7)	8	142	168 (100)
(d) Distant metastasis				
(-)	23 (6.6)	13	310	346 (100)
(+)	5 (45.4)	1	5	11 (100)
Total	28 (7.8)	14	315	357 (100)

each group. During the post-operative follow-up, recurrence occurred in 60 patients. As summarised in Table VI, thyroid cancer recurrence was predominant in patients with either extrathyroidal invasion or lymph node metastasis.

The survival curves were also determined by categorizing the study population according to tumour extent or lymph node metastasis. In papillary carcinomas, the survival curve was worse ($p < 0.0001$) in cases showing extrathyroidal invasion as compared to cases with no invasion (Figure 4a). In contrast, there was no statistical difference in the survival curve between each case in follicular carcinomas (Figure 4b). The cases without lymph node metastasis showed a better survival curve as compared to cases with lymph node metastasis in papillary and follicular carcinomas, but there was no statistical difference.

To determine which of the covariates had the prognostic significance with regard to survival time, we also applied a multivariate analysis (Table VII). As a result, age group (45 years of age or older), extrathyroidal invasion and distant metastasis proved to be independent risk factors in all the thyroid cancer patients.

Discussion

There have been numerous reports concerning the diagnosis, treatment and prognosis of thyroid carcinoma. Age and sex are clinically important prognostic factors in thyroid cancer patients (Bohr *et al.*, 1979; Carcangiu *et al.*, 1985; Schroder *et al.*, 1985). Contrary to some reports, sex was not a significant prognostic factor, although there was a slight

TABLE V
COMPARATIVE ANALYSIS OF THE TUMOUR EXTENT AND LYMPH NODES METASTASIS

	Extrathyroidal invasion		Total
	(-)	(+)	
N (-)	129	60	212
N (+)	83	85	145
Total	189	168	357

tendency toward a poorer prognosis in men (Segal *et al.*, 1994). Cady *et al.* (1979) reported a highly significant difference in the rates of recurrence and death between men over 40 years old and women over 50 years old with follicular or mixed histological findings (higher risk group) when compared with the rest of the study population. Such prognostic significance of age was also unanimously supported in the other studies reviewed.

Bacourt *et al.* (1986) found that age of less than 40 at the initial presentation to be a prognostic factor significantly associated with longer survival. By studying 135 well-differentiated thyroid carcinoma patients, Beenken *et al.* (1989) also found that no patients died of cancer if they were younger than 40 years of age at the time of initial surgery. In our

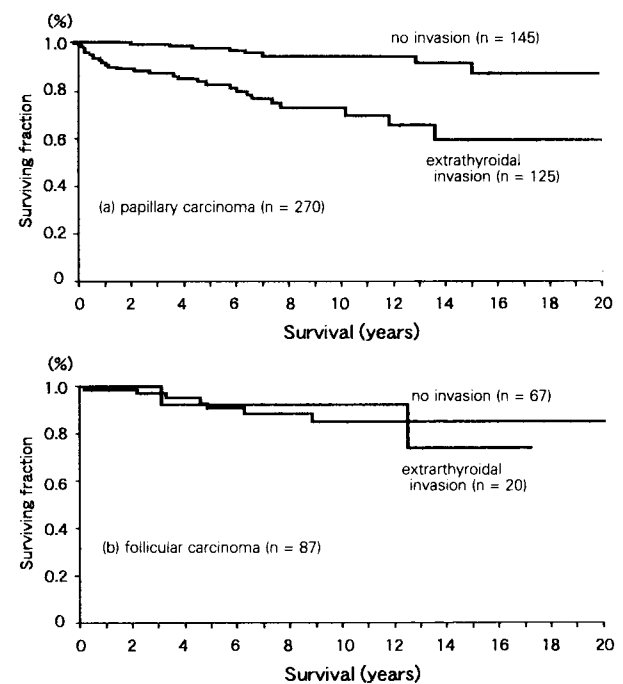


FIG. 4

Survival curves of thyroid cancer patients with ($n = 145$) or without ($n = 125$) extrathyroidal tumour invasion according to histological type.

TABLE VI
RECURRENCE ACCORDING TO TUMOUR EXTENT (A) AND LYMPH NODE METASTASIS (B)

(a) Extrathyroidal invasion			
	- %	+ %	Total %
Recurrence	24 (11.3)	36 (24.8)	60 (16.8)
Total	212 (100)	145 (100)	357 (100)
(b) Lymphnode metastasis			
	- %	+ %	Total %
Recurrence	20 (10.6)	40 (23.8)	60 (16.8)
Total	189 (100)	168 (100)	357 (100)

observation of 357 thyroid carcinomas, 76 patients (20 per cent) were younger than 40 years of age at the time of initial surgery, but none died of their disease. In this study, we compared the survival between the age group of those younger and older than 45 years by referring to the UICC TNM classification (Hermanek and Sobin, 1987) in which the age of 45 is adopted for stage grouping of the papillary and follicular thyroid carcinoma. Indeed, there was a statistically significant difference in the survival curve between the younger and older age group in papillary carcinomas (Figure 3a). In follicular carcinomas, a younger age group tended to show a better prognosis although there was no significant difference.

The prognostic significance of the regional lymph nodes, or distant organ metastasis in thyroid carcinoma remained controversial. Using a life table analysis, Samaan *et al.* (1983) also recognised that 61 per cent of those presenting with distant metastasis died of their disease. In contrast, Akslen (1993) reported that only the factors such as age, sex, tumour extent, but not lymph node nor distant metastasis, were significantly associated with survival. Beenken *et al.* (1989) also reported that lymph node involvement is not associated with death from thyroid carcinoma. He emphasised the importance of a direct spread of cancer to the extrathyroidal organs. By analysing 262 patients treated for invasive thyroid carcinoma to such areas as the trachea or laryngeal nerve, McCaffrey (1994) reported the overall 10 years survival to be 63 per cent. In our study, extrathyroidal invasion was found in 145 cases and the 10-year survival was 77.9 per cent. A statistical difference in the survival curve observed in papillary carcinomas (Figure 4a) also confirmed the prognostic significance of this factor.

The surgical procedures for thyroid lesions varied from less than a lobectomy to a total thyroidectomy.

A lobectomy was performed most often, particularly in the first decade. A total thyroidectomy was predominantly applied to patients with distant metastasis so as to optimise the effect of iodine ¹³¹I therapy. However, controversy still exists regarding the extent of surgery against thyroid carcinomas (Samaan *et al.*, 1983; Tubiana *et al.*, 1985; Bacourt *et al.*, 1986; Simpson *et al.*, 1987; Beenken *et al.*, 1989). Many surgeons insist that total thyroidectomy is the only reliable method for removing all tumour cells in thyroid carcinoma. Although the only argument against a total thyroidectomy was its high morbidity such as hypoparathyroidism or permanent recurrent nerve paralysis, many authors reported the morbidity to be less than three per cent (Bacourt *et al.*, 1986; Beenken *et al.*, 1989). Samaan *et al.* (1983) described that a total thyroidectomy resulted in a low recurrence rate and a longer disease-free survival. At present, total thyroidectomy plus ¹³¹I therapy seems to provide a low recurrence rate and better survival (Beenken *et al.*, 1989). In our experience, a total thyroidectomy was performed in only 73 (20.5 per cent) of 357 cases and the rate of death was almost equal in the cases of total, subtotal and lobectomy or less. We are therefore now beginning to perform a total thyroidectomy more frequently in thyroid carcinoma cases.

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TABLE VII
MULTIVARIATE COX REGRESSION ANALYSIS OF RISK FACTORS AMONG 357 THYROID CANCER PATIENTS

Variable	Regression coefficient	Standard error	p-value	Relative risk	95% CI
Age	-3.1083	1.0622	0.0000	0.0447	0.0056-0.3583
Extrathyroidal invasion	1.4725	0.4298	0.0002	4.3603	1.8778-10.124
Distant metastasis	2.2832	0.5033	0.0003	9.8080	3.6573-26.303

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