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Management of non-Hodgkin's lymphoma of the thyroid: the Royal Marsden Hospital experience

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Abstract. A retrospective review was conducted of patients treated for thyroid non-Hodgkin's lymphoma (TNHL) at the Royal Marsden Hospital between 1936 and 1996 to determine the effect of radiotherapy (RT) on outcome. 91 patients were identified from the Thyroid Unit Database. There were 77 females and 14 males with a median age of 65 years (range 22–87 years). RT was delivered according to two separate policies: (1) involved field radiotherapy (IFRT) to the thyroid bed and cervical lymph nodes; (2) extended field radiotherapy (EFRT) covering the thyroid bed, cervical and mediastinal lymph nodes. 89 patients received RT as part of definitive treatment following surgery, to a dose of approximately 40 Gy. 25 patients received IFRT and 64 patients EFRT. 27 patients received cytotoxic chemotherapy. 18 patients (72%) treated with IFRT died of TNHL with a median relapse free survival (RFS) of 10 months and a median overall survival (OS) of 21 months. In contrast, only 29 patients (46%) treated with EFRT died of TNHL with a median RFS of 76 months ($p=0.01$ for RFS with respect to IFRT and $p=0.04$ for OS). Significantly more patients treated with IFRT relapsed locally (52% *vs* 27%). There was no difference in the rates of systemic relapse (20% *vs* 22%). EFRT alone for Stage I, but not for Stage II disease, yielded acceptable rates of local control and disease free survival with doses of at least 40 Gy. These historical data strongly support the addition of combination chemotherapy to the treatment regimen in all patients with Stage II disease. Indeed, in recent years this has become the standard of care for all cases of thyroid lymphoma unless the histology is of marginal zone type (mucosa associated lymphoma tissue (MALT) lymphoma).

Thyroid non-Hodgkin's lymphoma (TNHL) is an uncommon tumour, representing 2–8% of thyroid malignancies and approximately 1–2% of extranodal lymphomas [1–4]. It occurs most frequently in elderly females and has been linked to Hashimoto's thyroiditis and prior therapeutic irradiation of the thyroid bed. Staging should include CT scanning of the neck, thorax, abdomen and pelvis, together with bone marrow aspirate and trephine [1].

There exists no universally accepted standard of care for TNHL and a number of controversies exist regarding the roles of surgery, radiotherapy (RT) and chemotherapy in the management of this disease [5–12]. Previously, surgery occupied a pre-eminent place in management and most patients underwent extensive resections. In recent years, however, the appreciation that TNHL is sensitive to RT and chemotherapy has resulted in a move towards limited surgical intervention, usually in the form of a diagnostic biopsy followed by definitive RT (or chemotherapy followed by RT). However, there are opponents of this view who recommend excision or debulking of disease followed by post-operative RT [13–22].

In spite of the controversy regarding the surgical management of TNHL, radical RT became the treatment of choice in most centres, although there has now been a shift towards using a combination of chemotherapy and RT in all cases other than mucosa associated lymphoma tissue (MALT) lymphoma of the thyroid gland. As regards therapeutic irradiation, there remain a number of unresolved issues regarding the volume of tissue that should be treated and the dose prescription required. There are two main options in the selection of radiation treatment fields: (1) involved field RT (IFRT) which aims to include the entire thyroid gland and local neck nodes; and (2) extended field RT (EFRT) which involves treating the thyroid, neck, mediastinal and in some centres, axillary nodes.

These two options have never been formally compared in a randomized study and in view of the rarity of this condition; such a study is unlikely to be conducted. A a result, the choice between IFRT and EFRT has been a matter of clinical judgement based on prior experience.

Similarly, formal evaluation of the optimal radiation dose required for local control has never been undertaken. In line with treatment of nodal and non-thyroid extranodal NHL, most patients with TNHL have received doses in the order of 40 Gy. Previous studies have suggested that there is a threshold dose below which the chance of achieving local control is small. Tupchong et al [23] reported 0% local control rated for patients who received less than 20 Gy. Therefore, in this retrospective analysis, we have attempted to address these two important questions relating to the management of TNHL by RT.

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Patients and methods

Data collection

A search of the Royal Marsden Hospital (RMH) Thyroid Database was undertaken for a period that spanned the years between 1936 and 1996.

This database contains a thorough summary of over 2000 patients presenting to RMH with thyroid malignancy over the last six decades. A total of 91 patients with histologically proven NHL were identified. Case notes were reviewed in order to collect demographic data, details of disease-related symptoms and tumour stage, surgical and radiotherapeutic management and standard outcome measures, including relapse free (RFS) and overall survival (OS). For the purposes of data collection, the results of staging investigations were accepted at face value and no attempt was made to re-evaluate the staging assigned to patients treated at different times. Similarly, the pathological classification of NHL has undergone a number of changes during the period of time under study [24–29]. In a previous study of 46 patients with TNHL from RMH, all of whom are included in this analysis, it was shown that the majority (91%) presented with adverse (intermediate or high grade) histology. Similar findings were apparent for this group of patients. No attempt has been made to review previous pathological specimens or re-classify cases according to the current REAL classification. Of the 91 patients who were identified, 89 were eligible for analysis of the effect of definitive RT. The two patients excluded, received primary chemotherapy without RT.

Follow up

Follow-up data were obtained for all patients treated with RT. RFS and OS times were calculated for each patient to the nearest month, taken from the time of presentation to the time of first relapse (for RFS) or death/last recorded follow-up (for OS).

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS, Inc., Chicago, IL), statistical software. Survival curves were obtained by the Kaplan-Meier method and comparisons were made with the log-rank statistics. Factors found to be significant at univariate analysis were considered for multivariate analysis. Cox proportional hazards models were developed for the multivariate analysis of survival and any value of $p<0.05$ was considered to be statistically significant.

Results

Clinical features

Age and gender

The median age of the patients was 65 years (range 22–87 years). There was no significant difference between the median ages of the female (median 65 years, range 27–87 years) and male (median 63 years, range 22–85 years) patients. There were 77 females and 14 males, representing a female to male ratio of 5.5:1.

Table 1. Summary of patient characteristics for 91 patients with thyroid non-Hodgkin's lymphoma

Patient characteristic	No.	(%)
Female	77	(84.6%)
Male	14	(15.4%)
Stridor	30	(33.7%)
Dysphonia	28	(31.5%)
Previous goitre	31	(34.8%)
Pain	12	(14.1%)
Neck swelling	87	(97.8%)
Dysphagia	47	(53.3%)
Stage 1	35	(38.4%)
Stage 2	49	(53.8%)
Stage 3	4	(4.4%)
Stage 4	3	(3.4%)

Presenting symptoms

The presenting symptoms are documented in Table 1. For two patients, no presenting symptoms were recorded but the vast majority (98%) presented with neck swelling. Local obstructive symptoms (stridor, dysphagia and dysphonia) were frequently reported. A significant number (34%) had previously been noted to have goitre, in many cases of long-standing.

Stage

In keeping with data presented for other studies, the majority of patients presented with early stage disease. 35 had Stage I disease confined to the thyroid gland and 49 had Stage II disease. Only seven patients, were found to have more advanced Stage III or IV disease at presentation. From analysis of the database, it was apparent that these patients presented with massive thyroid enlargement and evidence of dissemination, rather than as patients with widely disseminated lymphoma with incidental involvement of the thyroid gland. Systemic B symptoms were uncommon, occurring in only two patients.

Surgery

All of the patients underwent an initial surgical procedure, the details of which are presented in Table 2.

Radiotherapy

Over the 60 year period in which patients were treated, a number of different treatment protocols were applied involving use of 220–250 kV X-rays, ^{60}Co gamma rays and 4–6 MV photons. The median tumour radiation dose was 40 Gy (range 4–72 Gy), which was delivered at a dose rate of between 1.2 Gy and 2.3 Gy per day.

Table 2. Initial surgical procedure performed on the 91 patients with thyroid non-Hodgkin's lymphoma

Surgical procedure	No.	(%)
Biopsy	43	(45.6%)
Enucleation	2	(2.2%)
Lobectomy	11	(12.0%)
Hemithyroidectomy	6	(7.6%)
Subtotal thyroidectomy	20	(22.8%)
Near total thyroidectomy	6	(6.5%)
Total thyroidectomy	3	(3.3%)

The majority (61 of 89) received a radiation dose of 40 Gy or more. Treatment was usually delivered using parallel-opposed anterior and posterior fields, although, direct anterior, anterior oblique or lateral fields were employed occasionally. Spinal cord shielding was not used. No attempt has been made to assess the effect of technique on outcome. 25 patients received IFRT to the thyroid bed and cervical lymph nodes and 64 patients received EFRT to the thyroid bed, cervical and mediastinal lymph nodes. In this latter group, there were no data detailing the number of patients in whom the superior mediastinal nodes, as opposed to all mediastinal nodes, were treated. The axillary nodes were not treated routinely.

Chemotherapy

27 patients received cytotoxic chemotherapy under a wide variety of circumstances. Two received definitive combination chemotherapy without RT. Five patients received induction chemotherapy prior to radical RT, eight received adjuvant chemotherapy following RT and 14 received chemotherapy following relapse after RT. Clearly, this experience reflects the state of what was considered optimal practice at the time that the patients presented. In current practice, it is likely that the majority of patients would receive combination chemotherapy followed by consolidation radiotherapy.

Regimens comprised cyclophosphamide, vincristine and prednisolone (COP), cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) or prednisolone, mitoxantrone, cyclophosphamide, etoposide, bleomycin and vincristine (PMitCEBO). Analysis of the role of chemotherapy in this cohort of patients was not possible because of the small numbers and the different regimens employed. Eight of 13 patients treated initially with chemotherapy as part of a planned combined approach were long-term survivors. However, results for relapsed disease were generally poor, with only two of eight patients relapsing after RT successfully salvaged with combination chemotherapy.

Outcome and prognostic factors

The overall 5-year survival rate was 48%, with a median RFS of 34 months. Univariate analysis of OS according to patient variables and treatment factors is shown in Table 3. Adverse prognostic factors were as follows: advanced stage, surgical procedure (only biopsy *vs* more debulking procedure), extent of radiation field, radiation dose of 40 Gy or more, and the presence of stridor at diagnosis. A number of these factors have been implicated previously [29–32]. Analysis of the effect of dysphagia, dysphonia and previous goitre on the OS revealed no significant impact. Independent predictive factors obtained from multivariate analysis are shown in Table 4.

Surgical procedure

Analysis of the extent of surgical resection (biopsy alone *vs* more extensive resection), revealed that only in the last decade was there a marked change towards less extensive procedures. Thus, prior to 1990 biopsy was performed in 30 patients compared with 43 who underwent an extensive resection. After 1990, 13 patients underwent biopsy compared with only 5 who had a more extensive resection.

Table 3. Significant factors on univariate analysis of overall survival

Prognostic factors	No	(%) 5 year survival	*p*-value
Stage			
I	34	(72%)	
II	48	(36%)	
III, IV	7	(0%)	<0.001
Surgical procedure			
Biopsy	42	(26%)	
Debulking	47	(66%)	<0.001
Radiation field			
IFRT	25	32%	
EFRT	64	55%	0.04
Radiation dose			
<40 Gy	27	26%	0.002
>40 Gy	62	56%	

IFRT, involved field radiotherapy; EFRT, extended field radiotherapy.

The type of surgical procedure performed had a significant impact on the outcome of subsequent RT as demonstrated in Table 3 ($p<0.001$).

Radiation field (IFRT vs EFRT)

18 of 25 patients (72%) treated with IFRT died of TNHL. The median RFS was only 10 months and the median OS was 21 months. In contrast, only 29 of 64 patients (45%) treated with EFRT died of TNHL. The median RFS was 76 months, while the median OS has not yet been reached. The 5-year survival data according to disease stage stratified by radiation field (IFRT or EFRT) are illustrated in Figures 1 and 2. Patients who received EFRT had higher survival rates ($p<0.005$), (log rank test). For patients treated with IFRT, 52% (20% local alone and 32% combined local and distant) had evidence of locoregional failure at the time of death, compared with only 26% (9% local alone plus 17% local and distant), of patients treated with EFRT. There was no significant difference in the rates of local control between two groups (20% for IFRT *vs* 22% for EFRT). The patterns of failure of patients dying following IFRT and EFRT are detailed in Table 5.

Radiation dose

When the survival data for patients who received <40 Gy were compared with those who received 40 Gy

Table 4. Significant independent factors on multivariate analysis of overall survival

	Hazard ratio (95% CI)	*p*-value
Stage		
I	1	
II	3.74 (1.77–7.92)	
III, IV	6.38 (2.13–19.11)	<0.001
Surgical procedure		
Debulking	1	
Biopsy	3.23 (1.72–6.06)	<0.001
Radiation field		
IFRT	1	
EFRT	0.45 (0.25–0.82)	<0.01

IFRT, involved field radiotherapy; EFRT, extended field radiotherapy.

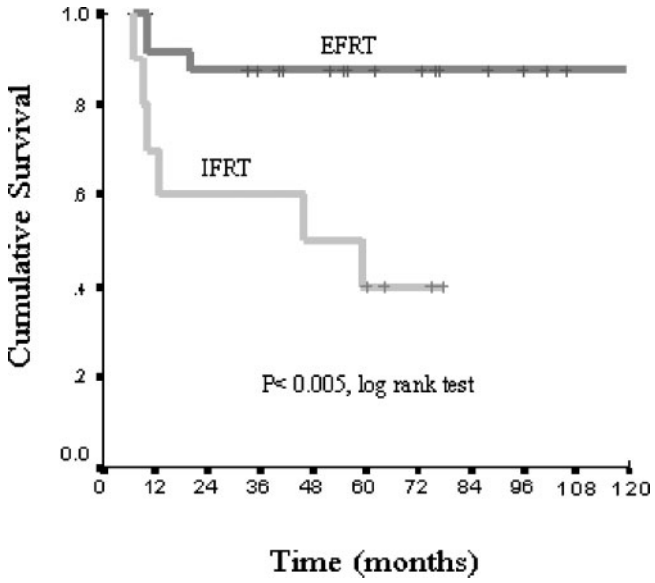

Figure 1. Kaplan-Meier curve showing overall survival of Stage I patients stratified by radiation field (extended field radiotherapy *vs* involved field radiotherapy).

or more, radiation dose was not significant in multivariate analysis of survival (hazard ratio 0.64, 95% confidence interval (CI): 0.33–1.24, $p=0.18$). However, the confidence intervals are wide and it is not possible to rule out an effect. Radiation dose was significant in multivariate analysis for local control (hazard ratio 0.42, 95% CI: 0.18–0.94, $p=0.04$). At 5 years, only 7 of 27 (26%) patients treated at the lower dose level were alive, compared with 35 of 62 (56%) treated to 40 Gy or more ($p<0.01$, log rank test). However, the first group included six patients who received doses of less than 30 Gy; none achieved local control and their maximal survival was 6 months. The effect of radiation dose on outcome is presented in Figure 3.

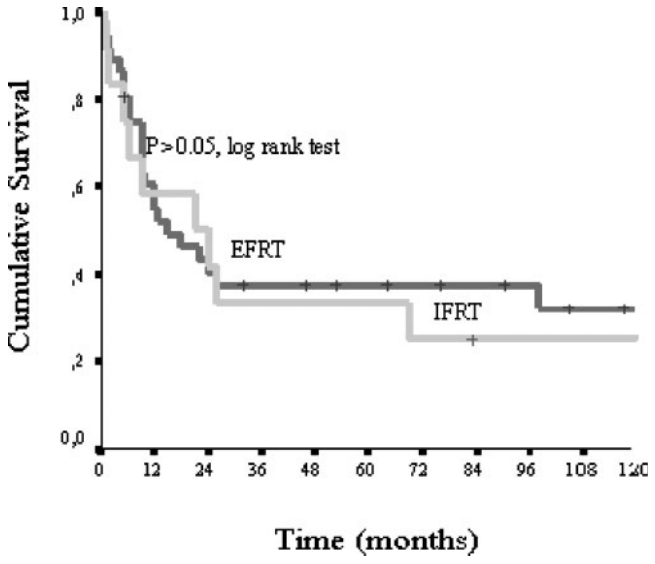

Figure 2. Kaplan-Meier curve showing overall survival of Stage II patients stratified by radiation field (extended field radiotherapy *vs* involved field radiotherapy).

Table 5. Survival according to stage of disease and extent of irradiated volume

Irradiated volume	Stage I	Stage II	Stage III/IV
IFRT	4/10 (40%)	3/12 (25%)	0/3 (0%)
EFRT	22/25 (88%)	13/36 (36.1%)	0/3 (0%)
Total	26/35 (74.3%)	16/48 (33.3%)	0/6 (0%)

IFRT, involved field radiotherapy; EFRT, extended field radiotherapy.

Discussion

Analysis of the data from this large series of patients with TNHL treated over a prolonged period of time in a single centre provides valuable insights in to the management of this uncommon disease. RT has traditionally played a major role in treatment of TNHL and the findings of this study have direct bearing on its use. Multivariate analysis has highlighted the extent of radiation field as an independent prognostic factor. RFS and OS rates were significantly better for patients treated with EFRT compared with IFRT; this difference was not seen in Stage II disease. This effect seemed to be mediated at the level of the thyroid bed and adjacent lymph nodes in the neck and mediastinum because 52% of patients treated with IFRT experienced locoregional failure compared with only 27% of patients treated with EFRT. There was no difference between the two groups in terms of systemic relapse. Therefore, the poor results of IFRT in all disease stages mean that this approach should be abandoned in favour of more extensive radiation fields that encompass the mediastinal nodes. For patients with Stage I disease, definitive EFRT yielded excellent rates of local control and survival and represented the treatment of choice. However, more recently, combination chemotherapy followed by RT has become the standard of care for this disease and given the data from this study, EFRT should be considered as the standard RT technique.

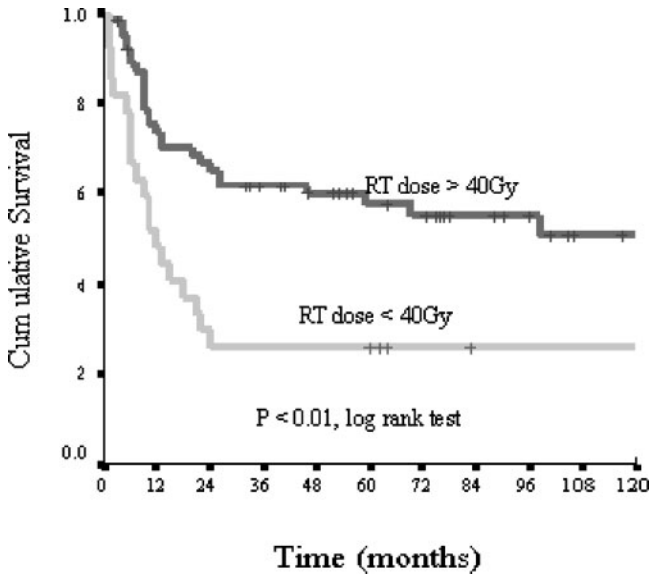

Figure 3. Kaplan-Meier curve showing overall survival of patients according to the radiation dose received (<40 Gy *vs* 40 Gy or more).

Similarly, analysis of outcomes at radiation doses below 40 Gy versus 40 Gy or more provides clear indications for clinical practice. A threshold dose of 40 Gy or more was shown to be associated with a significantly improved local control outcome. This is in keeping with previous data [23] and we suggest a standard dose of 40 Gy in 20 fractions for this disease.

The data on extent of surgical resection indicate a significantly improved outcome in patients who underwent a debulking procedure (defined as anything more than a biopsy) prior to RT and concur with those reported in previous studies [33, 34]. Patients who had total macroscopic removal of tumour had the highest rate of local control and long term survival ($p<0.001$). No significant differences were seen between lobectomy, subtotal or total thyroidectomy, although seven of nine long-term survivors (58–129 months) underwent total thyroidectomy. Despite these findings, it is unlikely that the trend towards performing open biopsy to make a tissue diagnosis will be reversed. The increasing role of combination chemotherapy and consolidating RT is likely to strengthen the move towards more conservative surgical intervention [32, 34–36].

The precise role of combination chemotherapy in TNHL remains to be defined, although in recent years it has become part of the standard management of this disease. This study demonstrates the generally poor results obtained with RT alone, even with EFRT, in patients with anything more than Stage I disease and provide strong support for the use of chemotherapy as part of the primary treatment. The ability of chemotherapy to "debulk" the tumour prior to starting RT (in an analogous fashion to surgical debulking) represents a further attraction. Indeed, despite the fact that low-grade MALT lymphomas have a low distant recurrence rate [26, 28], a review of the published literature suggests that the addition of chemotherapy to RT significantly reduces both distant and overall recurrence [37–41].

In conclusion, the following recommendations are made for the management of TNHL. IFRT yields unacceptable rates of disease free survival and OS and can not be recommended. EFRT to a dose of 40 Gy is effective for Stage I.

For Stage II–IV disease, EFRT is associated with poor outcome; these patients should receive induction chemotherapy followed by consolidation EFRT to a dose of 40 Gy.

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