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ORIGINAL

Radioactive iodine (RAI) therapy for distantly metastatic differentiated thyroid cancer (DTC) in juvenile *versus* adult patients

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Abstract. In general, juvenile differentiated thyroid carcinoma (DTC) demonstrate indolent characteristics and favorable prognosis are observed in comparison with many other carcinomas. However, recurrence is frequent, necessitating additional treatment, including radioactive iodine (RAI) therapy. In this report, the probability of recurrence, prognostic factors, treatment, and outcomes in both juvenile- and adult-onset DTC were analyzed and compared. At our institution, a total of 1552 DTC patients underwent thyroidectomy and/or lymph node dissection. The patients included 23 in their teens, 118 in their twenties, and 1412 in their thirties or older. The risk factors for distant metastases for DTC were male gender, follicular carcinoma, size of the PTC primary tumor, cervical lymph node metastases from PTC, and the presence of more than two distant metastatic foci. Patients with the highest risk underwent RAI ablation in line with institutional guidelines. Although the overall outcome in our juvenile patients was excellent, during follow-up, 4 (17.4%) of the 23 patients developed recurrent disease: 91.3% achieved complete remission, 4.35% partial remission, and 4.35% stable disease, with no disease-related deaths. Among the 118 patients in their twenties to thirties, 1 (0.8%) experienced progressive disease and disease-related death. A younger age at diagnosis and less radical primary surgery without subsequent RAI ablation are factors strongly predictive of distant metastases in patients with juvenile-onset DTC. To reduce the rate of relapse and improve surveillance for recurrent disease, total thyroidectomy followed by RAI appears to be the most beneficial initial treatment for patients with high- and intermediate-risk juvenile DTC.

Key words: Differentiated thyroid cancer, Total thyroidectomy, Radioactive iodine (RAI) therapy, Juvenile patients

JUVENILE-ONSET differentiated thyroid carcinoma (DTC) (specifically, papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC)) is a rare malignancy, accounting for 0.5-3.0% of all childhood carcinomas [1, 2]. It is well known that DTC has a generally indolent character and shows a favorable prognosis in comparison with many other carcinomas. The therapeutic strategy for patients with DTC in Japan has differed from that in Western countries. Total thyroidectomy followed by radioactive iodine (RAI) ablation has been standard in Western countries, whereas limited hemi-thyroidectomy and subtotal thyroidectomy have become widely accepted in Japan. PTC accounts for over 90% of all thyroid cancers in Japan, and its incidence is higher than in Western countries, possibly because of the sufficient dietary intake of iodine in Japan [3, 4]. In terms of histological type, based on investigations by our institution since 1993, the incidence of papillary carcinoma has been 92.0%, that of follicular carcinoma 5.9%, that of medullary carcinoma 1.0%, and that of anaplastic carcinoma 1.2%. DTC in childhood shows aggressive clinical onset; 60-80% of patients have cervical nodal involvement, often associated with distant metastasis but without overall higher mortality compared with that in adults [1, 5-8]. However, the risk of cancer relapse is high, with more frequent local recurrence than in adults. Recurrence in cervical lymph nodes requires surgical intervention, with a potential risk of post-surgical complications [9-11]. Despite the high recurrence rate, the overall outcome and prognosis of juvenile-onset DTC are

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favorable. In the present study, we analyzed and compared the probability of recurrence, prognostic factors, treatment (specific RAI), and outcomes in both juvenile- and adult-onset DTC.

Materials and Methods

Patients

From January 1993 through August 2013, a total of 1552 patients with DTC (1447 PTCs and 105 FTCs) underwent thyroidectomy or/and lymph node dissection at Kanaji Thyroid Hospital. Distant metastases appeared in 115 cases (95 PTCs and 20 FTCs). Among these previous DTC patients, we retrospectively reviewed the medical records of 23 juvenile patients (20 girls and 3 boys; mean age, 16.3 y; range, 9-19 y) who had not received prior RAI therapy. Staging for all patients was done in accordance with the International Union Against Cancer TNM classification system [12]. Our study was approved by the institutional ethics committee, and the requirement to obtain informed consent was waived. At the time of surgery, the DTC patients ranged in age from teens to thirties or above (Fig. 1).

Treatment

Surgical treatment for PTC

Total thyroidectomy prevents recurrence in the remnant thyroid but does not reduce the incidence of recurrence in lymph nodes, or distant metastasis. However, we recommend and perform total thyroidectomy for high-risk patients [3, 4] who have a maximal tumor diameter of >5 cm (pathologically >2 cm), extrathyroid extension to the mucosa of the trachea or esophagus, a large number of clinically evident lymph node metastases, a lymph node metastasis diameter of >3 cm, or distant metastasis. Low-risk patients are those with a maximal tumor diameter of <2 cm and absence of clinical lymph node metastasis (T1N0M0 by the TNM classification), and hemi-thyroidectomy is acceptable for such patients. Other patients are classified as lying within a "gray zone" with regard to the extent of thyroidectomy, but the majority of institutions encourage total thyroidectomy for patients with tumors larger than 2 cm (pathologically) or clinical lymph node metastasis (N1) (Fig. 2).

Surgical treatment for FTC

Most follicular carcinomas are diagnosed by postoperative pathological examination. As initial surgery, most patients undergo lobectomy or hemi-thyroidectomy under a diagnosis of follicular tumor or neoplasm. Widely invasive carcinoma has a significantly worse prognosis than minimally invasive carcinoma, and the degree of vascular invasion in particular is of prognostic significance. We have recommended and performed completion total thyroidectomy for patients with widely invasive carcinoma who have initially undergone lobectomy or hemi-thyroidectomy. Completion total thyroidectomy with a search for, or treatment of, distant metastasis using RAI has been recommended for patients with widely invasive fol-

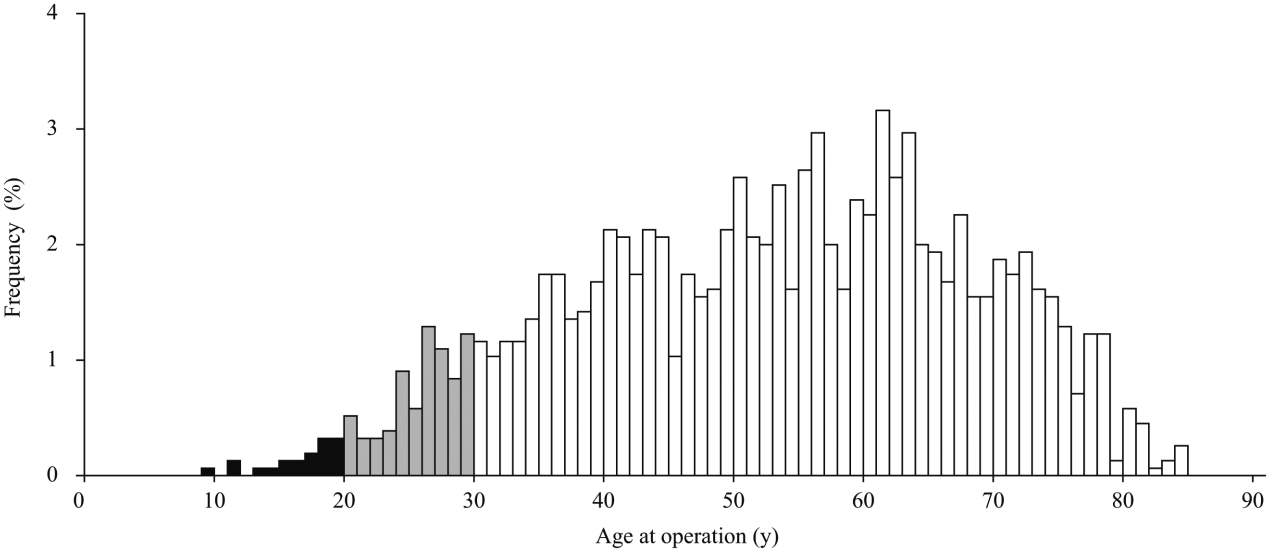

Fig. 1 Age distribution of patients with differentiated thyroid cancer at the time of surgery. Black bars indicate patients in their teens, gray bars those in their twenties, and white bars those in their thirties or older.

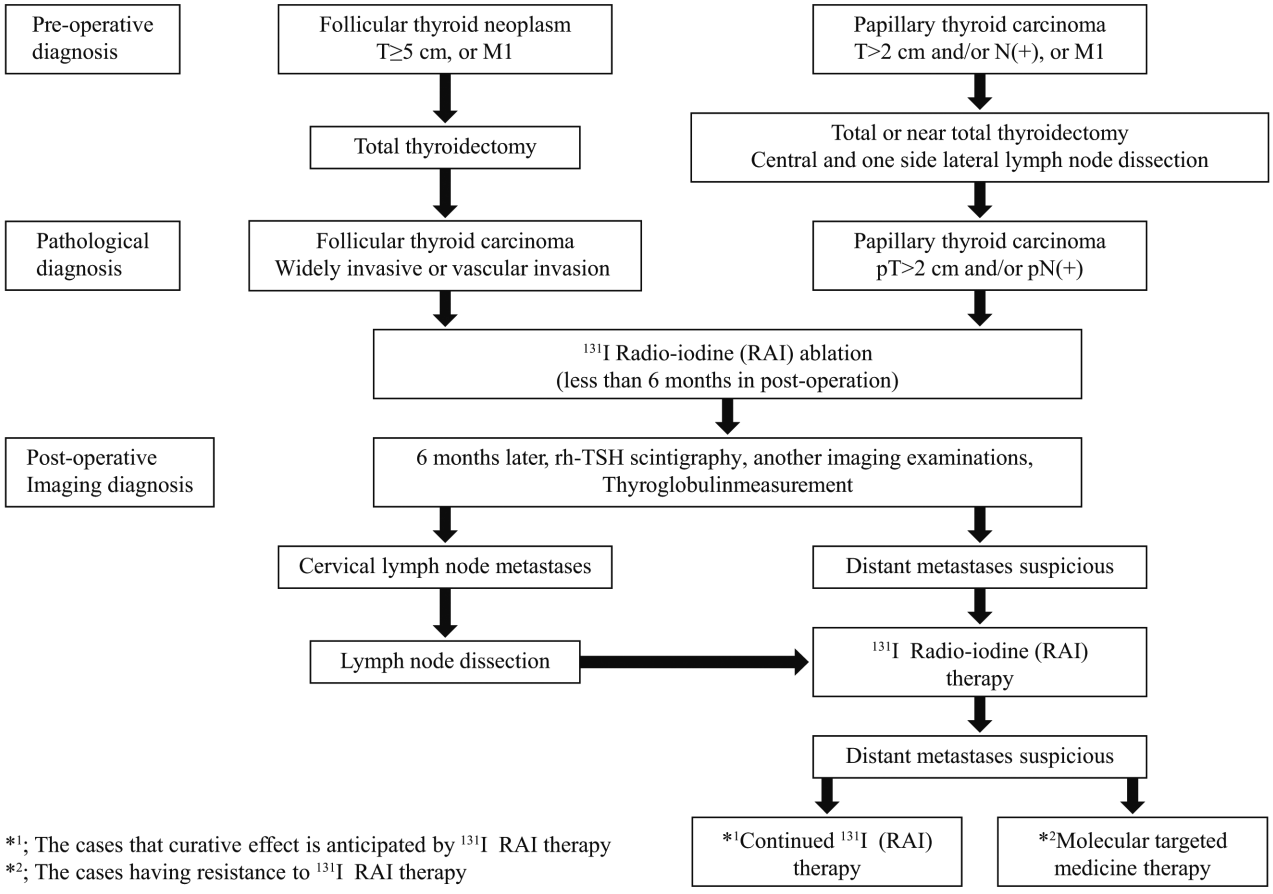

Fig. 2 The standard therapeutic guidelines for high-risk differentiated thyroid carcinoma at Kanaji Hospital.

licular carcinoma, and those with poorly differentiated compartments such as an insular component (Fig. 2).

Ablation with RAI

RAI at Kanaji Thyroid Hospital has been performed for high-risk patients with DTC in accordance with standard therapeutic guidelines (Fig. 2). The average time for ablation was 2-6 months after the primary surgical procedure, classified as total or near-total thyroidectomy. RAI ablation was performed 4 weeks after withdrawal of L-thyroxine therapy or use of rh-TSH twice with L-thyroxine therapy. In pre-pubertal children, the dose was administered on a body weight basis (1.35-2.7 mCi/kg). However, the dose of ^{131}I administered after puberty ranged from 30 to 120 mCi for patients with regional lymph node metastases but without distant metastases (N1M0); 100 to 120 mCi of ^{131}I was used for RAI therapy in patients with distant metastases (M1 or more).

Follow-up

The median follow-up period was 10 y (range, 1-21 y). Almost all patients received L-thyroxine treatment at suppressive doses and were regularly monitored every 3 months during the first year, and every 6 months thereafter. A ^{131}I whole-body scan (WBS) with a dose of 10 mCi using rh-TSH was performed approximately 6 months after the initial RAI ablation. Successful ablation was confirmed by the absence of any pathologic uptake of ^{131}I and by an undetectable level of Tg (<0.01 mg/mL). Additional RAI therapy was administered if there was persistent elevation of the Tg level during suppressive therapy.

Patients were classified as having complete remission (CR) (no evidence of disease), partial remission (PR) (decrease in number of sites and intensity of radioiodine uptake on ^{131}I WBS combined with a decrease in the Tg level), recurrent disease (appearance of disease in any patient who had been free of disease for at least 4 months), progressive disease (PD) (elevation of the Tg level or an increase in lesion size or the number of sites), or stable disease (SD) (no apparent change

in tumor size, the number of sites, or the Tg level) [1].

Patients in whom relapse was confirmed underwent additional radioiodine therapy (dose of 100-120 mCi). In patients with PR or SD, or PD in the lungs, additional RAI was administered as necessary during follow-up. In patients with PR or SD, or PD in bone, additional combination of RAI, and zoledronic acid 4 mg/4 weeks or RANMRK 120 mg/4 weeks were administered as necessary during follow-up. WBS and single-photon emission CT (SPECT) were performed at every RAI treatment for persistent or recurrent disease.

Statistical analysis

The significance of differences in continuous variables was analyzed using Student's *t* test. The significance of differences in categorical variables was analyzed using χ^2 test or Fisher's exact test. The probability of recurrence and the influence of prognostic factors were estimated with the Kaplan-Meier method. The significance of differences in the survival curves was analyzed by log-rank test using statistical software (Dr. SPSS II based on SPSS Version 11.0J, SPSS Inc.). Differences at $P < 0.05$ were considered significant.

Results

Baseline, histology and clinical presentation

Table 1 shows a comparison of the baseline and histological characteristics between all DTC patients and those with distant metastases. The risk factors for distant metastasis in DTC were male gender (p=0.003), follicular carcinoma ($p=3.0\times10^{-5}$), the size of the PTC primary tumor (27.2±13.8 mm, $p=4.8\times10^{-10}$), presence of cervical lymph node metastases for PTC ($p=2.0\times10^{-8}$). Prognostic factors for DTC patients with distant metastasis are shown in Table 2 and Fig. 3. These included follicular carcinoma ($p=3.1\times10^{-4}$, $p=8.6\times10^{-4}$), a PTC primary tumor size of more than 20 mm (p=0.008, p=0.017), and presence of more than two distant metastatic foci ($p=5.1\times10^{-4}$, p=0.041) (P: Fisher's exact test and log-rank test).

Initial treatment and follow-up

Initial treatments and responses for the 23 DTC patients in their teens are shown in Table 3. Twenty (87.0%) of these patients had PTC and 3 (13.0%) had FTC. Six of the 20 PTC patients initially underwent

Table 1 Comparison of baseline and histological characteristics between patients with distant metastases and DTC patients overall

	Patients with distant metastases (n=115)	All DTC patients (n=1552)	*P* value
Age at operation (y)	53.5 ± 16.7	52.2 ± 15.4	0.389[a]
Sex			0.003[b]
Male	28 (24.3)	222 (14.3)	
Female	87 (75.5)	1330 (85.7)	
Histopathology [d]			3.0×10^{-5} [b]
Papillary carcinoma	95 (82.6)	1447 (93.2)	
Follicular carcinoma	20 (17.4)	105 (6.8)	
Primary tumor size (mm) [d]			
Papillary carcinoma	27.0 ± 13.8	17.2 ± 13.6	4.8×10^{-10} [a]
Follicular carcinoma	41.0 ± 23.2	34.2 ± 23.2	0.250[a]
Cervical lymph node metastases for PTC [d]			2.0×10^{-8} [b]
N0, x	25 (26.3)	692 (47.8)	
N1a	12 (12.6)	301 (20.8)	
N1b<	58 (61.1)	454 (31.4)	
Site of distant metastasis [e]			
Bone	30 (26.1)	30 (1.9)	
Lung	95 (82.6)	95 (6.1)	
Final outcome			8.7×10^{-10} [c]
Alive	94 (81.4)	1505 (97.0)	
Dead	21 (18.3)	47 (3.0)	

[a] Student's *t*-test; [b] χ^2 test; [c] Fisher's exact test; [d] Pathological result; [e] Including overlap cases.
Continuous variables are expressed as mean±standard deviation.
Categorical variables are expressed as number (percentage).

Table 2 Prognostic factors for distant metastasis

Factor	Dead, n (%)	Alive, n (%)	*P* Value[a]	*P* Value[b]
Age at operation			0.585	0.351
<45y	4 (19.0)	25 (26.6)		
≥45y	17 (81.0)	69 (74.2)		
Sex			0.779	0.632
Male	4 (19.0)	24 (25.5)		
Female	17 (81.0)	70 (74.5)		
Histopathology [c]			3.1×10^{-4}	8.6×10^{-4}
Papillary carcinoma	11 (52.4)	84 (88.4)		
Follicular carcinoma	10 (47.6)	10 (11.6)		
Primary tumor size [c]				
Papillary carcinoma			0.008	0.017
≤20mm	0 (0.0)	33 (39.3)		
>20mm	11 (100.0)	51 (60.7)		
Site of distant metastasis			0.005	0.092
Osseous	11 (52.4)	19 (20.2)		
Nonosseous	10 (47.6)	75 (79.8)		
Number of distant metastasis site			5.1×10^{-4}	0.041
Two or more	8 (38.1)	6 (6.4)		
Single	13 (61.9)	88 (93.6)		

[a] Fisher's exact test; [b] Log-rank test; see Fig. 3; [c] Pathological result

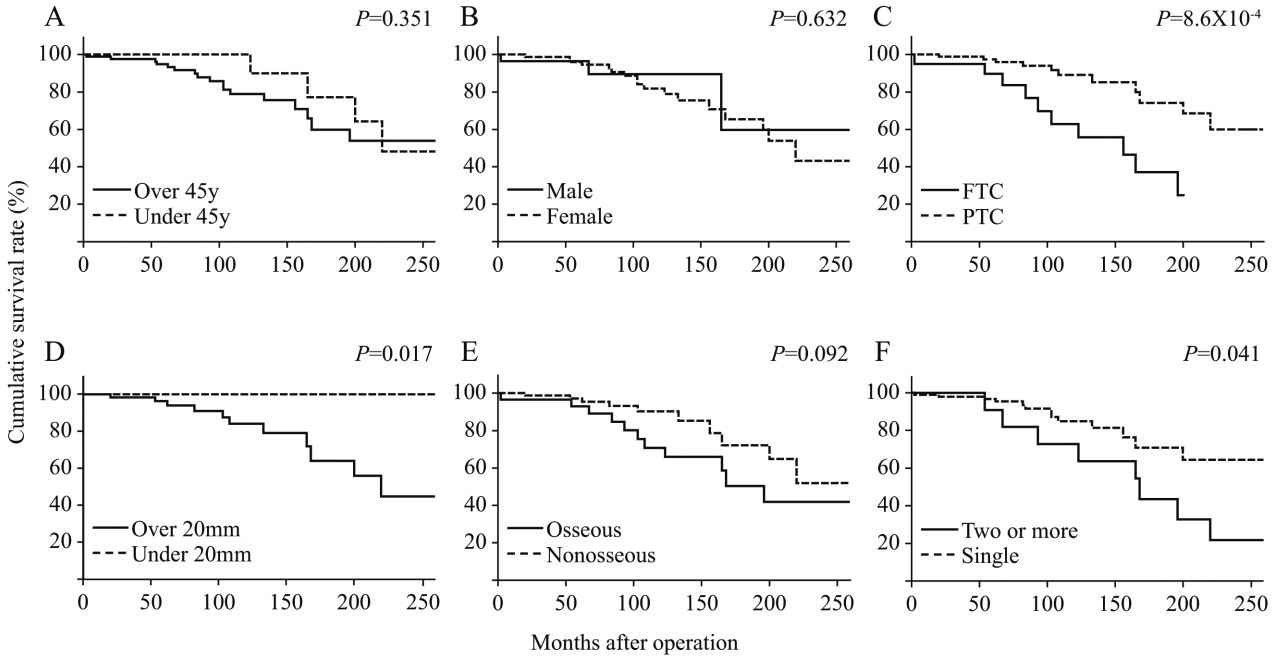

Fig. 3 Comparison of cancer-specific survival curves for several prognostic factors. A, age at operation; B, sex; C, histopathology; D, tumor size for PTC; E, osseous metastasis; F, number of distant metastases. Survival outcomes were compared using the log rank test.

Table 3 Baseline characteristics of patients aged < 20 y who underwent surgery

Patient	Age(y) at operation	Primarily disease	T	N	M	Initial treatment	Initial treatment outcome	Recurrence site	Additional treatment	Additional treatment outcome	Cumulative RAI dose (mCi)	Overall outcome (see text)
1	13	PTC	3	1b	1*	TTx+MNLNR+RAI(A)	PR		RAI(T)	PR	518	CR
2	15	PTC	2	1b	0	TTx+MNLNR	CR	*, CLN	LNR+RAI(A)+(T)	PR	401	CR
3	18	PTC	3	x	1*	TTx+MNLNR+RAI(A)	PR		RAI(T)	PR	234	PR
4	18	PTC	1b	1b	0	NTTx+MNLNR	CR	*	RAI(A)+(T)	PR	1066	SD
5	17	PTC	1 b	1b	1*	STTx+MNLNR+RAI(A)	PR		RAI(T)	PR	150	CR
6	19	PTC	1 b	1b	0	STTx+MNLNR	CR					CR
7	18	PTC	1 b	1b	0	STTx+MNLNR	CR					CR
8	18	PTC	4 a	1b	0	STTx+MNLNR	CR					CR
9	15	PTC	2	1b	0	HTx+MNLNR	CR					CR
10	19	PTC	3	1a	0	NTTx+MNLNR	CR					CR
11	14	PTC	1 b	1b	0	HTx+MNLNR	CR	**	CTTx+RAI(A)	CR	60	CR
12	16	PTC	1 b	0	0	STTx+MNLNR	CR					CR
13	17	PTC	2	1b	0	STTx+MNLNR	CR					CR
14	11	PTC	2	1b	0	STTx+MNLNR	CR					CR
15	16	PTC	2	1b	0	STTx+MNLNR	CR					CR
16	9	PTC	2	x	0	HTx	CR					CR
17	19	FTC	2	0	0	HTx+CLNR	CR	**	CTTx+RAI(A)+(T)	PR	167	CR
18	11	PTC	2	0	0	HTx+CLNR	CR					CR
19	17	PTC	2	1b	0	STTx+MNLNR	CR					CR
20	19	PTC	1 a	x	0	HTx	CR					CR
21	19	FTC	2	x	0	HTx	CR					CR
22	18	PTC	2	1b	0	TTx+MNLNR	CR					CR
23	19	FTC	3	x	0	HTx	CR		CTTx+RAI(A)	CR	60	CR

* Lung metastasis

** Metastasis in remnant thyroid.

TTx, total thyroidectomy; NTTx, near-total thyroidectomy; STTx, sub-total thyroidectomy; HTx, hemi-thyroidectomy; MNLNR, modified neck lateral lymph node resection; RAI(A), radioactive iodine ablation; RAI(T), radioactive iodine for therapy; CLN, cervical lymph node; LNR, lymph node resection; CTTx, completion total thyroidectomy; CLNR, central lymph node resection.

near-total or total thyroidectomy with modified neck lateral lymph-node resection (MNLNR), 9 underwent subtotal thyroidectomy with MNLNR, 5 underwent hemi-thyroidectomy with MNLNR or central lymph node resection (CLNR), and the 3 with FTC underwent hemi-thyroidectomy. Only two PTC patients initially underwent total thyroidectomy with MNLNR and RAI ablation, but suffered relapse in the form of distant metastasis (lung) during follow-up and additional treatment (RAI therapy) was necessary. Finally, one patient achieved CR and another achieved PR. Two of the 20 PTC patients initially underwent near-total thyroidectomy with MNLNR but no RAI ablation. During follow-up, one patient suffered relapse in the form of lung metastases with lymph node recurrence, and RAI therapy became necessary. Finally, one patient achieved CR and one had SD. One of the 20 PTC patients initially underwent hemi-thyroidectomy with MNLNR but suffered relapse in the remnant thyroid during follow-up, and therefore completion total thyroidectomy with RAI ablation was added, and she finally achieved CR. Two of the 3 FTC patients initially underwent hemi-thyroidectomy, and histopathological diagnosis revealed widely invasive disease. Completion total thyroidectomy with RAI ablation was therefore added, and neither of the patients suffered recurrences.

Overall outcome

Patients were classified as having complete remission (CR) (no evidence of disease), partial remission (PR) (decrease in the number of sites or intensity of radioiodine uptake on ^{131}I WBS combined with a decrease in the Tg level), recurrent disease (appearance of disease in any patient who had been disease-free for at least 4 months), progressive disease (PD) (elevation of the Tg level or an increase in lesion size or the number of sites), or stable disease (SD) (no apparent change in tumor size, the number of sites, or the Tg level) [1].

Table 4 Comparison of baseline and histological characteristics between patients aged <20 y, 20 y-30 y and ≥30 y

	< 20y (n=23)	20y-30y (n=118)	≥ 30y (n=1411)	*P* value
Sex				0.675[a]
Male	3 (13.0)	14 (11.9)	205 (14.5)	
Female	20 (87.0)	104 (88.1)	1206 (85.5)	
Histopathology [c]				0.001[a]
Papillary carcinoma	20 (87.0)	101 (85.6)	1326 (94.0)	
Follicular carcinoma	3 (13.0)	17 (14.4)	85 (6.0)	
Primary tumor size (mm) [c]				
Papillary carcinoma	21.5 ± 14.2	21.0 ± 14.4	16.9 ± 13.6	0.005[b]
Follicular carcinoma	27.0 ± 2.8	36.4 ± 22.4	34.7 ± 24.2	0.867[b]
Cervical lymph node metastasis for PTC [c]				7.1×10^{-6} [a]
N0, x	5 (25.0)	32 (31.7)	656 (49.4)	
N1a	1 (5.0)	22 (21.8)	278 (21.0)	
N1b<	14 (70.0)	47 (46.5)	392 (29.6)	
Site of distant metastasis [d]				0.430[a]
Bone	0 (0.0)	2 (1.7)	28 (2.0)	
Lung	5 (21.7)	7 (5.9)	83 (5.9)	
Final outcome				0.236[a]
Alive	23 (100.0)	117 (99.2)	1365 (96.7)	
Dead	0 (0.0)	1 (0.8)	46 (3.3)	

[a] χ^2 test; [b] One-way ANOVA; [c] Pathological result; [d] Including overlap cases.
Continuous variables are expressed as mean±standard deviation. Categorical variables are expressed as number (percentage).

Initially, 20 (87.0%) of the 23 patients in their teens achieved CR, and 3 (13.0%) achieved PR. During follow-up, 4 (17.4%) of the 23 patients developed recurrent disease within a median period of 4 y (range, 1-10 y). The incidence of distant metastasis after initial treatment was significantly higher in teenage patients (21.7%) than in DTC patients overall (7.4%) (p=0.03). Among the 118 patients in their twenties to thirties, 1 (0.8%) had PD and the final outcome was disease-related death (Table 4). Patients with recurrent disease, PR, SD and PD were re-treated with either surgery or surgery and RAI, and received cumulative doses of up to 120 mCi. The overall outcome in our juvenile patients was excellent: CR in 91.3%, PR in 4.35%, SD in 4.35%, and no disease-related deaths.

Discussion

In the absence of exposure to external radiation, thyroid cancer is rather infrequent (2-10%) in patients 20 years old or younger [1, 13, 14, 15]. In our present series, there was a 1.5% (23/1552) incidence of juvenile DTC, and 17.4% (4/23) of those patients developed recurrent disease. These data are in agreement with the previously reported recurrence rates (11-32%) [1, 15].

Among the 20 juvenile PTC patients in our series, 6 initially underwent near-total or total thyroidectomy with MNLNR, 9 underwent subtotal thyroidectomy with MNLNR, and 5 underwent hemi-thyroidectomy with MNLNR or central lymph node resection (CLNR). All of the 3 patients with FTC underwent hemi-thyroidectomy. Initially, RAI ablation was performed in only 3 cases. Among previous studies of recurrent disease in juvenile patients with DTC receiving various types of initial treatment, Mihailovic *et al*. reported that patients who underwent total thyroidectomy with RAI had a lower incidence of recurrence than those who had initially undergone less intense therapy (subtotal thyroidectomy) [1]. Other authors have reported that the extent of initial surgery is correlated with recurrence. Jarzab *et al*. showed that total thyroidectomy was associated with a recurrence-free survival rate of 97%, whereas lobectomy was associated with recurrence rates of 59% and 85% after 5 and 10 years, respectively. Treatment involving less than total thyroidectomy increased the risk of relapse by a factor of 10. In addition, subsequent RAI strongly affected the rate of relapse, decreasing the relative risk of recurrence by a factor of 5 [16]. Popovtzer *et al*. concluded that total thyroidectomy led to a significantly lower recurrence rate (7.5%) than hemi-thyroidectomy (38%) (p <0.005) [17]. There is insufficient evidence to indicate that total thyroidectomy improves cause-specific survival of patients with papillary car-

cinoma relative to that of patients who undergo hemi-thyroidectomy. Total thyroidectomy prevents recurrence in the remnant thyroid but does not reduce the incidence of recurrence in lymph nodes, or distant metastasis. However, we recommend total thyroidectomy for high-risk patients [3, 4], who are classified as those with a maximal tumor diameter of >5 cm (pathologically >2 cm), extrathyroid extension to the mucosa of the trachea or esophagus, a large number of clinically evident lymph node metastases, a lymph node metastasis diameter of >3 cm, and the presence of distant metastasis. Low-risk patients are those with a maximal tumor diameter of <2 cm and absence of clinical lymph node metastasis (T1N0M0 by the TNM classification). Hemi-thyroidectomy is acceptable for such low-risk patients [3].

In our present series, two juvenile patients with PTC initially underwent total thyroidectomy with MNLNR and RAI ablation, but suffered relapse in the form of lung metastasis during follow-up and additional RAI therapy became necessary. Finally, one patient achieved CR and the other PR. Two of the 20 juvenile patients with PTC initially underwent near-total thyroidectomy with MNLNR and no RAI ablation. One suffered relapse in the form of lung metastasis with lymph node recurrence during follow-up, and RAI therapy became necessary. Finally, one of the patient achieved CR and one had SD. One of the 20 PTC patients initially underwent hemi-thyroidectomy with MNLNR but suffered relapse in the remnant thyroid during follow-up, necessitating completion total thyroidectomy with RAI ablation, and finally she achieved CR. These results suggest that the initial treatment for high-risk PTC patients should be total thyroidectomy with RAI ablation. It is important to note that total thyroidectomy does not reduce the incidence of distant metastasis, and that the use of total thyroidectomy with RAI is clearly decreasing. Ruel *et al*. have reported that the use of RAI therapy was associated with improved overall survival in intermediate-risk PTC patients [18].

In this series, 2 of 3 juvenile patients with FTC initially underwent hemi-thyroidectomy, and histopathological diagnosis revealed wide invasion. Completion total thyroidectomy with RAI ablation was therefore added, and finally neither of the patients suffered recurrence. These results suggest that for patients with widely invasive FTC, completion total thyroidectomy with RAI therapy should be added. Most follicular carcinomas are diagnosed by postoperative pathological examination, and most patients initially undergo hemi-thyroidectomy under a diagnosis of follicular tumor or neoplasm. The classification of widely invasive and minimally invasive types allows some degree of prognostication. Widely invasive carcinoma has a significantly worse prognosis than minimally invasive carcinoma, and the degree of vascular invasion is of particular prognostic significance. Completion total thyroidectomy with a search for, or treatment of, distant metastasis using RAI is recommended for patients with widely invasive follicular carcinoma, and those with poorly differentiated compartments such as an insular component [3].

In our study we evaluated the outcome of RAI therapy in terms of tumor response and the level of Tg. Patients were classified into 4 outcome groups: CR, PR, PD, or SD. These Tg patterns are useful for diagnosis of resistance to RAI therapy.

In this series the incidence of distant metastasis after initial treatment was significantly higher in teenage patients (21.7%) than in DTC patients overall (7.4%) (p=0.03). Among 118 patients in their twenties to thirties, 1 (0.8%) had PD and the final outcome was disease-related death. The overall outcome in our juvenile patients was excellent: CR in 91.3%, PR in 4.35%, SD in 4.35%, and no disease-related deaths. Mihailovic *et al*. also reported excellent overall outcomes for juvenile DTC patients: CR in 90.2%, PR in 3.9%, SD in 1.9%, and disease-related death in 1.9%.

The optimal forms of surgical treatment and subsequent use of RAI therapy for DTC are still controversial and remain a matter for discussion. Because thyroid carcinoma spreads in an intraglandular manner and can show multifocality, thyroid remnants are at risk of local relapse [1]. In contrast lobectomy or hemi-thyroidectomy have possibility advantage of non- medication (sodium levothyroxine) for patients. Some authors have suggested that radical initial surgery performed by highly experienced surgeons is the best policy [1, 5]. Enomoto *et al*. have suggested that RAI should be used only in patients with large lymph node and distant metastases at diagnosis [15].

Our present data support the contention that total thyroidectomy and modified neck resection followed by RAI therapy will prevent relapse or reduce the incidence of recurrence of high- and intermediate-risk DTC in juveniles. Five female patients who underwent RAI subsequently had children, and therefore the treat-

ment appears to have no adverse effect on subsequent pregnancies. There were no cases of secondary malignancy within 20 years after treatment.

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Disclosure

None of the authors have any potential conflicts of interest associated with this research.

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