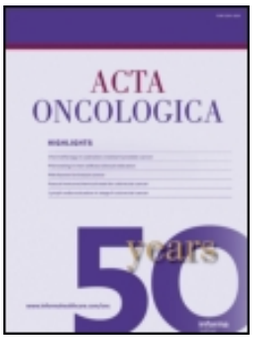

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NON-HODGKIN'S LYMPHOMA OF THE THYROID

A clinical study of twenty-two cases

KEISUKE SASAI, HIROHIKO YAMABE, HIRONORI HAGA, KAZUSHIGE TSUTSUI, YOSHIHIRO DODO, TAKASHI ISHIGAKI, YUTA SHIBAMOTO and MITSUYUKI ABE

Non-Hodgkin's lymphoma (NHL) of the thyroid gland is a rare disease. In the present study, the survival rate and characteristics were retrospectively analyzed in 22 patients with stage IE and IIE thyroid NHL treated with radiotherapy with or without combination chemotherapy. Seventeen NHL had histological evidence of lymphoma of mucosa-associated lymphoid tissue (MALT) type. The 5-year survival rate was 85% in all patients, with 100% and 63% respectively, for stage IE and stage IIE patients. The highly significant factor correlated with decreased determinate survival was concomitant stridor.

Non-Hodgkin's lymphoma (NHL) originating from the thyroid gland is a rare disease, representing only 2.2–2.5% of all lymphomas (1) and 0.6–5% of all thyroid malignancies (2). Previously, we reported our clinical results in patients with extranodal non-Hodgkin's lymphoma (3), in 13 of whom thyroid NHL was present. We have since treated 9 other patients with stage IE or IIE thyroid NHL at Kyoto University Hospital with radiation therapy, with or without combined chemotherapy. In this retrospective study, we investigated the characteristics of NHL originating from the thyroid gland in an attempt to develop an effective treatment policy for this disease.

Material and Methods

Patient characteristics

Between 1979 and 1993, 161 patients with stage I and II NHL were referred to the Department of Radiology, Kyoto University Hospital. There were 22 patients with stage IE and IIE NHL originating from the thyroid gland and all of them were treated with radiotherapy with or without combined chemotherapy. Three additional patients with stage III or IV NHL of thyroid were treated at our department, one with gastric involvement, one with liver dissemination, and one with multiple lymph node involvement. The characteristics of the 22 patients are summarized in Table 1.

The latest follow-up was performed on October 31, 1994. Complete follow-up was obtained in all cases. Three patients died due to intercurrent disease (one from a brain stroke 15 years after diagnosis, one from a heart attack at 51 months, and the third one from pulmonary tuberculosis at 19 months) without any evidence of recurrent disease. Three patients died of malignant lymphoma. The follow-up period for the 16 survivors ranged from 14 months to 10 years (median: 57 months).

Histology and T/B phenotype

Lymphomas of the mucosa-associated lymphoid tissue (MALT) type were diagnosed according to Hyjek & Isaacson (4). In 21 patients, immunohistochemical studies were performed using paraffin sections, the avidin-biotin peroxidase complex technique, and a panel of monoclonal antibodies (L26, MB1, LN1, CD3, MT1 and UCHL1), as described previously (3). Table 2 shows the histological classification and other clinical and pathologic data in each patient. Of the 22 primary lymphomas, 17 were of the MALT type, 13 without and 4 with high-grade

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From the Department of Radiology (K. Sasai, T. Ishigaki), and Laboratory of Anatomic Pathology (H. Yamabe, H. Haga), Kyoto University Hospital, Kyoto, and Department of Oncology, Chest Disease Research Institute, Kyoto University, Kyoto (Y. Shibamoto), Department of Radiology, Wakayama Redcross Hospital, Wakayama (K. Tsutsui), Department of Radiology, Kurashiki Central Hospital, Kurashiki, Okayama (Y. Dodo), National Kyoto Hospital, Kyoto (M. Abe), Japan.
Correspondence to: Keisuke Sasai, Department of Radiology, Kyoto University Hospital, Sakyo-ku, Kyoto 606-01, Japan.

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Table 1

Characteristics of patients with non-Hodgkin's lymphoma of the thyroid gland.

Sex	
Male	9 (41%)
Female	13 (59%)
Age	
Meidan	71
Range	28–82
Histology	
Lymphomas of MALT type	17 (77%)
Others	5 (23%)
T/B phenotype	
B cell	20 (95%)
T cell	1 (5%)
n.a.*	1
Stage	
IE	14 (64%)
IIE	8 (36%)
Hashimoto's thyroiditis	
Yes	18 (82%)
No	4 (18%)
Residual tumor	
Yes	17 (77%)
No	5 (23%)
Chemotherapy	
Yes	19 (86%)
No	3 (14%)
Dyspnea	
Yes	6 (27%)
No	16 (73%)
Stridor	
Yes	3 (14%)
No	19 (86%)
Hoarseness	
Yes	7 (32%)
No	15 (68%)
Dysphagia	
Yes	7 (32%)
No	15 (68%)
Laryngeal nerve palsy	
Yes	6 (27%)
No	16 (73%)
Tracheal deviation	
Yes	5 (23%)
No	17 (77%)
Mediastinal extension	
Yes	4 (18%)
No	18 (82%)
Pain	
Yes	3 (14%)
No	19 (86%)
Bulky tumor	
> 6 cm	16 (73%)
≤ 6 cm	6 (27%)

*n.a.: not available

(large cell) transformation. The remaining 5 cases were classified according to Working Formulation (5). All but one were of the B-cell type. One case (No. 10) was of a mixed small and large T-cell type with lymphoepithelial lesions and this might be classified as a T-cell MALT lymphoma.

Staging

The diagnosis was based on total thyroidectomy in 6 patients, open biopsy in 5 patients, and needle biopsy in 11 patients. Seventeen patients had residual disease at the commencement of the treatment. Each patient was evaluated by history and physical examination, chest x-ray, gallium-67 scanning, bone marrow aspiration, and gastrointestinal series. Cervical, thoracic and abdominal CT scanning, ^{99m}Tc scintigraphy and cervical and abdominal ultrasonography were also part of the routine initial work-up. Four patients underwent lymphangiography. No staging laparotomies were performed. Although the patients were staged according to the Ann Arbor classification, diffuse involvement of the thyroid gland without any other lesions outside of the gland was not classified as stage IV.

Treatment

All patients were treated with curative intent. However, a variety of treatment policies were used over the 15-year period. The reason for the choice of one specific policy was not always clear in this retrospective review. Three patients received radiotherapy alone and the other 19 both radiation therapy and chemotherapy. Radiation therapy was delivered via parallel opposed beams using megavoltage equipment, commonly ^{60}Co. Table 2 shows the radiation fields and dose for each patient. Most cases were treated with doses ranging from 30 Gy to 60 Gy. The patient (No. 1) who received 70 Gy to the tumor was diagnosed as a primary anaplastic thyroid cancer at the start of the treatment. To one patient (No. 15) we started combination chemotherapy at her own request when her tumor had been given 21 Gy. The spinal cord in most patients received less than 46 Gy. However, some patients received up to 50 Gy in the spinal cord.

In 12 of the patients treated with combined modality approach, the chemotherapy consisted of modified VEPA (3) (doxorubicin:30 mg/m^2 i.v., day 1, vincristine: 1 mg/m^2 i.v., day 1, cyclophosphamide: 350 mg/m^2 i.v., day 1, and prednisolone 30 mg/m^2 orally, day 1 to 3, 4 to 10 cycles are given at 2- or 3-week intervals) and in 4 it consisted of vincristine, cyclophosphamide, and prednisolone. One patient each was treated with cyclophosphamide and prednisolone, with methotraxate, vincristine, cyclophosphamide, and prednisolone, and with modified VEPA, but pirarubicin ((2"R)-4'-o-tetrahydropyranyladriamycin: THP-doxorubicin)instead of doxorubicin. The chemotherapy was performed before the radiation therapy course in one patient, after the irradiation therapy in 7, during and after irradiation in one, and both before and after irradiation in 10 patients.

Table 2

Clinical and pathologic data for 22 patients with NHL of the thyroid

Patient No.	Age/ Sex	Stage	Histology[1] T/B phenotype		Hashimoto's thyroiditis	CT[2]	RT[3] Dose (Gy)	Field	Prognosis (months)
1	71/F	IIEA	M	B	Yes	V, P[4]	70.0	WN[5]	180, death: NED[6]
2	66/M	IIEB	DL	B	Yes		59.9	M	10, dead of disease
3	69/F	IIEA	DL	B	Yes	C, H, V, P	40.0	WN	9, dead of disease
4	56/F	IIEA	M	B	Yes	C, M, V, P	60.0	WN	124, NED
5	67/F	IEA	M/T	B	No	C, V, P	51.6	WN	122, NED
6	64/F	IEA	DL	B	No	C, H, V, P	56.7	WN + Med	95 NED
7	74/M	IIEA	M	B	Yes	C, H, V, P	40.5	WN + Med	113, NED
8	82/M	IEA	M	B	No	C, V, P	50.7	WN + Med	51, death: NED
9	49/F	IEA	M	B	Yes	C, H, V, P	49.6	WN + Med	78, NED
10	59/F	IEB	DM	T	Yes	C, H, V, P	30.0	WN + Med	77, NED
11	71/M	IIEA	M	B	Yes	C, H, V, P	34.5	WN + Med	74, NED
12	73/M	IEA	M	B	Yes	C, V, P	45.0	WN + Med	62, NED
13	73/M	IIEA	LI	B	Yes	C, H, V, P	59.6	WN + Med	14, dead of disease
14	71/F	IEA	M	B	Yes	C, H, V, P	30.4	WN + Med	57, NED
15	70/F	IEA	M/T	B	Yes	C, H*, V, P	20.8	WN + Med	54, NED
16	68/F	IEA	M	B	Yes	C, H, V, P	40.6	WN + Med	49, NED
17	71/M	IEA	M/T	B	No	C, H, V, P	51.6	WN + Med	46, NED
18	60/F	IEA	M	B	Yes	C, H, V, P	40.6	WN + Med	45, NED
19	28/M	IEA	M	B	Yes	C, H, V, P	40.6	WN + Med	40, NED
20	78/F	IIEA	M	B	Yes	C, V, P	49.6	WN + Med	19, death: NED
21	78/M	IEA	M/T	B	Yes		50.4	WN + Med	22, NED
22	76/F	IEA	M	n.a.[7]	Yes		49.8	WN + Med	14, NED

[1] M: Low grade lymphoma of mucosa-associated lymphoid tissue (MALT) type, M/T: M with high grade (large cell) transformation, DM: Diffuse mixed type (Working formulation), DL: Diffuse large cell type (Working formulation), LI = Large cell immunoplastic type (working formulation).
[2] CT: Chemotherapy
[3] RT: Radiation therapy
[4] V: Vincristine, P: Predonisolone, C: Cyclophosphamide, H: Doxorubicin, M: Methotraxate, H*: THP-doxorubicin
[5] WN: Whole neck and supraclavicla fossa, M: Mantle, Med: Upper mediastinum
[6] NED: No evidence of disease
[7] n.a.: not available

Statistical analysis

Actuarial overall survival, determinate survival and relapse-free survival rates were calculated from the date of commencement of the first treatment, using the Kaplan-Meier method. Determinate survival is defined as a cause-specific survival calculation adjusted for deaths due to conditions clearly unrelated to lymphoma or its treatment. Comparison of survival and relapse-free survival curves were calculated using the generalized Wilcoxon test.

Results

Treatment results

The 5-year actuarial overall survival, determinate survival and disease-free survival rates were 73%, 85%, and 73% respectively for the whole group of 22 patients. The prognosis was better for patients with stage IE disease than for those with stage IIE (Figure). Three patients, one treated with radiation alone and two with radiation and combination chemotherapy, recurred 5 to 14 months after complete response. None of these patients had a lymphoma of MALT type. Although they were treated after the recurrence with combination chemotherapy, they all died from the disease. Relapse in the gastrointestinal tract

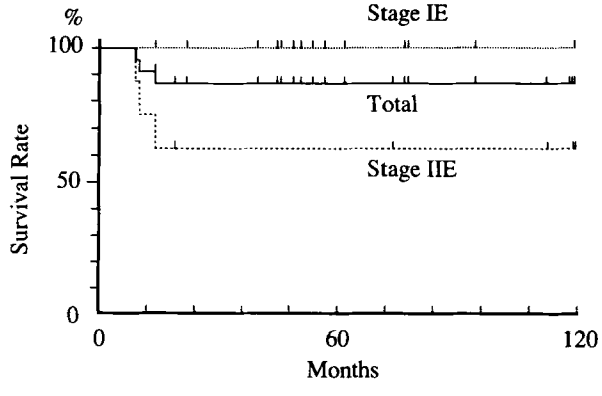

Figure. Survival rate in all patients and those with stage IE and stage IIE non-Hodgkin's lymphoma of the thyroid gland. The 5-year survival rate is 85% in all patients, with 100% and 63% respectively for stage IE and stage IIE patients.

Table 3

Univariate analysis of the relation of prognostic factors to the determinate survival rate for patients with stage IE and IIE non-Hodgkin's lymphoma of the thyroid

Factor	p-value
Secondary effects of tumor bulk	0.067
Stridor	0.00001
Mediastinal extension	0.00019
Tracheal deviation	0.0013
Laryngeal nerve palsy	0.005
Hoarseness	0.012
Dysphagia	0.28
Lymphoma of MALT type (good prognosis)	0.0012
Pain	0.0036
Stage (IE vs IIE)	0.024
Size of tumor (≤ 6 cm vs > 6 cm)	0.26
Surgery (total thyroidectomy vs biopsy)	0.26
Residual tumor following surgery	0.32
Presence of Hashimoto's thyroiditis	0.38
Gender	0.47
LDH (normal range vs higher than normal range)	0.64

was noted in two of these three patients. Another patient relapsed within the radiation field with synchronous relapse in the nasopharynx and inguinal nodes.

Analysis of prognostic factors

The results of univariate analysis of significant prognostic factors are presented in Table 3. A highly significant decrease in determinate survival was seen in the 3 patients who had concomitant stridor. Although the other factors were significantly related to the determinate survival, all patients who had recurrent disease and died of lymphoma had concomitant stridor.

Treatment toxicity

Almost all patients who received radiotherapy complained of self-limiting pharyngitis and/or esophagitis during and after radiation therapy. One patient (No. 2) treated by mantle field radiotherapy showed severe radiation-induced pneumonitis which precluded sequential chemotherapy, and died of recurrent NHL. One patient who had received total thyroidectomy with temporary tracheostomy showed recurrent laryngeal nerve palsy. Another patient who had total thyroidectomy is presently suffering from hypoparathyroidism. One patient complained of hoarseness three years after the treatment without any evidence of recurrent disease or any objective changes of the larynx.

Discussion

Non-Hodgkin's lymphoma originating from the thyroid gland has usually been treated with radiotherapy including the superior mediastinal lymph nodes and the neck (6-10). Routine use of chemotherapy in early-stage thyroid lymphoma has not been recommended (7, 9, 10). With the recent development of multiagent chemotherapy, combined modality treatment has become more frequently used as initial therapy for NHL in other sites, even in stage I or II. Table 4 shows the results of a literature survey of patients with thyroid NHL. Except for the results of the MD Anderson Hospital group (7), patients treated with radiation therapy alone have an overall 5-year survival rate of 35–60%, whereas Tsang et al. (11), Skarsgard et al. (12) and Matsuzaka et al. (13) all reported higher survival rates in patients treated with combined modality. Tsang et al. (11) reported that the patients who were treated with combined radiation and chemotherapy showed significantly better survival than those treated by radiation alone by adjusting for the effect of the imbalance of tumor size. Doria et al. (14) also observed that additional chemotherapy to radiation significantly lowered distant and overall recurrence of the thyroid lymphoma. The survival rates which we observed are comparable to those reported by other groups who treated patients with combined treatment modality. These results suggest that in order to reach a very high control rate patients with primary thyroid lymphoma may initially require combined modality treatment. There must be a group of patients who can be treated effectively by radiation alone, for example, as Tsang et al. (11) pointed out, selected patients with stage IEA disease and postoperative tumor bulk < 3 cm. However, at the present time the characteristics of this group cannot be identified, because of the lack of sufficient data.

Lymphomas of the gastrointestinal tract including Waldeyer's ring, the salivary glands, lung and thyroid, are grouped together as tumors arising in MALT (14–18). Although some investigators question any special relationship between thyroid and gastrointestinal lymphoma (19), others have reported that relapse after treatment of thyroid lymphomas is frequently located in the gastrointestinal tract (12, 20, 21), as was also observed in our study. Most relapses seem to occur within the first 2 years after diagnosis (6, 7, 9, 10, 22). Late relapses have, however, also been reported (11, 12). Lymphomas arising from MALT tend to remain localized until late in the course of the disease (15, 16). Therefore, long-term investigative follow-up to check for recurrent disease, especially in the gastrointestinal tract, may be necessary.

The highly significant prognositic factor is the presence of concomitant stridor, and this is probably due to tumor bulk. In NHL in other sites or organs, the tumor bulk is an important prognostic factor, although the size of the tumor itself does not affect the survival when the cut-off point is 6 cm as in this study. Almost all of our patients had Hashimoto's thyroiditis, and pre-existing Hashimoto's

Table 4

Results of literature survey of treatment and outcome of patients with non-Hodgkin's lymphoma of the thyroid

Authors/Year	Overall 5-year survival (%)			Comments
	Total	Stage I	Stage II	
Souhami et al. (6)* 1980	35 (20) #			Majority: RT
Blair et al. (10) 1985	57 (38)			Majority: RT
Vigoliotti et al. (7) 1986	72 (38)	91 (12)	62 (26)	Entire group
	93 (15)	100 (7)	88 (8)	RT
	77 (13)	100 (3)	64 (10)	RT + CT
	60 (5)	–	60 (5)	CT
	33 (3)	50 (2)	0 (1)	Surgery along
Tupchong et al. (8) 1986	40 (46)			Majority: RT
Logue et al. (9)* 1992	42 (70)	63 (32)	27 (38)	Two received CT
Skarsgard et al. (12) 1991	70 (25)	100 (7)	67 (18)	Majority: RT + CT
Tsang et al (11) 1993	64 (39)			Half: RT + CT
Matsuzaka et al. (13) 1993			100 (16) +	RT + CT
			75 (21) ++	
Present study	73 (22)	85 (14)	50 (8)	Majority: RT + CT

*: Number in parentheses indicates the reference
#: Numbers in parentheses indicate the number of patients
**: RT: Radiation therapy, CT: Chemotherapy
+: 6 courses of CHOP
++: 1 or 2 courses of CHOP or MOPP (nitrogen mustard, vincristine, procarbazine, and prednisolone)

thyroiditis and related goiter may have been superimposed on the tumor itself. Therefore, the secondary effects of tumor bulk are better indicators of prognosis than is the tumor size itself. Other investigators have demonstrated other prognostic factors, such as radiation dose, field area, symptom duration, fixation of tumors, respiratory obstruction, residual disease, axillary lymph nodes and Hashimoto's thyroiditis (7–10).

Although some investigators have pointed out that the surgical operation methods and the presence of residual disease after the surgery are important prognostic factors (8, 12), these factors were not found to have any significance in our study. Logue et al. (9) treated patients mainly with radiation alone and reported that relapse in the radiation field was observed in only 4 of 29 relapsing patients. Tsang et al. (11), who treated patients with combined radiotherapy and chemotherapy, also reported that loco-regional failure was infrequent in their patients with thyroid lymphomas. In our group, no solitary loco-regional recurrence was observed. In radiation therapy for NHL of the thyroid, failure outside of the radiation field seems to be a very important prognostic factor. This is a possible reason for the fact that neither the operation method nor the presence of residual disease had any significant prognostic effect in our patients. Open biopsy or needle biopsy is adequate as a diagnostic method (23). Other investigators have already described the role of surgery as being limited for making a histological diagnosis (22). Matsuzaka et al. (13) introduced 6 courses of combined chemotherapy as the adjuvant to the radiation therapy for the NHL of the thyroid, and reported that neither total nor partial thyroidectomy is necessary for the treatment of this disease.

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