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Effect of Age on Presentation, Management, and Outcome of Patients with Differentiated Thyroid Carcinoma: Retrospective Study

SM Chow, CK Kwan, PCM Poon, SCK Law

Department of Clinical Oncology, Queen Elizabeth Hospital, Hong Kong

ABSTRACT

Objective: *To investigate the effect of age on presentation, management, and outcome of differentiated thyroid carcinoma.*

Patients and Methods: *Records of a cohort of 1369 patients who presented between 1960 and 2000 to the Department of Clinical Oncology at the Queen Elizabeth Hospital with papillary or follicular thyroid carcinoma were studied after stratification into the following age groups: younger than 30 years, 30 to 45 years, 46 to 60 years, and older than 60 years.*

Results: *At presentation, patients older than 60 years had advanced T and M stage disease: for follicular thyroid carcinoma, 32.9% had T3 disease, 17.1% had T4 disease, and 29.3% had distant metastasis; for papillary thyroid carcinoma, 60.6% had T4 disease and 21.3% had distant metastasis. The oldest patients had the worst prognosis: after a mean follow-up of 10 years, only 45.1% of patients older than 60 years who had follicular thyroid carcinoma and 57.6% of those with papillary thyroid carcinoma were alive without disease. Within this age group, distant metastasis occurred frequently among those with follicular thyroid carcinoma (42.7%). Differentiated thyroid carcinoma was the cause of death for 25.6% of the oldest patients with follicular thyroid carcinoma and 20.8% of those with papillary thyroid carcinoma. The 10-year cause-specific survival for patients with follicular thyroid carcinoma who were younger than 30 years, aged 30 to 45 years, 46 to 60 years, and older than 60 years was 97.6%, 92.7%, 81.5%, and 67.8%, respectively; the corresponding figures for papillary thyroid carcinoma were 100%, 98.8%, 90.6% and 75.4%.*

Conclusions: *The prognosis of differentiated thyroid carcinoma gets worse with advancing age. Total thyroidectomy with consideration for radioactive iodine (I 131) ablation or external beam radiation therapy should be the protocol of treatment for patients of all age groups.*

Key Words: *Age factors; Neoplasm metastasis; Neoplasm staging; Survival analysis; Thyroid neoplasms; Treatment outcome*

INTRODUCTION

Differentiated thyroid carcinoma (DTC) is a rare form of cancer. However, despite its low incidence worldwide (age-standardised rate, 3.0 per 100,000 females and 1.2 per 100,000 males),[1] DTC is the most common endocrine malignancy in Hong Kong,[2] and the second most common malignancy in Hong Kong females aged between 15 and 34 (15.7%).[3] The disease is characterised by a strong dependency of prognosis on age, a female predominance, slow growth, and late recurrence. In addition, thyroid-stimulating hormone (either endogenous or recombinant form) will stimulate its growth.

Younger patients consistently have a better prognosis than do older patients.[4-17] This difference is recognised in risk-group classifications and staging systems.[5,17-20] In fact, no other malignant disease incorporates age as a major staging factor. Data from Hong Kong reveal that the mean age at diagnosis is 49 years for follicular thyroid carcinoma (FTC)[16] and 45.1 years for papillary thyroid carcinoma (PTC).[21] In a study of 215 Hong Kong

Correspondence: *Dr. SM Chow, Department of Clinical Oncology, Block R, Queen Elizabeth Hospital, 30 Gascoigne Road, Kowloon, Hong Kong.*
Tel: (852) 2958 5507; Fax: (852) 2359 4782;
E-mail: chowsm@ha.org.hk

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patients with FTC, the relative risk of distant metastasis among patients who were older than 45 years was 3 times that of patients younger than 45 years.[16] Furthermore, the relative risk of dying from PTC among patients older than 45 years was 5.4 times that of others.[4] An age of more than 60 years is associated with the highest mortality and recurrence.[9,22] For example, reports of patients older than 70 years have shown that the 10-year survival rate is only 48% to 50%.[23,24] The exact way in which age affects prognosis and outcome is not well defined.

In this study, we attempted to assess the magnitude of the influence of age on survival, locoregional control, and distant metastasis in Hong Kong patients. Previous studies have found that FTC differs from PTC in both clinical presentation and outcome aspects.[25] Thus, this retrospective review analysed FTC and PTC separately.

PATIENTS AND METHODS

We reviewed records of 1369 patients who received a diagnosis of DTC between 1960 and 2000 at the Department of Clinical Oncology at the Queen Elizabeth Hospital — a tertiary referral centre in Hong Kong. The histological classification system of the World Health Organization was employed. The 2 major types of DTC were PTC (1106; 80.8%) and FTC (263; 19.2%). Patients with special variants of PTC included 8 with a diffuse sclerosing variant (reported previously[26]) and 13 with a tall-cell variant. A total of 222 (16.5%) patients were lost to follow-up after a mean of 7 years. The female-to-male ratio was 4:1. Most patients were Chinese (98%). The mean follow-up duration was 10.0 years (standard deviation, 7.2 years).

We analysed the clinical and pathological features of DTC in relation to the age at presentation — specifically, the age at diagnosis. The primary management of DTC was surgery followed by an evaluation for radioactive iodine (RAI) treatment or external radiotherapy, as previously described.[4,16,21] Overall, 82.5% patients received RAI treatment, whereas 17.5% received external radiotherapy. Distant metastasis developed in 182 (13.3%) patients.

The clinical features and treatment modalities were analysed with the chi-square test, Fisher's exact test, analysis of variance, or the Kruskal-Wallis test. Values for cause-specific survival, locoregional failure-free survival, and distant metastasis failure-free survival were generated by the Kaplan-Meier method. The Statistics Package for the Social Sciences version 10.0 was used for data analysis (SPSS Inc, Chicago, IL, United States). Differences in results that had p values of less than 0.05 were considered statistically significant.

RESULTS

The clinical characteristics (Table 1) and outcomes (Table 2) of PTC and FTC were stratified into the following age groups: younger than 30 years, 30 to 45 years, 46 to 60 years, and older than 60 years. The incidence of FTC among the oldest age group was about twice that among the youngest age group (31.2% vs 16.0%), whereas the proportions of patients in these age groups who had PTC were similar (21.3% vs 19.4%). The 10-year overall cause-specific survival was 83.2% for FTC and 92.4% for PTC.

For both FTC and PTC groups, the tumour size and the incidence of extrathyroidal extension generally increased as age increased. The rate of distant metastasis also generally increased with age: among patients with FTC, the rate of distant metastasis ranged from 4.8% for those younger than 30 years to 29.3% for those older than 60 years, whereas among patients with PTC, the corresponding rates ranged from 2.3% to 7.6%. For patients with FTC, distant metastasis at diagnosis was 6 times as common in the oldest group than in the youngest group (29.3% vs 4.8%; Table 1), and distant metastasis during the whole clinical course about 4 times as common in the oldest group (42.7% vs 9.5%; Table 2). For FTC overall, distant metastasis occurred in 42.7% of the patients older than 60 years, with the rate of bone metastasis being 1.5 times that of lung metastasis (31.7% vs 20.5%).

At presentation, patients older than 60 years had tumours that were at a more advanced T and M stage than those of patients in the other age groups; those with PTC had tumours at a more advanced N stage. Among the oldest patients with FTC, 32.9% had T3 disease, 17.1% had T4 disease, and 29.3% had M1 disease (distant metastasis). For patients with PTC, corresponding proportions were 3.0%, 60.6%, and 21.3% (Table 1).

Among patients with PTC, those older than 60 years had the lowest female-to-male ratio and largest lymph node with metastasis. Profiles of older patients with PTC also significantly differed from those of younger patients regarding the rates of lymph node metastasis, lymph node surgery, and radiation therapy.

Table 1. Comparison of clinical characteristics of patients with follicular thyroid carcinoma (FTC) and papillary thyroid carcinoma (PTC), according to age group.

	FTC, n = 263				p Value	PTC, n = 1106				p Value
	Age (y)					Age (y)				
	<30	30-45	46-60	>60		<30	30-45	46-60	>60	
No. of patients (%)	42 (16.0)	66 (25.1)	73 (27.8)	82 (31.2)		215 (19.4)	361 (32.6)	294 (26.6)	236 (21.3)	
Sex ratio (F:M)	4.25:1	3.1:1	2.5:1	2.7:1	0.7	5.9:1	5.9:1	3.5:1	2.9:1	0.001
Mean tumour size (SD) [cm]	2.7 (1.3)	3.2 (1.9)	3.6 (2.4)	5.2 (2.9)	<0.001	2.5 (1.6)	2.1 (1.4)	2.3 (2.0)	2.9 (2.2)	<0.001
Mean size of lymph node metastasis (cm)	3.8	4.8	2	5.1	0.3	1.7	2.2	2.2	2.9	<0.001
Multifocal disease, No./Total (%)	11/33 (33.0)	10/57 (17.5)	10/58 (17.2)	16/63 (25.4)	0.2	56/193 (29.0)	95/336 (28.3)	118/274 (43.1)	59/203 (29.1)	<0.001
Extrathyroidal extension, No./Total (%)	3/37 (8.1)	4/63 (6.3)	14/68 (20.6)	16/61 (18.7)	0.05	62/203 (30.5)	122/348 (32.9)	130/281 (46.3)	143/225 (63.6)	<0.001
Lymph node metastasis, No./Total (%)	6/41 (14.6)	2/66 (3.0)	7/71 (9.9)	10/80 (12.5)	0.2	89/207 (43.0)	112/355 (31.5)	82/291 (28.2)	75/236 (31.8)	0.005
Distant metastasis, No. (%)	2 (4.8)	3 (4.5)	9 (12.3)	24 (29.3)	<0.001	5 (2.3)	8 (2.2)	15 (5.1)	18 (7.6)	0.005
Lung	1 (2.4)	2 (3.0)	1 (1.4)	9 (11.0)	0.024	4 (1.9)	7 (1.9)	13 (4.4)	16 (6.8)	0.007
Bone	0	1 (1.5)	8 (11.0)	17 (20.7)	<0.001	0	1 (0.3)	2 (0.7)	4 (1.7)	0.1
Brain	1 (2.4)	0	0	0	0.15	0	0	1 (0.3)	2 (0.8)	0.2
Thyroidectomy, No. (%)					0.021					<0.001
Total/subtotal	38 (90.5)	56 (84.8)	61 (83.6)	63 (76.8)		198 (92.1)	336 (93.1)	275 (93.5)	186 (78.8)	
Hemithyroidectomy	3 (7.1)	9 (13.6)	11 (15.1)	8 (9.8)		15 (7.0)	22 (6.1)	15 (5.1)	27 (11.4)	
Biopsy/no surgery	1 (2.4)	1 (1.5)	1 (1.4)	11 (13.4)		2 (0.9)	3 (0.8)	4 (1.4)	23 (9.7)	
Lymph node sugery, No. (%)					0.38					0.001
No excision	38 (90.5)	63 (95.5)	64 (87.7)	76 (92.7)		4 (1.9)	2 (0.6)	3 (1.0)	0	
Excision	1 (2.4)	2 (3.0)	3 (4.1)	3 (3.7)		71 (33)	79 (21.9)	49 (16.7)	52 (22.0)	
Neck dissection	3 (7.1)	0	3 (4.1)	3 (3.7)		21 (9.8)	42 (11.6)	30 (10.2)	20 (8.5)	
No record	0	1 (1.5)	3 (4.1)	0		4 (1.9)	2 (0.6)	3 (1.0)	0	
Postoperative residual tumour in neck, No. (%)					0.044					<0.001
None	34 (81.0)	52 (78.8)	54 (74.0)	51 (62.2)		162 (75.2)	293 (81.2)	210 (71.4)	116 (49.2)	
Gross	1 (2.4)	3 (4.5)	7 (9.6)	18 (22.0)		16 (7.4)	28 (7.8)	52 (17.7)	95 (40.3)	
Microscopic	1 (2.4)	1 (1.5)	2 (2.7)	3 (3.7)		16 (7.4)	21 (5.8)	17 (5.8)	15 (6.4)	
Undertermined	6 (14.3)	10 (15.2)	10 (13.7)	10 (12.2)		21 (9.8)	19 (5.3)	15 (5.1)	10 (4.2)	
Radiation therapy as primary treatment, No. (%)					0.37					<0.001
RAI	31 (73.8)	54 (81.8)	62 (84.9)	57 (69.5)		135 (62.8)	244 (67.6)	201 (68.4)	113 (47.9)	
EXT	0	0	0	1 (1.2)		2 (0.9)	4 (1.1)	6 (2.0)	15 (6.4)	
RAI + EXT	3 (7.1)	2 (3.0)	1 (1.4)	3 (3.7)		11 (5.1)	31 (8.6)	35 (11.9)	54 (22.9)	
None	8 (19.0)	10 (15.2)	10 (13.7)	21 (25.6)		67 (31.2)	82 (22.7)	52 (17.7)	54 (22.9)	
RAI, No. (%)	34 (81.0)	56 (84.8)	63 (86.3)	60 (73.2)	0.16	146 (67.9)	275 (76.2)	236 (80.3)	167 (70.8)	0.006
EXT, No. (%)	3 (7.1)	2 (3.0)	1 (1.4)	4 (4.9)	0.42	13 (6.0)	35 (9.7)	41 (13.9)	69 (29.2)	<0.001
Stage, AJCC 5th edition, No. (%)					<0.001					<0.001
I	40 (95.2)	63 (95.5)	5 (6.8)	0		210 (97.7)	353 (97.8)	49 (16.7)	25 (10.6)	
II	2 (4.8)	3 (4.5)	35 (47.9)	38 (46.3)		5 (2.3)	8 (2.2)	51 (17.3)	39 (16.5)	
III	0	0	12 (16.4)	11 (13.4)		0	0	160 (54.4)	150 (63.6)	
IV	0	0	9 (12.3)	24 (29.3)		0	0	15 (5.1)	18 (7.6)	
U	0	0	12 (16.4)	9 (11.0)		0	0	19 (6.5)	4 (1.7)	
T stage, AJCC 5th edition, No. (%)					<0.001					<0.001
0	0	2 (2.0)	2 (0.4)	0		1 (0.5)	0	1 (0.3)	3 (1.3)	
1	1 (2.4)	1 (1.5)	4 (5.5)	2 (2.4)		18 (8.4)	76 (21.1)	58 (19.7)	27 (11.4)	
2	24 (57.1)	37 (56.1)	28 (38.4)	22 (26.8)		99 (46.0)	125 (34.6)	73 (24.8)	49 (20.8)	
3	3 (7.1)	11 (16.7)	11 (15.1)	27 (32.9)		13 (6.0)	13 (3.6)	11 (3.7)	7 (3.0)	
4	3 (7.1)	4 (6.1)	14 (19.2)	14 (17.1)		62 (28.8)	122 (33.8)	130 (44.2)	143 (60.6)	
X	11 (26.2)	11 (16.7)	14 (19.2)	17 (20.7)		22 (10.2)	25 (6.9)	21 (7.1)	7 (3.0)	
N stage, No. (%)					0.3					0.001
1	6 (14.3)	2 (3.0)	7 (9.6)	10 (12.2)		89 (43.0)	112 (31.5)	82 (28.2)	75 (31.8)	
M stage, No. (%)					<0.001					0.005
1	2 (4.8)	3 (4.5)	9 (12.3)	24 (29.3)		5 (2.3)	8 (2.2)	15 (5.1)	18 (21.3)	

Abbreviations: RAI = Radioactive iodine; EXT = external radiation therapy; AJCC = American Joint Committee on Cancer.

Table 2. Treatment outcome of patients with follicular thyroid carcinoma (FTC) and papillary thyroid carcinoma (PTC), according to age at diagnosis.

	FTC, n = 263				p Value	PTC, n = 1106				p Value
	Age (y)					Age (y)				
	<30	30-45	46-60	>60		<30	30-45	46-60	>60	
No. of patients (%)	42 (16.0)	66 (25.1)	73 (27.8)	82 (31.2)		215 (19.4)	361 (32.6)	294 (26.6)	236 (21.3)	
Status at last follow-up, No. (%)					<0.001					<0.001
Alive without disease	38 (90.5)	54 (81.8)	47 (64.4)	37 (45.1)		202 (94.0)	336 (93.1)	249 (84.7)	136 (57.6)	
Alive with locoregional disease	0	0	0	1 (1.2)		3 (1.4)	4 (1.1)	6 (2.0)	11 (4.7)	
Alive with distant metastasis	0	7 (10.6)	3 (4.1)	8 (9.8)		6 (2.8)	2 (0.6)	2 (0.7)	8 (3.4)	
Alive with locoregional disease and distant metastasis	0	1 (1.5)	2 (2.7)	2 (2.4)		1 (0.5)	1 (0.3)	1 (0.3)	1 (0.3)	
Died of thyroid carcinoma	2 (4.8)	4 (6.1)	17 (23.3)	21 (25.6)	<0.001	2 (0.9)	10 (2.8)	26 (8.8)	49 (20.8)	<0.001
Died of thyroid carcinoma with locoregional disease	1 (2.4)	0	2 (2.7)	4 (4.9)		0	2 (0.6)	9 (3.1)	28 (11.9)	
Died of thyroid carcinoma with distant metastasis	0	3 (4.5)	15 (20.5)	10 (12.2)		2 (0.9)	7 (1.9)	9 (3.1)	17 (7.2)	
Died of thyroid carcinoma with locoregional disease and distant metastasis	1 (2.4)	1 (1.5)	0	7 (8.5)		0	1 (0.3)	8 (2.7)	4 (1.7)	
Died of unrelated cause	2 (4.8)	0	4 (5.5)	13 (15.9)		1 (0.5)	8 (2.2)	10 (3.4)	31 (13.1)	
10-year cause-specific survival (%)	97.6	92.7	81.5	67.8	<0.001	100	98.8	90.6	75.4	<0.001
10-year locoregional failure-free survival (%)	91.9	90.0	91.4	71.7	0.004	85.0	88.0	80.7	63.2	<0.001
10-year distant metastasis failure-free survival (%)	95.2	83.4	75.6	53.4	<0.001	95.8	94.6	88.8	81.8	<0.001
Locoregional failure, No. (%)										
Uncontrolled locoregional disease after primary therapy	1 (2.4)	1 (1.5)	2 (2.7)	13 (15.9)	0.001	1 (0.5)	3 (0.8)	9 (3.1)	45 (19.1)	<0.001
Locoregional relapse after primary therapy	3 (7.1)	5 (7.6)	9 (12.3)	9 (11.0)	0.72	37 (17.2)	36 (10.0)	43 (14.6)	32 (13.6)	0.08
Distant metastasis as relapse, No. (%)	2 (4.8)	11 (16.7)	15 (20.5)	14 (17.1)	0.16	11 (5.1)	15 (4.2)	17 (5.8)	20 (8.5)	0.16
Lung	2 (4.8)	6 (9.1)	9 (12.3)	8 (9.8)	0.6	10 (4.7)	12 (3.3)	12 (4.1)	14 (5.9)	0.49
Bone	1 (2.4)	7 (10.6)	7 (9.6)	9 (11.0)	0.42	0	3 (0.8)	3 (1.0)	7 (3.0)	0.02
Liver	0	1 (1.5)	1 (1.4)	0	0.6	1 (0.5)	3 (0.8)	1 (0.3)	1 (0.4)	0.83
Mediastinum	0	1 (1.5)	0	0	0.39	1 (0.5)	1 (0.3)	2 (0.7)	0	0.61
Brain	0	0	0	0	0.53	1 (0.5)	2 (0.6)	1 (0.3)	1 (0.4)	0.98
Overall distant metastasis, No. (%)	4 (9.5)	13 (19.7)	22 (30.1)	35 (42.7)	<0.001	16 (7.4)	21 (5.8)	32 (10.9)	39 (16.5)	<0.001
Lung	3 (7.1)	8 (12.1)	10 (13.7)	17 (20.7)	0.19	14 (6.5)	19 (5.3)	25 (8.5)	30 (12.7)	0.009
Bone	1 (2.4)	8 (12.1)	15 (20.5)	26 (31.7)	<0.001	0	4 (1.1)	6 (2.0)	11 (4.7)	0.002
Liver	0	1 (1.5)	1 (1.4)	2 (2.4)	0.88	1 (0.5)	3 (0.8)	2 (0.7)	1 (0.4)	0.91

For both FTC and PTC groups, the proportion of patients who underwent thyroidectomy decreased with age (Table 1). Among the oldest patients, 13.4% of those with FTC and 9.7% of those with PTC underwent biopsy only or no surgery at all. This finding reflected the fact that elderly patients generally had more locally or regionally advanced disease, more prevalent medical illness, or higher surgical risks. All these factors rendered their tumours inoperable. Moreover, the oldest patients were also less willing to undergo radical surgery. Compared with other patients, those older than 60 years more commonly had stage III or IV disease, gross locoregional residual disease after primary surgery, and poor locoregional control (Table 1). Stage III or IV disease constituted 42.7% of cases of FTC and 71.2% of cases of PTC in this age group. Furthermore,

none of the oldest patients with FTC had stage I disease, but roughly one third (29.3%) had stage IV disease. After primary surgery, 22.0% of patients older than 60 years with FTC and 40.3% of those with PTC showed gross locoregional residual disease (Table 1). Distant metastasis was the major cause of death (17/82; 20.7%) among the oldest patients with FTC. Thyroid carcinoma was the cause of death for 25.6% of over-60-year-olds with FTC and 20.8% of those with PTC (Table 2).

At the last follow-up visit, only 45.1% of the oldest patients with FTC were alive without disease, which was about half of the proportion of under-30-year-olds who were alive without disease (90.5%). The 10-year cause-specific survival of the 4 FTC age groups in order of advancing age was 97.6%, 92.7%, 81.5%, and 67.8% (Table 2 and Figure 1). In addition, only 57.6% of the oldest patients with PTC were alive without disease, which was about two thirds of the proportion of under-30-year-olds who were alive without disease (94.0%). The 10-year cause-specific survival of the 4 PTC age groups in order of advancing age was 100%, 98.3%, 90.6%, and 75.4% (Table 2 and Figure 2).

Interestingly, patients younger than 30 years who had PTC had a greater rate of nodal metastasis (43.0%) than others, as well as slightly higher locoregional relapses after primary treatment (17.2%). Compared with patients with PTC who were aged 30 to 45 years, those younger than 30 years had a slightly lower locoregional failure-free survival (85% vs 88%; Table 2 and Figure 3). Hence, despite the higher rate of locoregional recurrence among under-30-year-olds, the chance of survival and final locoregional control was not jeopardised.

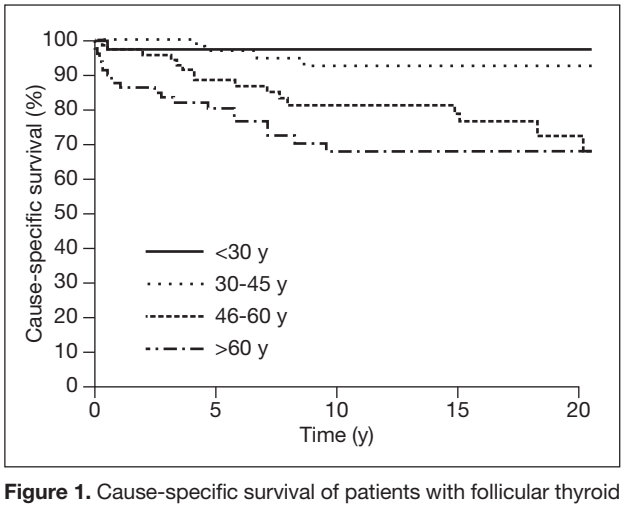

Figure 1. Cause-specific survival of patients with follicular thyroid carcinoma according to age group.

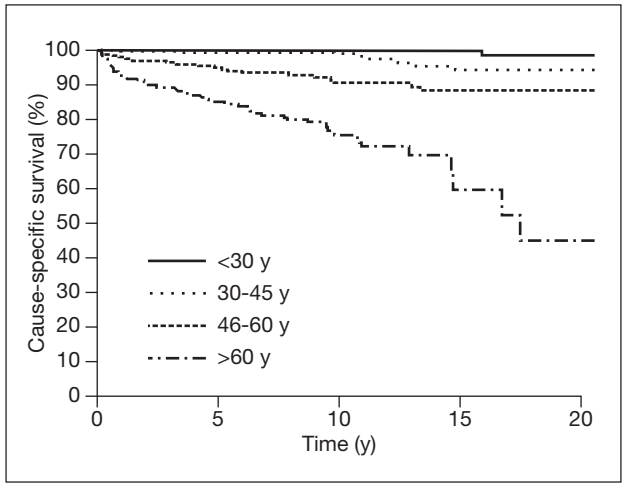

Figure 2. Cause-specific survival of patients with papillary thyroid carcinoma according to age group.

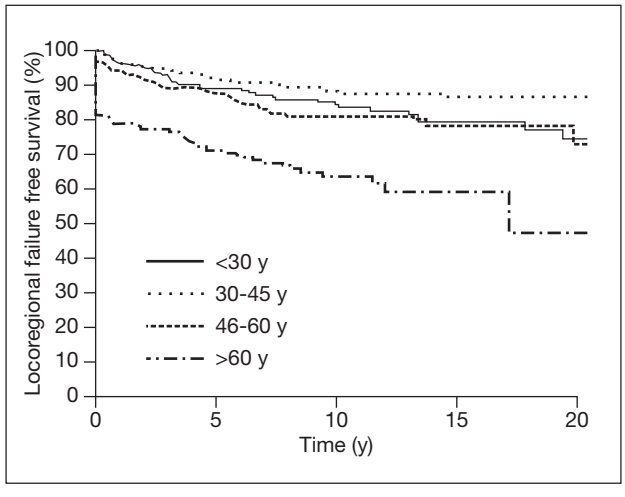

Figure 3. Locoregional failure-free survival of patients with papillary thyroid carcinoma according to age group.

DISCUSSION

The prognosis of DTC strongly depends on age. Multivariate analyses have previously shown that age beyond 45 years is a poor prognostic factor.[16,21] For PTC, patients older than 45 years had poorer cause-specific survival, locoregional failure-free survival, and distant metastasis failure-free survival.[21] For FTC, being older than 45 years was an independent prognostic factor for distant metastasis.[16] Owing to the intrinsic differences in FTC and PTC, distant metastasis occurs significantly more commonly in older patients with FTC. Poorer prognosis is found among patients with FTC because of the lethality of distant metastasis. Patients with PTC who are younger than 30 years have more advanced locoregional disease, a higher rate of lymph node metastasis, and a higher rate of locoregional relapse. Nevertheless, treatment after locoregional relapses is very successful and yields very high survival rates.[27]

In a review of elderly patients with DTC,[28] the 10-year survival for patients older than 60 years was 20% to 30% for PTC and 25% to 30% for FTC, as calculated from data derived from survival curves.[29] In the series in our study, the 10-year cause-specific survival was 67.8% for FTC and 75.4% for PTC. Some authors have suggested that the poor prognosis among elderly patients might be related to their increased prevalence of pathological risk factors,[23] decreased rate of uptake of RAI,[24,30] and probably reduced cancer-cell doubling time.[24] All these factors should indicate that elderly patients with DTC should not be treated with less aggressive approach. Total thyroidectomy, supplemented by RAI ablation and external radiotherapy when indicated, should be the standard approach. Close surveillance by taking serum thyroglobulin measurements, followed by the use of imaging modalities when necessary (e.g., computed tomography of the neck and thorax, and ultrasonography of the neck), is the best approach for the early detection of relapse.

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