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Primary Lymphoma of the Thyroid: A Review of the Mayo Clinic Experience Through 1978

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At the Mayo Clinic, 103 patients with primary malignant lymphoma of the thyroid have been diagnosed and treated through 1978. This study examines the clinical findings in the 57 new cases seen since the last review in 1966; pathology and survival are evaluated for the series as a whole, including the 46 patients reported previously. Age and sex patterns were unchanged since the earlier review; thyroid lymphoma tended to occur in middle- to older-aged women, and patients typically presented with a fairly rapidly enlarging, painless, and firm thyroid mass. The most common histologic subtype of lymphoma encountered was diffuse large cell (diffuse histiocytic). Hashimoto's disease was found in 36% of the pathologic specimens available for review. Follow-up was completed for all patients up to 1979. Age, sex, and histologic subtype of tumor did not appear to be significant determinants of prognosis. Patients in whom the lymphoma was confined to the thyroid (intrathyroidal type) had a better overall 5-year survival rate (86%) than those in whom tumor invaded soft tissues surrounding the thyroid or involved regional cervical nodes (38% for the extrathyroidal type). Almost all of the patients who had intrathyroidal tumors underwent surgical resection before irradiation. However, 3 of the 5 patients in this group who were treated by radiotherapy alone survived more than 5 years. There were approximately equal numbers of patients with the extrathyroidal type of lymphoma who were treated either by radiotherapy combined with surgical resection or by radiotherapy alone. The one form of therapy was just as effective as the other.

The Mayo Clinic experience with primary lymphoma of the thyroid was last reported more than 14 years ago. At that time Woolner et al. [1] described the clinical and pathologic features and the therapeutic results in 46 patients who had been diagnosed and treated at this institution up to December, 1964. Since then, some 4 to 5 new cases have been seen every year, so that experience with an additional 57 patients has now accumulated. The clinical findings in this new group of patients are reviewed in the following study. For better evaluation of pathologic patterns and survival, the 46 cases from the earlier report have been pooled with the 57 new cases, to make a combined series of 103 patients.

One of our principal aims in undertaking this retrospective review was to reexamine and possibly extend previous observations concerning the relative importance of various clinical and pathologic determinants of prognosis. We were also intrigued by the possibility of comparing the results of 2 different forms of treatment for the same stage of disease, namely, radical extirpative surgery plus external radiotherapy versus radiotherapy alone. Given the rarity of this disease, with only about 250 cases reported to date in the medical literature [2], the opportunity to study a cohort of 103 patients, all of whom have been managed in a single institution, is unique.

Materials and Methods

The records of all patients with thyroid lymphoma seen at the Mayo Clinic through 1978 were reviewed. After cases had been rejected in which

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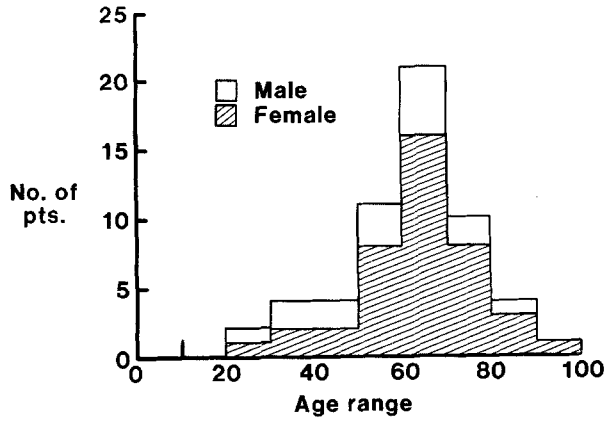

Fig. 1. Age and sex distribution for 57 patients with primary lymphoma of the thyroid seen at the Mayo Clinic from 1964 through 1978.

there was evidence of systemic tumor involvement at the time of surgery, 103 patients remained. Specimens were available from 86 of the 103 cases for detailed histopathologic review. The diagnoses of histologic subtype were classified according to the formulation proposed in the recent National Cancer Institute multi-institutional comparison study of non-Hodgkin's lymphoma *(personal communication)*. Particular attention was paid to the manner of clinical presentation, gross findings at surgery, specific pathologic diagnosis, evidence of associated lymphocytic thyroiditis, form of treatment, and length of survival. All patients were followed up until death or to 1979.

Results

Clinical Data

Woolner et al. [1] detailed the clinical data for all patients who presented at our institution with thyroid lymphoma before 1964. Of the 57 new patients seen since 1964, 41 were women and 16 were men, the sex ratio being 2.6 females to 1 male. Their ages ranged from 25 to 90 years (Fig. 1), with a mean age of 61.5 years and a median age of 64 years. Almost 75% of the patients were between 50 and 80 years of age.

The usual presenting complaint was of a painless, enlarging mass in the neck (Table 1). Three patients gave a history of long-standing goiter, and 6 had previous thyroidectomies (all for benign disease). Only 10 patients presented with symptoms other than a mass. All had a palpably enlarged thyroid gland on physical examination. It was unusual for the mass to be painful, although pressure symptoms such as stridor, shortness of breath, and dysphagia were not uncommon. Fourteen patients complained of hoarseness at the time of presentation, but only 9 of the 14 had vocal cord paralysis. The median duration of symptoms was just 2 months.

Table 1. Presenting complaints and physical findings in 57 patients with primary lymphoma of the thyroid (1964–1978).

Complaint or finding	% of patients
Lump in the neck	82
Hoarseness	25
Stridor, shortness of breath	17
Dysphagia	21
Local pain	9
Palpable neck mass	100
Vocal cord paralysis	10
Tracheal deviation	9

Seventeen patients had evidence of tracheal narrowing and/or deviation on chest x-ray, and in 5 the enlarged thyroid gland could be seen as a superior mediastinal mass. A thyroid scintiscan was obtained in 29 patients and showed either a patchy uptake or no uptake at all in the area of the tumor. Total serum thyroxine levels were obtained in 32 patients, and 19 were in the subnormal range. The preoperative diagnosis was either thyroid malignancy (with the specific possibility of lymphoma mentioned in 5 cases) or thyroiditis.

Type of Treatment

Since 1964, all but 1 patient received external radiation therapy to the thyroid gland after biopsy or resection. Doses ranged from 1600 to 6000 rads, with an average dose of approximately 3900 rads. The precise radiation field varied according to the extent of known or presumed tumor involvement.

Radical resection of tumor was attempted in 45 of the 57 patients seen since 1964. Open biopsy was performed in 9 patients and percutaneous needle biopsy in 3. Prophylactic tracheostomy was performed at the time of open biopsy in 10 patients in anticipation of subsequent compromise of an already narrowed airway. One other patient, who underwent total thyroidectomy for complete excision of the tumor, also had a tracheostomy at the time of surgery because of concern that both recurrent laryngeal nerves had been injured (they had not).

Table 2 details the postoperative complications encountered in 7 of the 37 patients (19%) who had their surgery at the Mayo Clinic since 1964. It was impossible to make an accurate assessment of the operative morbidity in the 20 patients who had their surgery or biopsy elsewhere, but it is worth mentioning that 1 patient who had a subtotal thyroidec-

Table 2. Surgical complications in a series of 37 patients operated on at the Mayo Clinic.

Patient no.	Operative procedure	Complication
1	Total thyroidectomy and excision of lymph nodes	Left vocal cord paralysis, hypoparathyroidism
2	Total thyroidectomy and tracheostomy	Hypoparathyroidism
3	Bilateral subtotal thyroid-ectomy and tracheostomy	Infected tracheostomy site, gastrointestinal bleeding
4	Bilateral subtotal thyroid-ectomy and tracheostomy	Myocardial infarction
5	Subtotal right lobectomy	Acute airway obstruction
6	Open biopsy and tracheostomy	Pneumonia, lung abscess, wound infection leading to generalized sepsis and death on 24th post-operative day
7	Open biopsy	Acute airway obstruction

Table 3. Histopathologic findings in 86 cases of thyroid lymphoma in which thyroid specimens were available for review.

Histologic subtype*	Number of patients (n = 86)	Associated Hashimoto's disease (n = 31)	Extra-thyroidal	Intra-thyroidal
Small lymphocytic	4	2	2	2
Follicular small cleaved	4	1	3	1
Follicular mixed	5	1	4	1
Plasmacytoma	3	1		3
Diffuse small cleaved	16	4	12	4
Diffuse mixed	16	7	11	5
Follicular large cell	1	1	1	
Diffuse large cell (FCC)†	34	13	26	8
Immunoblastic	1	1		1
Unclassifiable	2			2

*National Cancer Institute formulation of non-Hodgkin's lymphoma (*personal communication*).
†Follicular center cell.

tomy and tracheostomy at a referring hospital was found to have bilateral vocal cord paralysis and hypoparathyroidism when seen here.

Pathology

Specimens were available from 86 of the 103 patients for detailed histopathologic review. The breakdown of histologic subtypes is given in Table 3, along with information relating to the local extent of tumor. Thirty-one (36%) specimens also showed evidence of associated Hashimoto's disease, as defined by Woolner et al. [3], in areas of residual tissue adjacent to the lymphoma.

It was apparent from the pathology reports or operative records that tumor had spread beyond the confines of the thyroid capsule to invade surrounding soft tissues or regional lymph nodes in 74 of the 103 patients (72%).

Survival

Follow-up data were available for all patients up to 1979. Standard actuarial survival curves were calculated for the combined series of 103 patients seen at the Mayo Clinic through 1978, and for the early and late periods of the study (Fig. 2). The overall 5-year survival rate for the patient group as a whole was 50%. Survival curves were compared for the effects of age (Fig. 3), sex (Fig. 4), histologic type (Fig. 5), extent of tumor (Fig. 6), and completeness of tumor excision (Fig. 7).

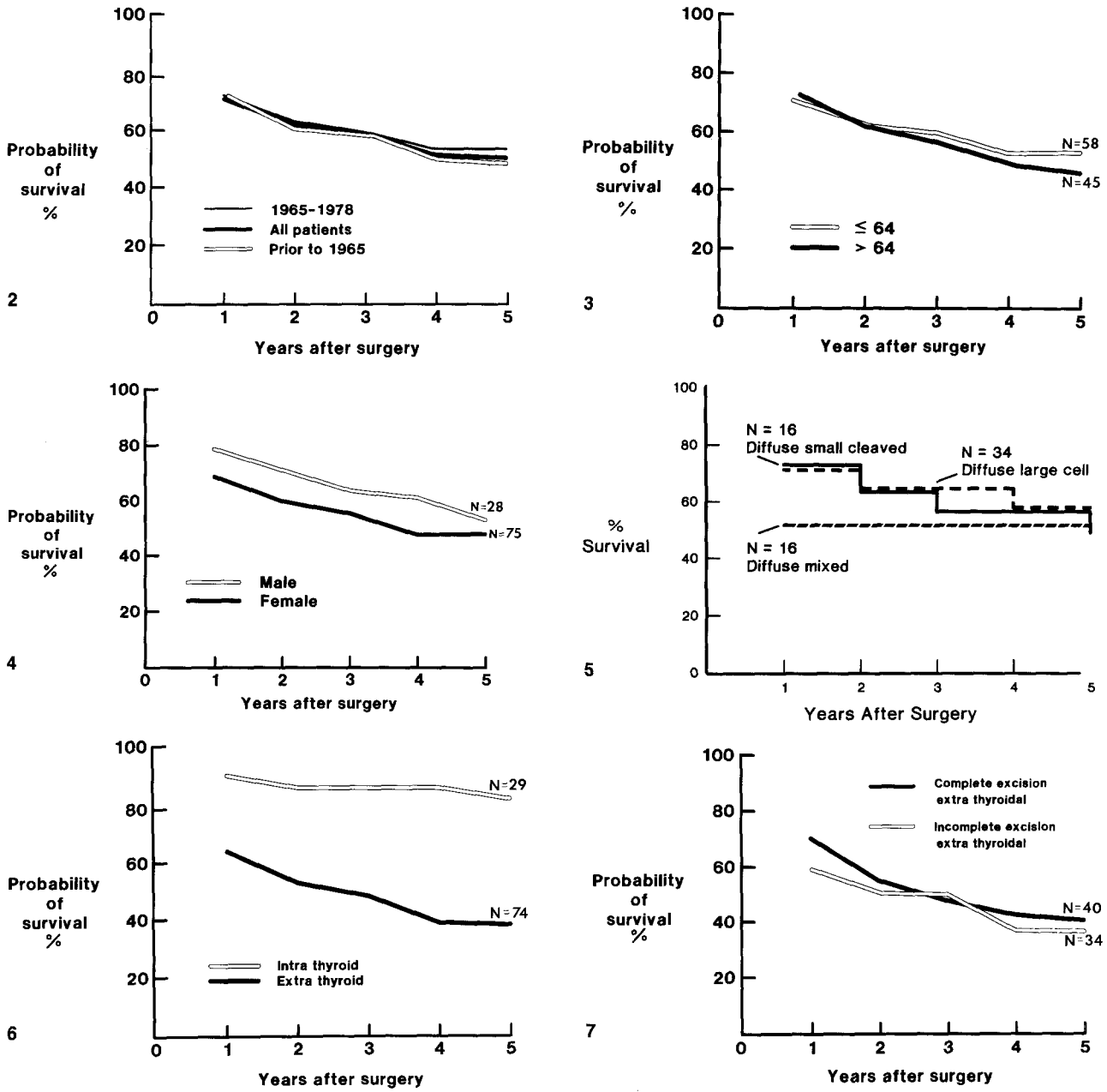

Fig. 2. Actuarial survival curves for 103 patients with primary lymphoma of the thyroid seen at the Mayo Clinic through 1978, with a comparison of results in 2 time periods.

Fig. 3. Effect of age on survival of 103 patients with primary lymphoma of the thyroid. The curves are not significantly different ($P > 0.05$).

Fig. 4. Effect of sex on survival of 103 patients with primary lymphoma of the thyroid. The curves are not significantly different ($P > 0.05$).

Fig. 5. Effect of histologic subtype of primary thyroid lymphoma on survival. Prognosis for the 3 most common histologic subtypes is compared. The numbers of patients belonging to other subtypes were insufficient for statistical analysis.

Fig. 6. Effect of extent of tumor on survival of 103 patients with primary lymphoma of the thyroid. Survival rate was significantly better when the tumor was confined to the thyroid at the time of treatment ($P < 0.01$).

Fig. 7. Effect of completeness of surgical resection of tumor on survival of 74 patients with the extrathyroidal type of primary lymphoma of the thyroid. Curves were not significantly different for the complete versus incomplete tumor resection treatment groups when the lymphoma was extrathyroidal. The sample size was too small for valid statistical comparison of complete and incomplete excision of the intrathyroidal type of lymphoma.

Discussion

The typical clinical profile of primary thyroid lymphoma is a middle- to older-aged woman who presents with a fairly rapidly enlarging (and usually painless), firm thyroid mass. This composite picture emerges clearly from the present study and confirms similar observations made by others [1, 2, 4–6]. We could find no evidence to support the recent suggestion by Sirota and Segal [2] that the epidemiology of this disease might be changing because of increased exposure to chemical or radiation risk factors. Age and sex patterns and the preponderant histologic subtypes of lymphoma were unchanged from those reported in the last review from this institution [1].

Hashimoto's disease was found in the resected or biopsy specimens in 31 of the 86 cases (36%) available for detailed review. This figure probably underestimates the true frequency of association of these 2 diseases because in some cases the biopsy provided an insufficient sample of thyroid tissue outside of the tumor, while in others the lymphoma replaced the entire gland and left no residual thyroid tissue for evaluation of thyroiditis. It is consistent, however, with other reports in the literature that describe coexistent Hashimoto's thyroiditis and thyroid lymphoma in 25% [2] to 77% [5] of cases. Burke et al. [5] suggested that the strong association between the 2 diseases may indicate a causal relationship in which chronic antigenic stimulation of lymphocytes causes their eventual transformation into lymphoma cells. As evidence of this, they report having often observed "an apparent subtle transition of the hyperplastic type of thyroiditis with large reactive germinal centers to a massive nodular type of malignant lymphoma." If such a causal relationship exists, however, it is not clear why so few patients with Hashimoto's disease go on to have thyroid lymphoma.

The overall 5-year survival rate for the combined series of 103 patients seen at the Mayo Clinic through 1979 was 50%. This figure is similar to the 54% 5-year survival for 32 patients recently reported by the group from the M.D. Anderson Hospital [5]. There are no other published series of comparable size with which we can make any valid statistical comparisons. Woolner et al. [1] reported an actuarial 5-year survival rate of 44% in the 1966 report from this institution. The last review of the medical literature concerning thyroid lymphoma was in 1958 [7], at which time the 5-year survival rate was reported to be only 20%. Perhaps these data can be taken as evidence of some progress in the treatment of this condition. The only significant change in the mode of therapy during the past 50 years was the introduction, in approximately 1955, of cobalt-60 teletherapy in place of 250-kilovolt x-ray therapy [8]. Both Crile [8] and Woolner et al. [1] speculated that the higher dose of local irradiation delivered by cobalt-60 teletherapy was probably responsible for the improvement in results seen after the late 1950's.

We attempted to correlate the course of the disease with a number of variables, including age, sex, histologic subtype of tumor, extent of tumor, and completeness of tumor excision. We were unable to confirm the observation of Burke et al. [5] that survival was better for patients in the group under 65 years of age. From our study it appeared that the only factors that might be considered as having any significant bearing on prognosis were extent of tumor and completeness of tumor excision. In accordance with what others have reported (*personal communication*), there was no difference in 5-year survival rates among the 3 most common histologic types of tumor (Fig. 5). These 3 types had earlier been categorized in an "intermediate" predictive grouping with regard to long-term survival (*personal communication*).

With regard to extent of tumor, extrathyroidal spread of tumor, either by direct soft tissue invasion or by regional lymph node involvement, had a distinctly adverse effect on prognosis. The 5-year survival rate for the 74 patients in whom lymphoma had spread beyond the confines of the thyroid capsule was 38%, in contrast to 86% for those in whom the tumor was still confined to the thyroid ($p < 0.01$).

Regarding completeness of tumor excision, the usefulness of surgery in the management of primary thyroid lymphoma has been debated for years. Crile [8] and Heimann et al. [9] claimed that radiation therapy alone was as effective as the combination of radiotherapy and surgical resection in these cases, while others [6] have maintained just the opposite. Woolner et al. [1], in their 1966 review of the Mayo Clinic experience, admitted to being encouraged by the results of heavy irradiation alone in 4 patients with presumably inoperable tumors who were apparently cured of their disease. The tendency in the past has been to attempt surgical resection whenever a tumor was small or confined to the thyroid, and to resort to radiotherapy alone only when the lymphoma was of the inoperable extrathyroidal type. This has to be taken into account when interpreting published survival statistics because the inevitable effect is to bias adversely the results of treatment by radiotherapy alone. It is important, therefore, when comparing the results of different modes of treatment, to separate patients into intrathyroidal and extrathyroidal tumor groups. When this was done with the data from the present study, we found that no significant survival advantage was

afforded by combining surgical resection with radiotherapy to treat lymphoma of the extrathyroidal type; patients treated with radiotherapy alone did just as well. This observation held true even when surgical resection was thought to have eradicated all gross local tumor (Fig. 7). The 5-year survival rate was 40% for the 40 patients with extrathyroidal tumor who had all gross tumor excised prior to radiotherapy, compared with 37% for the 34 patients who had incomplete tumor excision or just a simple biopsy before neck irradiation.

Only 5 of the 29 patients with intrathyroidal lymphomas did not undergo surgical resection of their tumors. The sample is too small for statistical comparison with the 24 other patients who had the tumors locally eradicated before irradiation. However, of the 5 who had radiotherapy alone, 2 died within a year whereas 3 survived 5 years or longer (60%). The 5-year survival rate for patients who had combined surgical resection and radiotherapy was 91%.

Our data do not permit any firm conclusions regarding optimal therapy for primary lymphoma of the thyroid gland when the disease is apparently confined to the thyroid (intrathyroidal type). Probably resection of the tumor by total thyroidectomy should be performed, with subsequent local irradiation in these cases. In patients in whom thyroid lymphoma is locally invasive into the surrounding soft tissues or when it also involves regional lymph nodes (extrathyroidal type), it would seem reasonable to avoid surgical resection, with all its attendant risks and potential complications (Table 2). Having confirmed the diagnosis by fine needle aspiration cytology [10, 11] or by core needle biopsy [11] (these techniques are so accurate that open biopsy should rarely be needed), one can proceed directly with radiotherapy.

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