



Prognostic factors and the effect of radioiodine on patients with locally advanced differentiated thyroid cancer

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Background: Locally advanced differentiated thyroid cancer (DTC) is rare. The optimal treatment remains controversial. This study was to investigate the natural history and prognostic factors of patients with locally advanced DTC and assess the effects of radioiodine therapy for locally advanced DTC.

Methods: A retrospective study was performed in 259 patients with locally advanced DTC. The clinicopathological features, prognostic factors and the effects of radioiodine therapy were evaluated using univariate and multivariate statistical analysis.

Results: Among the clinicopathological characteristics of locally advanced DTC, the patient's age (unfavourable >55 years), extent of primary tumour (more widely extrathyroidal extension showed a worse prognosis than others), tumor size, histopathological classifications and distant metastases were the significant prognostic factors. With regard to the effects of RAI on local invasive DTC, neither T3b nor T4 patients without distant metastases could benefit from performance of ¹³¹I therapy for over survival and locoregional relapse-free survival.

Conclusions: In patients with locally advanced DTC, the independent prognostic factors were age, extent of extrathyroidal invasion, tumor size, histopathological classifications and distant metastases. Adjuvant postoperative RAI did not affect overall survival and locoregional control in patients with locally advanced DTC who had no distant metastasis disease. Given the results, we suggested radioiodine would not be applied for metastasis-free patients with locally advanced DTC postoperatively.

Keywords: Locally advanced differentiated thyroid cancer; clinicopathological features; prognosis; radioiodine therapy

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Introduction

Well differentiated thyroid carcinoma (DTC) accounts for more than 80% of all thyroid malignancies with a 10-year survival rate of over 95% (1,2). In most cases, the tumor is

confined to the thyroid capsule. Extrathyroidal invasion, which occurs in 10% of cases, is associated with a worse prognosis for recurrence, distant metastases and the overall survival of DTC patient (3). Locally advanced

diseases according to the 8th edition of the American Joint Committee on Cancer-TNM classification (2017), is defined as a tumour of any size with extrathyroidal extension. The surgical resection of involved structures, radioiodine therapy (RAI), and thyroid-stimulating hormone (TSH)-suppressing therapy are the three main treatments used in the management of DTC patients. However, the optimal treatment modality in patients with locally advanced DTC remains controversial. In the present study, we investigated the natural history and prognostic factors of patients with locally advanced DTC and intended to assess the effects of radioiodine therapy for locally advanced DTC. We present the following article in accordance with the STROBE reporting checklist (available at <http://dx.doi.org/10.21037/atm-18-1301>).

Methods

Patients

Between 2005 and 2015, 259 patients with a new diagnosis of locally advanced differentiated thyroid cancer were seen at the Department of Head and neck surgery, Jiangsu Cancer Hospital. Patients referred with recurrent disease were excluded. The patients were homogeneously evaluated in the preoperative work-up and operated on by the same surgical team. The trial was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethical Committee of Nanjing Medical University Affiliated Cancer Hospital (No. 2020032). Written informed consent was provided by all of the study participants.

Variables

Table 1 shows the age (<55 or ≥55 years), gender, sites of extrathyroidal extension, tumor size (<1, 1–4 or >4 cm), T stage, N stage, M stage, diagnostic, therapeutic and histopathological variables and the outcome of the patient population. According to the Eighth Edition of AJCC Cancer Staging System, T3b category included 65 patients, while 194 patients belonged to T4 category. All patients received surgical treatment, consisting of non-total thyroidectomy, total thyroidectomy with involved structures and lymph node dissection. A subtotal thyroidectomy on 40 (15.4%), a unilateral lobectomy on 91 (35.1%), a total or near-total thyroidectomy was performed on 128 patients (49.4%). En-bloc resection of invasive organ included the

strap muscle, RLN, larynx, pharynx, trachea and esophagus with the goal of complete microscopic or macroscopic resection. Neck lymph node dissections were performed on 248 patients (95.8%) (central 83, central and lateral 165). Moreover, lymph nodes were found to be metastatic in 213 cases (85.9%). After surgery, 78 patients (30.1%) received ¹³¹I therapy, whereas 24 patients (9.3%) were treated with external radiotherapy. L-Thyroxine at TSH-suppressing doses was then administered in all patients.

Follow-up

Patients were followed up at 3, 6 and 12 months after treatment, and then annually. All patients were followed up. The mean follow-up was 103 months (range, 6–172 months). Follow-up consisted of clinical examination, measurement of serum thyroglobulin and anti-thyroglobulin levels and high-resolution neck ultrasonography. After follow-up, 39 patients (15.1%) had died, 220 patients (84.9%) were alive with or without disease. There were 47 patients (18.1%) suffering from local-regional recurrence. Among them, thyroid bed recurrence was occurred in 12 patients (4.6%), while lateral neck recurrence was found in 40 patients (15.4%).

Statistical analysis

Patient data were analysed at the Statistical Department of Jiangsu Cancer Hospital. Univariate analysis was performed using the log-rank test for effect of ¹³¹I therapy on overall survival rate and multivariate analysis using the Cox proportional hazard model. Overall survival probability was calculated using the Kaplan-Meier method. $P < 0.05$ was considered to be significant. The prognostic variables examined are shown in *Table 1*. All statistical procedures were performed using the statistical package SPSS for Windows, release 20.0 (SPSS Inc., Chicago, Illinois, USA).

Results

At univariate and multivariate statistical analysis (*Table 2*), with regard to overall survival, the significant prognostic variables were found to be the patient's age (unfavourable >55 years, HR, 0.227; 95% CI, 0.109–0.475, $P = 0.000$), extent of primary tumour (more widely extrathyroidal extension showed a worse prognosis than others, HR, 2.417; 95% CI, 1.312–4.454, $P = 0.005$), tumor size (HR, 2.033; 95% CI, 1.161–3.558, $P = 0.013$), histopathological

Table 1 Characteristics and initial treatment of patients with locally advanced DTC (n=259)

Patients' characteristics	No.	(%)
Age (years)		
<55	162	62.6
≥55	97	37.4
Gender		
Male	88	34.0
Female	171	66.0
Histopathological classifications		
Well differentiated thyroid cancer	156	60.2
Classical papillary	150	57.9
Follicular	6	2.3
Aggressive variant DTC	97	37.5
Tall cell variant	93	35.9
Columnar cell variant	2	0.7
Hobnail variants	1	0.4
Sclerosing variant	1	0.4
DTC with poorly or anaplastic differentiated component	6	2.3
Sites of extrathyroidal extension		
Sternothyroid muscle or perithyroid soft tissues	65	25.1
Laryngeal nerve	81	31.3
Trachea	60	23.2
Larynx	13	5.0
Esophagus	51	19.7
Carotid vessels	8	3.1
T stage		
T3b	65	25.1
T4	194	74.9
T4a	166	64.1
T4b	28	10.8
Tumor size (cm)		
<1	21	8.1
1–4	172	66.4
>4	66	25.5
Multifocality		
Single	171	66.0
Multifocal	88	34.0

Table 1 (continued)**Table 1** (continued)

Patients' characteristics	No.	(%)
Neck lymph node metastasis (N stage)		
N0	46	17.8
N1a	59	22.8
N1b	154	59.4
Metastatic neck lymph node size (cm)		
N0	46	17.8
1–3	172	66.4
>3	41	15.8
Distant metastasis at presentation (M stage)		
M0	239	92.3
M1	20	7.7
Resection margins		
R0	187	72.2
R1	69	26.6
R2	3	1.2
Thyroid surgery		
Total/near total thyroidectomy	128	49.5
Subtotal thyroidectomy	40	15.4
Lobectomy (unilateral thyroidectomy)	91	35.1
Lymph node surgery		
None	11	4.2
Central compartmental dissection	248	95.8
Unilateral selective/radical neck dissection	115	44.4
Bilateral selective/radical neck dissection	50	19.3
RAI		
No	181	69.9
Yes	78	30.1
RT (EXT)		
No	235	90.7
Yes	24	9.3
Summary of RAI and RT treatment (treatment modality)		
RAI alone	67	25.9
RT alone	13	5.0
Both RAI and RT	11	4.2
No RAI nor RT	168	64.9

DTC, differentiated thyroid carcinoma; RAI, radioiodine therapy.

Table 2 Univariate and multivariate analysis of prognostic factors for overall survival in 259 patients with locally advanced DTC

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Gender (male:female)	0.409	0.218–0.767	0.005	0.595	0.304–1.166	0.131
Age (yrs) (≥ 55 :<55)	0.168	0.082–0.345	0.000	0.227	0.109–0.475	0.000
T stage (T3b:T4a:T4b)	3.042	1.722–5.223	0.000	2.417	1.312–4.454	0.005
Tumor size (cm) (<1:1–4:>4 cm)	2.437	1.390–4.435	0.000	2.033	1.161–3.558	0.013
Multifocality (single:multifocal)	0.684	0.333–1.403	0.300	–	–	–
Metastatic neck lymph node size (cm) (N0:1–3:>3)	2.054	1.186–3.557	0.010	1.402	0.646–3.045	0.055
N stage (N0:N1a:N1b)	1.450	0.903–2.328	0.124	–	–	–
Distant metastasis (M0:M1)	2.429	1.016–5.805	0.046	3.286	1.332–8.107	0.010
Resection margins (R0:R1:R2)	2.172	1.240–3.804	0.007	1.483	0.804–2.734	0.089
Histopathological classifications (well differential thyroid cancer: aggressive variant DTC: DTC with poorly differentiated or anaplastic component thyroid carcinoma)	7.994	4.264–14.986	0.000	8.111	4.106–16.021	0.000

DTC, differentiated thyroid carcinoma.

classifications (the poorer the differentiation, the worse the prognosis, HR, 8.111; 95% CI, 4.106–16.021, $P=0.000$) and distant metastases (HR, 3.286; 95% CI, 1.332–8.107, $P=0.010$). *Figure 1* showed the overall survival curves for independently statistically significant prognostic factors. With regard to the effect of RAI on local invasive DTC, univariate analysis showed neither T3b nor T4 patients without distant metastases could benefit from performance of ^{131}I therapy for over survival and locoregional relapse-free survival. *Figure 2* showed overall survival and local regional relapse-free survival curves for RAI applied to T4 patients without distant metastases. In T4 stage patients who had no distant metastasis disease without RT, the 10-year overall survival rates were not significantly different statistically between the two groups at 82.7% for the no-RAI group and 78.6% for the RAI group ($P=0.355$). The locoregional control rates at 10 years were not significantly different (RAI 74.8% and no RAI 73.5%; $P=0.666$).

Discussion

In general, DTC is characterized by a good prognosis after standard treatment. However, local tumor invasion may lead to high morbidity and mortality. Tumor invading to the adjacent tissues is considered as the most important unfavourable prognostic factor for local recurrence and

distant metastases during follow-up (4–6). Therefore, an extensive surgical approach is recommended. On the contrary, limited operation for locally invasive DTC combined of surgery with ^{131}I therapy and/or external radiotherapy is recommended in attempt to avoid higher morbidity and mortality. In our experience, successful surgical management was achieved by resection of the tracheal rings, pharyngeal and esophageal mucosa and laryngectomy. It offers the patient a favourable outcome, in terms of overall survival. The 10-year overall survival rate was 81.5%. The statistical analysis performed on our data in *Table 2* showed that the patient's age, extent of extrathyroidal invasion, tumor size, histopathological classifications, and distant metastases were the independent prognostic factors for overall survival.

Radioiodine (RAI) has been applied in the postsurgical treatment of DTC for years (7). Considering the side effects of radioiodine therapy for thyroid carcinoma such as carcinogenesis, lung fibrosis, and anemia etc, the role of RAI in locally advanced DTC, however, is matter of debate (8–12). In our data, in T4 stage patients who had no distant metastasis disease without RT, the 10 year-overall survival rates were not significantly different statistically between the two groups at 82.7% for the no-RAI group and 78.6% for the RAI group ($P=0.355$). The locoregional control rates at 10 years weren't significantly different (RAI 74.8% and

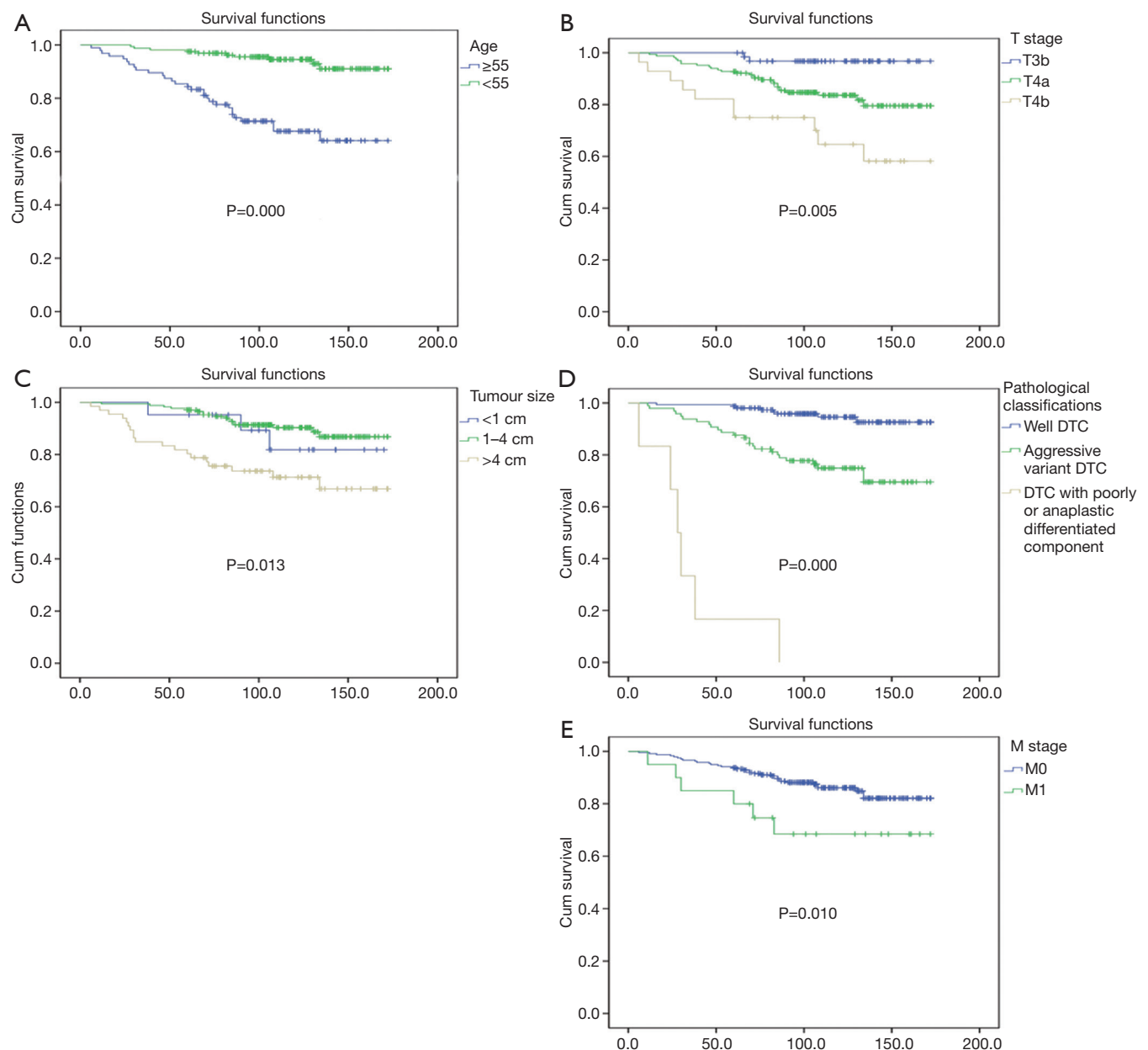


Figure 1 Comparisons are shown of overall survival (OS) curves for independently statistically significant prognostic factors: age at diagnosis (A), tumor stage (B), tumor size (C), histopathological classifications (D) and distant metastasis at presentation (E) ($P < 0.05$).

no RAI 73.5%; $P=0.666$). The data from our series showed that ^{131}I therapy did not seem to play a beneficial role, both with regard to the overall survival and local-regional control.

This study is a retrospective single-center study. Further prospective multi-center studies are required to avoid the bias.

In conclusion, on the result of our data in the present study, in patients with locally advanced DTC, the independent prognostic factors were age, extent of extrathyroidal invasion, tumor size, histopathological classifications and distant metastases. Adjuvant postoperative RAI did not affect overall survival and locoregional control in patients with locally advanced

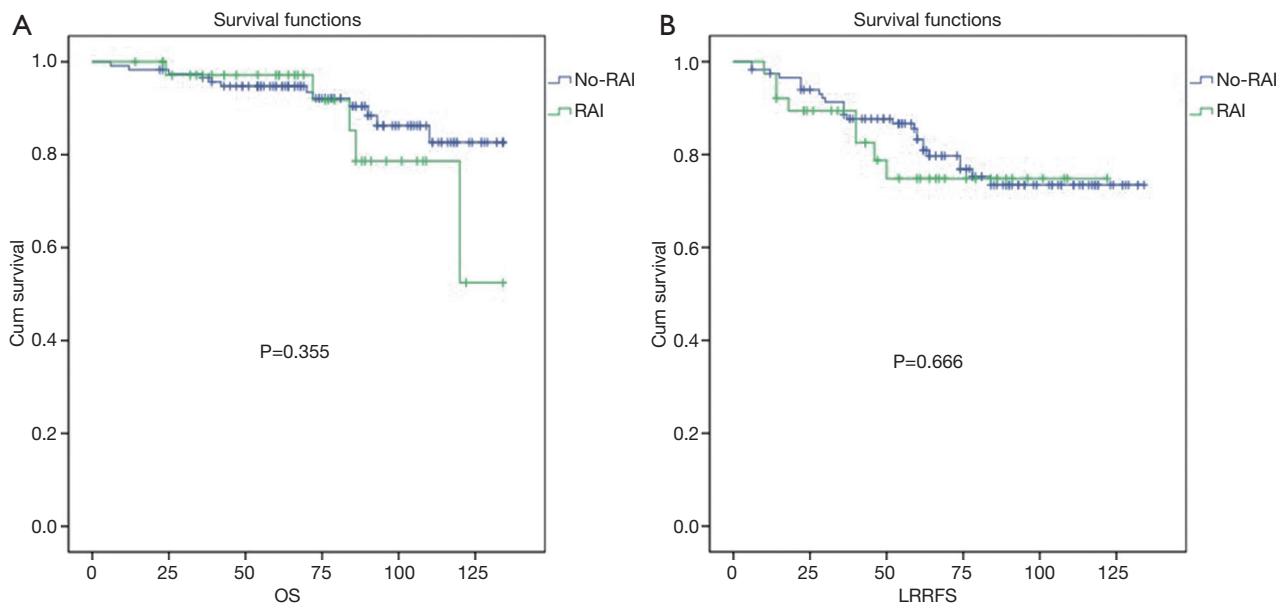


Figure 2 Comparisons are shown of overall survival (OS) (A) and local-regional relapse-free survival (LRRFS) (B) curves for T4 patients without distant metastases ($P>0.05$).

DTC who had no distant metastasis disease. Given the results, we suggested radioiodine would not be applied for metastasis-free patients with locally advanced DTC postoperatively.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at <http://dx.doi.org/10.21037/atm-18-1301>

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The trial was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethical Committee of Nanjing Medical University Affiliated Cancer Hospital (No. 2020032). Written informed consent was provided by all of the study participants.

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