World J. Surg. 16, 604–610, 1992

World Journal of Surgery

Non-Hodgkin's Lymphoma of the Thyroid: Is More than Biopsy Necessary?

Christopher M. Pyke, M.B., Clive S. Grant, M.D., Thomas M. Habermann, M.D., Paul J. Kurtin, M.D., Jon A. van Heerden, M.B., Erik J. Bergstralh, M.S., Allen Kunselman, B.S., and Ian D. Hay, M.B., Ph.D.

Departments of Surgery and Pathology, Divisions of Hematology, Biostatistics, and Endocrinology, Mayo Clinic and Foundation, Rochester, Minnesota, U.S.A.

Whereas excisional surgery and radiotherapy have resulted in a favorable outcome when non-Hodgkin's lymphoma of the thyroid (NHLT) is confined to the thyroid gland, controversy persists over the potential advantage of aggressive debulking in favor of diagnostic biopsy alone when disease cannot be completely resected. Our aims in this study were to delineate the present role of surgery in NHLT in pre-operative staging, the impact of the extent of resection on achieving complete remission and cause-specific survival, and patterns of failure. All 62 patients who underwent primary surgery for NHLT at the Mayo Clinic between 1965 and 1989 were analyzed. By postoperative staging, 50 patients were stage IE or IIE. Overall survival was 53% and 46% at 5 and 10 years; 80% for stage IE confined to the thyroid, 58% for stage IE-extrathyroid, 50% for stage IIE, and 36% for stages IIIE and IVE. Complete remission was achieved in 88% of patients who underwent diagnostic biopsy plus adjuvant therapy alone compared to 85% for patients in whom debulking plus adjuvant therapy was used. There was no difference in cause-specific survival in these two groups or in cause-specific survival in two subgroups who achieved complete remission. Relapse after complete remission occurred in 12 (26%) of 46 patients, only 2 of whom survived long-term after salvage therapy. The role of surgery in NHLT is diminishing and advances that will increase complete remission and relapse-free survival will not likely involve more aggressive surgical resections.

In general, the role of surgery in non-Hodgkin's lymphoma has been limited to providing an adequate diagnostic biopsy. Because non-Hodgkin's lymphoma is usually a systemic disease, a surgical approach alone, because of its rather localized nature, has seen limited application in the treatment of this entity. Radiotherapy and chemotherapy provide effective definitive treatment. Even in early stage extra-nodal lymphoma such as primary gastric lymphoma, radiation therapy is usually an adjunct to gastric resection. The logical extension of these well accepted concepts has caused the role of surgery in non-Hodgkin's lymphoma of the thyroid (NHLT) to come under increasing scrutiny during the last decade.

A number of factors regarding NHLT have been clarified. Facilitated by the diagnostic use of monoclonal antibody techniques, NHLT has been recognized more frequently in cases previously misclassified either as Hashimoto's thyroiditis [1] or small-cell anaplastic carcinoma [2]. The Working Formulation has been adopted for consistent histopathological classification [3]. Mucosa-associated lymphoid tissue (MALT), with its associated favorable prognosis, has been postulated to be the origin of many cases of NHLT [4, 5]. Moreover, the fact that all NHLT arise from B-cell lymphocytes [6] and that there may be one of two chromosomal abnormalities consistently found in these tumors [7] have been reported. Pre-operative fine needle aspiration (FNA) cytology is usually strongly suspicious, if not clearly positive, for the diagnosis. The efficacy of Adriamycin has led to the suggestion that chemotherapy might supplant radiation therapy in the primary treatment of this disease [8].

Whereas excisional surgery and radiotherapy have resulted in a favorable outcome when NHLT is confined to the thyroid gland [9], controversy persists over the potential advantage of aggressive debulking in favor of diagnostic biopsy alone when disease cannot be completely resected due to local invasion or nodal metastasis. Some have suggested that radiotherapy is more successful in achieving a complete remission following debulking rather than biopsy alone [10, 11].

Our aims in this study were to delineate the present role of surgery in NHLT specifically in pre-operative staging, the impact of the extent of resection on achieving complete remission (CR) and relapse-free survival, and patterns of treatment failure.

Materials and Methods

The records of all 62 patients who underwent primary surgery for NHLT at the Mayo Clinic between 1965 and 1989 were studied. Excluded from this study were those who underwent primary surgical exploration elsewhere and those with systemic non-Hodgkin's lymphoma involving the thyroid secondarily. Pathology was reviewed and diagnoses reassigned according to the Working Formulation and Kiel Classifications.

In addition to demographic factors, particular attention was paid to the mode of diagnosis, staging, response to primary therapy, recurrence, and mortality. For inclusion in the study, primary therapy must have been given within 6 months of tissue diagnosis. Complete remission (CR) was defined as complete

Presented at the International Association of Endocrine Surgeons in Stockholm, Sweden, August, 1991.

Reprint requests: Clive S. Grant, M.D., Mayo Clinic, 200 First Street, SW, Rochester, Minnesota 55905, U.S.A.

Table 1. Pre-operative versus postoperative stage.

Pre-operative stage (n)	Postoperative Stage (n)				
	IE			IIIE or IVE	Unknown
	Localized to thyroid	Locally invasive	IIE		
IE (39)					
Localized to thyroid	4	11	6	2	0
Locally invasive	0	11	2	2	1
IIE (9)	0	1	7	1	0
IIIE or IVE (5)	0	0	0	5	0
Unsuspected (8)	1	5	1	1	0
Unknown (1)	1	0	0	0	0
Total	6	28	16	11	1

n: Number of patients.

Table 2. Pathologic classification by grade and stage.

Working Formulation				Keil	
Grade					
Low	9			12	
Intermediate	42				
High	5			44	
Stage					
	Low	Int[a]	High	Low	High
IE	6	25	1	7	25
IIE	1	9	3	2	11
IIIE + IVE	2	7	1	3	7

[a]Int: Intermediate.

resolution of disease following primary therapy. Radiotherapy was classified as adequate (≥3900 cGy) or inadequate (≤3900 cGy) [10]. Tumors were staged in accordance with the American Joint Committee on Cancer classification as modified from the Ann Arbor classification for Hodgkin's lymphoma. Within stage IE, NHLT was also subclassified as to whether it was localized within the thyroid capsule or invaded adjacent soft tissue.

Patients were followed by physician examination, patient questionnaire, or death certificate through March, 1991. Median follow-up was 50.5 months. A single patient was lost to follow-up and was included only in the demographic analysis.

Results

Demographics

There were 17 males and 45 females with a median age of 65 years (range, 25–90 years). A CR was achieved in 46 (74%) patients, of whom 12 had a recurrence. By postoperative staging, 50 patients were Stage IE or IIE and 11 (18%) patients were Stages IIIE and IVE (Table 1). Of 39 patients who were staged pre-operatively as IE, only 26 (67%) patients fit this designation postoperatively. At the completion of the study 36 patients were dead, of whom 21 had died of disease.

Pathology

Because 75% of the evaluable tumors were classified as intermediate grade by the Working Formulation (Table 2), comparison of survival with low and high grade tumors would not be statistically meaningful. Patient survival rates in the low or high grade tumors by the Kiel classification (Table 2) were not significantly different ($p = 0.430$). Only 9 of 56 tumors were considered MALT lesions and were no different in survival than non-MALT tumors ($p = 0.615$).

Pre-Operative Management

Lymphoma was diagnosed pre-operatively in 22 patients, whereas malignancy of unspecified type was identified in 32 patients pre-operatively. Diagnosis by FNA cytology was attempted in 20 patients and was positive in 5 patients, suspicious in 12 patients, and inconclusive in 3 patients. There were no false-negative results. Core-needle biopsies were performed on 4 patients, with 1 false-negative result (obtained prior to referral to our institution). Patients were staged pre-operatively according to their presumptive diagnosis, but in 8 patients NHLT was unsuspected. In the 11 patients where the disease was documented postoperatively to have spread beyond the mediastinum, i.e., Stage IIIE or IVE, 5 (45%) patients had been diagnosed pre-operatively (Table 1).

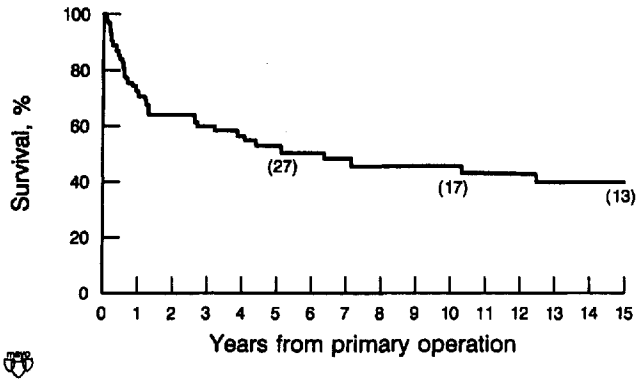

Fig. 1. Overall survival of entire patient series (n = 62). ( ): Number of patients remaining at 5, 10, and 15 years.

Treatment and Survival

Six patients underwent thyroidectomy without adjuvant therapy. Resection plus radiotherapy was used in 42 patients. Operation plus chemotherapy was the initial treatment in 10 patients, and a combination of all 3 treatments occurred in 4 patients. Overall survival of the entire patient group was 60%, 53%, and 46% at 3, 5, and 10 years, respectively (Figure 1). Individual five-year survival rates were: stage IE—confined to thyroid capsule: 80%; stage IE—with extrathyroidal invasion: 58%; stage IIE: 50%; and stages IIIE and IVE: 36% (Figure 2).

Of the stage IE patients, 2 underwent surgical resection as the only treatment, both of whom were thought to have no residual disease at the completion of the operation. They both had a CR and have remained free of disease. Considering all 50 patients with stage IE and IIE, primary therapy resulted in CR in 43

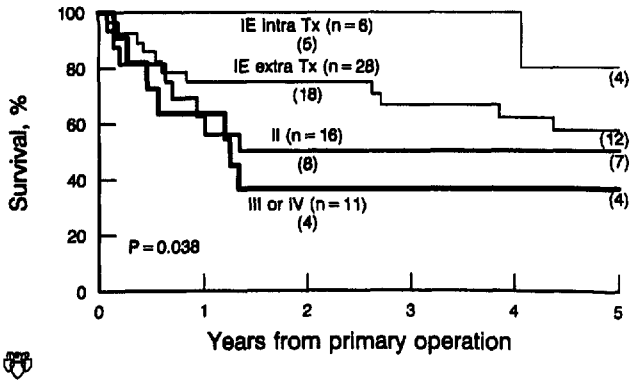

Fig. 2. Survival according to disease stage. ( ): Number of patients remaining at 2 and 5 years.

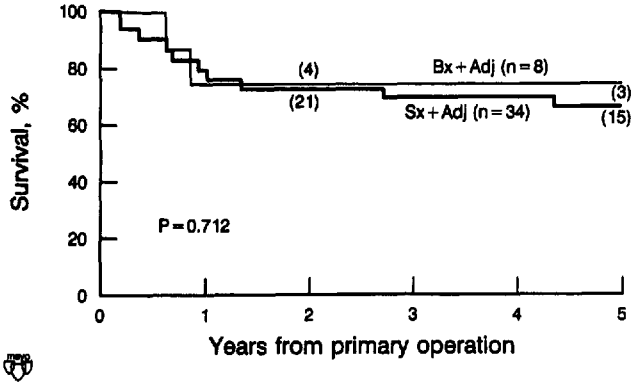

Fig. 3. Cause-specific survival by treatment type for stages IE—extrathyroid and IIE. ( ): Number of patients remaining at 2 and 5 years; Bx: Biopsy alone; Adj: Adjuvant therapy.

Table 3. Outcome according to stage and primary treatment.

Postoperative stage (n)	Primary treatment (n)	CR	Relapse
IE, intrathyroid (6)			
Bx + RTx	2	2	
Sx only	1	1	
Sx + RTx	3	3	
IE, extrathyroid (28)			
Bx + RTx	7	6	1
Bx + CTx	1	1	
Sx only	1	1	
Sx + CTx	1	1	
Sx + RTx	16	15	5
Sx + RTx + CTx	2	1	
IIE (16)			
Sx only	1	0	
Sx + CTx	2	1	1
Sx + RTx	11	9	3
Sx + RTx + CTx	2	2	1

n: Number of patients; CR: Complete remission; Bx: Biopsy alone; Sx: Surgical resection; RTx: Radiation therapy; and CTx: Chemotherapy.

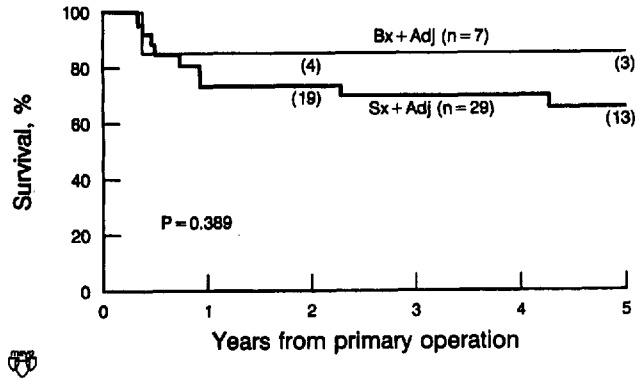

Fig. 4. Cause-specific survival by treatment type for stages IE—extrathyroid and IIE with complete remission. ( ): Number of patients remaining at 2 and 5 years; Bx + Adj: Biopsy plus adjuvant therapy; Sx + Adj: Surgery plus adjuvant therapy.

(86%) patients, of whom 37 did not undergo chemotherapy (Table 3).

In patients with stage IE (extra-thyroid) and stage IIE disease, 7 (88%) of 8 patients who underwent diagnostic biopsy plus adjuvant therapy alone achieved CR. This is compared to 29 (85%) of 34 patients in whom more substantial debulking of disease was followed by adjuvant therapy (Table 3). There was no significant difference comparing cause-specific survival (CSS) in these two groups (Figure 3) or in CSS in two subgroups who achieved CR (Figure 4).

No operative mortality occurred, and complications specifically related to the operative procedure occurred in 6.5%, including 2 patients with permanent recurrent laryngeal nerve injury, 1 patient with permanent hypoparathyroidism, and 1 patient with a wound infection. Four other patients experienced cardiac or respiratory problems.

Patterns of Recurrence

Recurrence was documented in 12 (26%) of 46 patients who had obtained a CR, the details of which are listed in Table 4. Only 3 patients with disseminated disease (Stage IIIE or IVE) achieved a CR. Recurrences became evident early, with only 2 patients relapsing >4 years following primary treatment. Following adequate radiation therapy, only 2 patients experienced relapse in the treatment field, both with high-grade disease. Of the 10 patients who recurred outside of the field of radiotherapy, 6 patients recurred in multiple sites. No patient had an isolated axillary recurrence, and relapses limited to subdiaphragmatic and retroperitoneal nodes were noted in only 2 patients.

Cervical recurrence occurred in 6 patients, 2 patients with nodal disease and 4 patients in the operative site. The 2 patients with nodal disease resolved with additional radiation therapy. Two of the other 4 patients responded to additional chemotherapy and 1 patient responded to salvage radiotherapy. The other patient had tracheal wall recurrence necessitating tracheostomy.

Persistent disease was noted in 2 patients, one of whom responded to additional radiotherapy. The other patient, whose initial therapy consisted of a combination of palliative debulking, radiotherapy, and chemotherapy, underwent completion thyroidectomy elsewhere, only to have further local recur-

Table 4. Treatment failures.

Pt. no.	Treatment	Intent of surgery	Post-op stage	Field of RTx	Adequate RTx dose?	Site of recurrence	Time to recurrence (mos)	Salvage therapy (mos)	Survival (mos)	Outcome
1	Sx + RTx	Cure	IE	Neck	Yes	Retroperitoneal nodes	11	RTx	1	DOD
2	Sx + RTx	Cure	IE	Neck, mediastinum, axilla	Yes	Jejunal perforation	4	None	0.5	DOD
3	Sx + RTx	Cure	IE	Neck, mediastinum	Yes	Left lung	20	Sx × 5	192	AWD
4	Sx + RTx	Palliate	IE	Mediastinum	Yes	Para-aortic nodes	54	None	1	DOD
5	Bx + RTx	Biopsy	IE	Neck, mediastinum	Yes	Lingual tonsil, pelvis, bowel	5	RTx	3	DOD
6	Sx + CTx	Palliate	IIE			Salivary glands, neck nodes, mediastinum		RTx	4	DOD
7	Sx + RTx	Cure	IIE	Neck, mediastinum	Yes	Trachea, superior mediastinum	4	CTx	5	DOD
8	Sx + RTx + CTx	Palliate	IIE	Neck, mediastinum	Yes	Operative site, mediastinum	103	Sx + CTx	20	DOD
9	Bx + RTx	Biopsy	IIIE	Neck, mediastinum	No	Operative site, mediastinum axilla	11	CTx	3	DOD
10	Sx + RTx	Palliate	IIE	Neck, mediastinum	No	Operative site, mediastinum, axilla, para-aortic node	5	RTx	2	DOD
11	Sx + RTx	Palliate	IE	Neck	No	Operative site, mediastinum, para-aortic nodes	24	RTx	5	DOD
12	Sx + RTx	Palliate	IE	Neck	No	Cervical node, axilla	5	RTx	144	Died

Post-op: Postoperative; Sx: Surgical resection; RTx: Radiation therapy; Bx: Biopsy; CTx: Chemotherapy; DOD: Dead of disease; AWD: Alive with disease; Died: Other cause.

rence. Eventually, additional chemotherapy with bone marrow transplant was attempted but was unsuccessful.

Following salvage therapy, 2 patients survived >10 years, and another survived 20 months. However, 10 of 12 patients died of disease, 9 of whom died within 5 months of recurrence.

Discussion

Because thyroid nodules are routinely diagnosed by FNA cytology, NHLT should today be at least strongly suspected pre-operatively. As with treatment of non-Hodgkin's lymphoma in general, the remainder of the evaluation is guided by treatment philosophy. If systemic treatment with chemotherapy is to be administered irrespective of apparent stage, only baseline tests need to be obtained. However, if a more selective approach is planned, utilizing only radiation if the disease appears confined, more thorough staging may be appropriate. In contrast to most malignancies where surgical resection forms the cornerstone of treatment, in NHLT surgery is but one component that must be considered in the context of other treatment modalities. Appropriate questions to help delineate the role of surgery in this disease include: 1) Is surgery alone ever curative? and 2) If complete resection is not possible, is there benefit to a debulking resection compared to diagnostic biopsy?

Is Surgery Alone Ever Curative?

Two patients in our study had apparent long-term cure with surgery alone, 1 patient with disease localized to the thyroid gland and the second patient with disease that invaded surrounding soft tissue and also involved adjacent lymph nodes. They are both alive and well at 18 and 21 years, respectively. With rare exceptions, however, over the past 25 years radiotherapy has become the routine treatment for this localized disease [12].

Is There Benefit to Debulking Compared to Biopsy?

This remains the single most controversial surgical issue in the treatment of this disease. Following the report by Devine and coworkers [9] which provided evidence that biopsy and radiotherapy effected cure as frequently as debulking and radiotherapy, our surgical policy has been more conservative. However, exceptions to this policy continue for some patients when obstructive symptoms are either evident or appear imminent. Nevertheless, success in achieving a CR, relapse-free survival, and accomplishing relapse-free survival in the subset of patients who achieved CR for stages IE and II patients were no different in these two treatment groups. Perhaps, despite comparable staging, because of the retrospective nature of this study, selection bias may have been a factor. The outcome of patients who were selected for debulking may have been enhanced by the resection and they might not have fared as well had they undergone only biopsy. In contrast to our results, Rosen and associates [11] reported that complete or near complete resection of disease in the neck led to both longer overall and relapse-free survival. Additionally, those whose disease did recur locally fared worse than those with distant recurrence. Perhaps part of the explanation for the differences in the studies

may lie in the fact that 12 (26%) of their 46 stage I and II patients did not achieve a CR as compared to only 8 (16%) of our 50 patients with stage I and II. Our pattern of relapse also appears to be at variance with this study by Rosen and colleagues who found local recurrence preceded distant disease in 23% of patients. In our experience, recurrence in the operative site in isolation occurred in 1 patient only, while in the other 3 patients with local recurrence, simultaneous distant recurrence was noted as well.

The pitfalls of aggressive surgical therapy in this disease, which is frequently locally infiltrative, include damage to parathyroid glands and recurrent laryngeal nerves at a far higher rate than in thyroidectomy for the more common malignancies. Because of this and the lack of demonstrable benefit associated with more aggressive surgical resection, to proceed with more than an adequate biopsy to establish the diagnosis, with the possible exception of debulking for local compression, may not be justified.

If one accepts that biopsy alone may provide adequate surgical treatment, the question has been raised by multiple authors whether an open surgical procedure can be avoided altogether [9, 11, 13]. Two approaches would seem plausible: 1) Core needle biopsy could be used if adequate tissue is obtained to accurately subtype the NHLT, followed by radiotherapy or chemotherapy [9]. 2) FNA cytology for diagnosis and estimation of proliferative index by percentage S-phase fraction could provide the basis for subsequent therapy [14].

The principal obstacle to either of these techniques is obtaining adequate material for both diagnosis and characterization of the NHLT. Whether either could be consistently successful in this regard, especially to differentiate NHLT from Hashimoto's thyroiditis or small cell anaplastic carcinoma (the major differential diagnoses in this condition) or to make management decisions, is yet to be proven. Another rationale for surgical resection is to relieve local pressure symptoms. However, because NHLT is almost uniformly responsive to either radiotherapy or chemotherapy, these symptoms can often be rapidly resolved using either method. It would seem attractive, therefore, to further investigate percutaneous biopsy techniques.

Can Current Practices Be Changed To Achieve Improved Results?

Being predominantly of B-cell type, sometimes of MALT origin, and usually following a sequential nodal disease progression similar to that of Hodgkin's disease [15], NHLT is frequently "regionalized" at the time of diagnosis [13]. This makes NHLT eminently suitable for regional forms of therapy, namely surgery plus radiotherapy, which was successful in achieving a CR in 38 (88%) of 43 stage IE and IIE patients in this series. However, results need to be improved in patients who failed to achieve a CR (5 of 43 patients with stages IE and IIE, and 8 of 11 with stages IIIE and IVE) and patients in whom a CR was obtained but later relapsed. Three possible causes for treatment failure may be indicted: 1) inaccurate pre-operative staging, 2) inadequate primary therapy, and 3) biologically aggressive disease.

In our series, inaccurate pre-operative stage could be implicated in 2 patients whose sole recurrence occurred in retroperitoneal nodes, suggesting that the disease may have been present but undetectable pre-operatively. Had chemotherapy been chosen instead of radiotherapy, these patients may not have relapsed. However, a policy that presumes NHLT is systemic frequently enough to warrant routine chemotherapy is not borne out by our data, and would have subjected many patients to the undesirable side effects of chemotherapy.

Inadequate primary therapy may have played a role in 4 of 6 patients who had recurrence in the field of radiotherapy. Their total dose was <4,000 cGy, the level found to be a critical minimum in a previous study from our institution [10]. However, the necessity to include the axillae in the primary field may not prove efficacious as all 3 patients with axillary relapses occurred in synchrony with, and may be an indicator of, systemic disease.

Chemotherapeutic regimens, especially those including Adriamycin, are generally effective in non-Hodgkin's lymphoma [8], and have been tried successfully in stages IE and IIE NHLT to induce a complete response [16]. Additionally, a high level of S-phase by cellular DNA analysis has been shown to correlate with high-grade histopathological subtype, and together with staging could help identify a high-risk subgroup that might benefit from more aggressive treatment.

Conclusion

NHLT may be strongy suspected by pre-operative FNA cytology. The disease extent at the time of diagnosis is usually regionally confined, which rationally allows the use of radiotherapy. When confined within the capsule of the thyroid gland, thyroidectomy with adjuvant radiotherapy offers excellent chance of long-term cure. If the disease has invaded surrounding tissue or has progressed to involve adjacent lymph nodes, aggressive debulking prior to radiotherapy has not been demonstrated to enhance achievement of CR or to improve survival. Therefore, the need for exhaustive pre-operative staging is lessened as surgical biopsy provides both the minimum and maximum procedure necessary in most cases. Patients with high-grade tumors are at increased risk of both incomplete response and subsequent relapse, which may justify intensified primary chemotherapy.

Résumé

L'exérèse chirurgicale et la radiothérapie permettent d'obtenir une évolution favorable en cas de lymphome non Hodgkinien de la thyroïde (NHTL) limité à la glande. Il persiste cependant une controverse sur l'intérêt d'une exérèse chirurgicale élargie par rapport à une simple biopsie diagnostique quand la tumeur ne peut pas être enbtièrement réséquée. Notre but a été dé décrire le rôle actuel de la chirurgie dans le NHLT suivant le stade préopératoire, l'impact de l'étendue de l'exérèse sur l'obtention d'une rémission complète (CR) et de survie sans rechute (RFS) et les critères d'échec. Nous avons étudié les 62 patients qui ont subi une chirurgie en première intention pour NHLT, à la Mayo Clinic, entre 1965 et 1989. Après le bilan post-opératoire, 50 patients avaient un stade IE ou IIE. La survie était globalement de 53% à 5 ans et 46% à 10 ans. Elle était de 80% pour les patients au stade IE limité à la thyroïde, de 58% pour les patients au stade IE avec envahissement extrathy-

roïdien, de 50% en cas de stade IIE et de 36% en cas de stade IIIE et IVE. Une rémission complète a été obtenue chez 88% des patients ayant eu une biopsie à visée diagnostique suivie d'un traitement adjuvant et chez 83% des patients ayant subi une exérèse élargie complétée par un traitement adjuvant. Il n'y avait aucune différence sur la survie sans rechute entre les deux groupes ou même dans les deux sous groupes ayant eu une rémission complète. Une rechute après rémission complète a été observée chez 12 sur 46 patients (26%). Seuls 2 d'entre eux ont survécu à long terme après traitement. Le rôle de la chirurgie dans le NHLT semble en voie de régression et les progrès qui permettront d'augmenter les rémissions complètes et la survie sans rechute ne semblent pas passer par des résections chirurgicales plus agressives.

Resumen

Puesto que la cirugía extirpativa y la radioterapia han demostrado resultados favorables en el tratamiento del linfoma no-Hodgkin del tiroides (LNHT) confinado a la glándula, persiste la controversia sobre la ventaja potencial del debultamiento agresivo en favor de la sóla biopsia diagnóstica en los casos en que la neoplasia no pueda ser completamente resecada. Los objetivos de nuestro trabajo fueron definir el papel actual de la cirugía en el LNHT respecto a la estadificación preoperatoria, al impacto de la amplitud de la resección en cuanto a remisión total (RT) y sobrevida libre de recurrencia (SLR) y a los patrones de falla. Se analizaron todos los 62 pacientes sometidos a operación primaria por LNHT en la Clínica Mayo entre 1965 y 1989. La estadificación postoperatoria reveló que 50 pacientes estaban en estado IE o IIE. La tasa global de sobrevida fue de 53% a 5 años y de 46% a 10 años; 80% para el estado IE confinado a la tiroides, 58% para estado IE—extratiroideo, 50% para estado IIE y 36% para estados IIIE y IVE. Se logró RT en 88% de los pacientes que fueron sometidos a biopsia diagnóstica más terapia adyuvante, en comparación con 83% de los pacientes en quienes se practicó debultamiento más terapia adyuvante. No se halló diferencia al comparar la SLR en estos dos grupos o en la SRL en dos subgrupos que exhibieron RT. Recurrencia después de RT fue observada en 12 de 46 (26%) pacientes, pero sólo 2 sobrevivieron durante un periodo prolongado luego de terapia de salvamento. El papel de la cirugía en el LNHT se reduce progresivamente, y es previsible que el avance en modalidades terapéuticas que logren mejores tasas de RT y de SLE posiblemente no habrá de incluir resecciones quirúrgicas más agresivas.

References

1. Hyjek, E., Isaacson, D.M.: Primary B cell lymphoma of the thyroid and its relationship to Hashimoto's thyroiditis. Hum. Pathol. *19*: 1315, 1988
2. Hölting, T., Möller, P., Tschahargane, C., Meybier, H., Buhr, H., Herfarth, C.: Immunohistochemical reclassification of anaplastic carcinoma reveals small and giant cell lymphoma. World J. Surg. *14*:291, 1990
3. National Cancer Institute: Study of classifications of non-Hodgkin's lymphomas: Summary and description of a working formulation for clinical usage. Cancer *49*:2112, 1982
4. Isaacson, P., Wright, D.H.: Extranodal malignant lymphoma arising from mucosa-associated lymphoid tissue. Cancer *53*:2515, 1984
5. Anscombe, A.M., Wright, D.H.: Primary malignant lymphoma of the thyroid—a tumour of mucosa-associated lymphoid tissue: Review of seventy-six cases. Histopathology 9:81, 1985
6. Aozasa, K., Ueda, T., Katagiri, S., Matsuzuka, F., Kuma, K., Yonezawa, T.: Immunologic and immunohistologic analysis of 27 cases with thyroid lymphomas. Cancer *60*:969, 1987
7. Taniwaki, M., Nishida, K., Misawa, S., Takino, T., Abe, T., Aozasa, K., Katagiri, S., Yonezawa, T., Matsuzuka, F., Kuma, K.: Correlation of chromosome abnormalities with clinical characteristics in thyroid lymphoma. Cancer *63*:873, 1989
8. Klimo, P., Connors, J.M.: MACOP-B chemotherapy for the treatment of diffuse large-cell lymphoma. Ann. Intern. Med. *102*:596, 1985
9. Devine, R.M., Edis, A.J., Banks, P.M.: Primary lymphoma of the thyroid: A review of the Mayo Clinic experience through 1978. World J. Surg. *5*:33, 1981
10. Blair, T.J., Evans, R.G., Buskirk, S.J., Banks, P.M., Earle, J.D.: Radiotherapeutic management of primary thyroid lymphoma. Int. J. Radiat. Oncol. Biol. Phys. *11*:365, 1985
11. Rosen, I.B., Sutcliffe, S.B., Gospodarowicz, M.K., Chua, T., Simpson, W.J.K.: The role of surgery in the management of thyroid lymphoma. Surgery *104*:1095, 1988
12. Woolner, L.B., McConahey, W.M., Beahrs, O.H., Black, B.M.: Primary malignant lymphoma of the thyroid. Am. J. Surg. *111*:502, 1966
13. Oertel, J.E., Heffess, C.S.: Lymphoma of the thyroid and related disorders. Semin. Oncol. *14*:333, 1987
14. Cavalli, C., Danova, M., Gobbi, P.G., Riccardi, A., Magrini, U., Mazzini, G., Bertoloni, D., Rutigliano, L., Rossi, A., Ascari, E.: Ploidy and proliferative activity measurement by flow cytometry in non-Hodgkin's lymphomas: Do speculative aspects prevail over clinical ones? Eur. J. Cancer Clin. Oncol. *25*:1755, 1989
15. Ultmann, J.E., Jacobs, R.H.: The non-Hodgkin's lymphomas. CA *35*:66, 1985
16. Leedman, P.J., Sheridan, W.P., Downey, W.F., Fox, R.M., Martin, F.I.R.: Combination chemotherapy as single modality therapy for stage IE and IIE thyroid lymphoma. Med. J. Aust. *152*:40, 1990

Invited Commentary

Per-Ola Granberg, M.D.

Department of Surgery, Karolinska Institutet, Stockholm, Sweden

Pyke and coworkers from the Mayo Clinic present material from 62 patients diagnosed with non-Hodgkin's lymphoma of the thyroid (NHLT) during a period of 25 years. The aim of the study was to define the role of surgery in the disease. Even though 2 patients were cured by surgery alone, there is an undertone in the presentation doubting the role of surgery in this rare disease. Aggressive debulking did not improve cure rate or survival. The only justified surgical intervention was biopsy.

My comments on the paper will only deal with the prognostic procedures. For me, NHLT has long been a non-surgical disease. Our colleagues at the Division of Clinical Cytology at the Department of Pathology have made us surgeons unnecessary.

In spite of earlier statements [1, 2], cytomorphology alone is