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Perspectives and Commentaries

Should Lymphomas of Gastrointestinal Tract be Treated Differently from other Disease Presentations?

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(A COMMENT ON: Steward WP, Harris M, Wagstaff J. A prospective study of the treatment of high-grade histology non-Hodgkin's lymphoma involving the gastro-intestinal tract. *Eur J Cancer Clin Oncol* 1985, **21**, 1195–1200.)

ALTHOUGH the majority of non-Hodgkin's lymphomas (NHL) arise in lymph nodes, they frequently present in extranodal sites, with a reported incidence ranging from 10 to 58% [1]. Most of the patients with primary extranodal involvement have a diffuse histological pattern of growth, in particular diffuse histiocytic type based on the Rappaport classification, or diffuse large cell lymphomas of intermediate and high grade malignancy according to the International Working Formulation for Clinical Use [2]. The most frequently observed extranodal sites are the gastrointestinal tract and the head and neck area (Waldeyer's ring, nasal cavity, maxilla, salivary glands, and orbit) followed by lung, skin, thyroid, testis, and bone. As far as gastrointestinal tract is concerned, the highest incidence of NHL in adults is the stomach, followed by small intestine, and the ileocecal region while in children the tumor arises almost always at the level of ileocecal valve.

During the past two decades, the treatment of gastrointestinal lymphomas, particularly gastric lymphomas, has been the subject of numerous publications. The conclusions, which were almost always based on retrospective analysis, often yielded conflicting results in terms of treatment approach and survival. Among the very few prospective studies [3], in this journal, Steward *et al.* [4] present the results of 36 patients with stage II–IV primary gastrointestinal NHL. Their findings, as well as those of previous investigators, provide the opportunity to re-examine whether lymphomas of the digestive tract might represent a distinct clinico-pathological entity which deserves a specific diagnostic and therapeutic approach.

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MAIN CLINICAL AND PATHOLOGICAL FEATURES

Patients with primary gastrointestinal NHL are defined as those who present with gastrointestinal symptoms and signs as a result of lymphomatous involvement, or those who have an obviously predominantly alimentary tract lesion.

In Europe and North America gastric involvement occurs in 50–60% of patients, small intestine in 25–35%, and large intestine in 10–15% (ileocecal region). Although there is a wide distribution from the first to the eighth decade, those originating in the gastrointestinal tract predominate, as in the other lymphomas, in the middle-aged and elderly patients. There is a slight overall male predominance particularly in patients with bowel involvement. With the exception of the Mediterranean-type lymphomas, there is no apparent racial predisposition for any of the lymphomas. The so-called Mediterranean lymphomas with alpha heavy chain production and/or secretion, as observed in various parts of Middle East, are localized in the upper small intestine and occur predominantly in young adults. These abdominal lymphomas are probably associated with specific

socioeconomic patterns since they seem to be linked with gastroenteritis in childhood suggesting the dysregulation of the gut-associated lymphoid tissue as a pathogenetic mechanism [5]. Possible predisposing factors in the development of intestinal lymphomas include celiac disease, dermatitis herpetiformis, Chron's disease, ulcerative colitis, and idiopathic late-onset immunoglobuline deficiency.

Regardless of the anatomical site, abdominal pain is the most common presenting symptom followed by anorexia and weight loss. In patients with gastric lymphoma clinical and radiological findings are frequently compatible with peptic ulcer while patients with intestinal lymphoma commonly present symptoms and signs of intestinal obstruction. Gastrointestinal bleeding varies from 15 to 60%. Physical examination discloses an abdominal mass in one fourth to one third of patients. This finding is much more common in children because of the frequent concomitant involvement of mesenteric lymph nodes. A peculiar aspect of gastrointestinal lymphomas is their association with lymphomas of the Waldeyer's ring. In fact, 10–20% of all cases with pharyngeal NHL also show involvement of the stomach or the intestine either at the time of initial presentation or within 2 yr of diagnosis, probably as a result of homing tendencies of gut-associated lymphoid tissue [6].

The gastroscopic findings, which became available only from recent series [7–9], can disclose tumor lesions in virtually all patients. However, in general, the endoscopic inspection alone cannot differentiate infiltration due to adenocarcinoma from that of lymphoma. Lymphoma can be suspected on the basis of a few findings such as arresting motility of the gastric wall, thickening of the gastric mucosa, and vegetations with or without ulcerations. Multiple specimens should be obtained by biopsy, particularly at the edges of ulcerations, to reach the submucosa. Gastroscopic biopsy specimens can document the presence of malignancy in 67–96%. A much less consistent endoscopic experience is at present available for NHL arising in the intestine.

On macroscopic examination there is a predominance of infiltrative lesions with localized mucosal ulceration and raised margins. There is frequent penetration through the serosa with consequent destruction of the full thickness of gastric and intestinal walls. An exophytic nodular or polypoidal appearance is the next most common feature while constrictive lesions are rare findings. As far as histopathological subgroups are concerned, in the series of patients studied with the Rappaport classifications diffuse histiocytic lymphoma was the commonest type and constituted 50–60% of the total [8, 10, 11]. In more recent series utilizing the Working Formulation, NHL of follicular center cell origin (i.e. small and large cleaved cell, large non-cleaved cell) prevailed in the stomach, and the large cell immunoblastic subtype prevailed in the bowel [8]. Filippa *et al.* [12] reported a prevalence of plasmacytoid and immunoblastic NHL among the 60 gastrointestinal lymphomas of their series while Henry and Farrer-Brown [13] reported plasma cell tumors without paraprotein secretion in 39% of 125 cases; these lymphomas were predominantly located in the terminal portion of the ileum and in the caecum. In children with involvement of the ileocecal region, the most frequent histological subtype is Burkitt lymphoma ($\geqslant$ 50%) followed by lymphoblastic and immunoblastic lymphoma.

STAGE AND PROGNOSIS

Most of the clinico-pathological evaluations of gastrointestinal NHL were undertaken before the widespread use of systemic staging procedures and the acceptance of modern histopathological classifications. Therefore, as correctly stated by Steward *et al.* [4] many of the clinical and pathological variables included in the various series account for most of the conflicting results.

The classical Ann Arbor staging system is difficult to apply to gastrointestinal NHL primarily because it fails to distinguish between perigastric and mesenteric lymph node metastases from retroperitoneal lymph nodal metastases. Considering that in about half patients the disease remains confined within the abdomen even at the time of death, for prognostic and therapeutic purposes the Manchester staging system proposed by Blackledge *et al.* [14] and modified by Rao *et al.* [15] appears more useful. In Stage I_E the tumor is confined to the gastrointestinal tract (10–20% of patients); Stage II_E: tumor spread to regional (gastric or mesenteric) lymph nodes (25–35%); Stage III_E: tumor with nodal involvement beyond the regional lymph nodes, such as para-aortic and iliac nodes (20–30%); Stage IV: tumor with spread to extranodal sites (15–30%).

Since prognosis is related to stage, modern diagnostic approach should include the procedures utilized for lymphomas arising in the lymph nodes. Following initial barium roentgenographic procedures, endoscopy with multiple biopsies should be performed, particularly in patients with gastric lesions. Once tissue diagnosis has been obtained, further investigations should include two needle bone marrow biopsies, lymphangiography and, whenever possible, laparoscopy with multiple liver biopsies. In most patients with tumor involvement apparently confined to either the small or large intestine, as well as in all children presenting with an abdominal mass, laparotomy represents almost

Table 1. Five-year relapse-free survival related to stage and type of treatment

First author	Stage	No. evaluable patients	5-year relapse-free survival in %			
			Surgery	Radiotherapy	Chemotherapy	Radiotherapy and chemotherapy
Hermann [16]	I	23	25	82		
	II	27	20	65		
Weingrad [17]	I	31	85*	83*		
	II	37	45*	50*		
Gospodarowicz [18]	IA	29	–	79		
	IIA	34	–	75		
Paulson [19]	I	7	100	100	100	
	II	18	0	33	70	
Maor [9]	I	29	67	71	100	100
	II	34	10	26	20	100
Rao [15]	I	15	100	100	–	
	II	17	–	79	100	
Sheridan [3]	I	10			100**	
	II	4			75**	
Mittal [20]	I	19	63	67	–	100
	II	15	–	55	–	75
Milan Series	I	18				94
	II	8				100

* Free from recurrence in primary site.
**Data are at 3 yr.

invariably the only procedure to clearly establish the histological diagnosis of lymphoma.

The early publications indicated that the 5-yr survival rates were ranging from 25 to 50% following surgery and/or radiotherapy. Many investigators reported better prognosis for gastric lymphoma than for intestinal lymphoma as well as for follicular vs. diffuse histiocytic lymphomas. The initial reports have been limited to adult patients with an apparent localized disease involving only the stomach or the intestine and the regional nodes. More recent reports have indicated that, both in adults and children, the histologic subtype of gastrointestinal lymphoma is only a minor determinant of prognosis which remains primarily related to stage and intensity of treatment (Table 1). Also tumor penetration beyond the serosa [8, 17, 21], bulky regional nodal involvement and number of involved anatomical sites [1] have adverse effect on survival.

Since the observations of Fu and Perzin [22] and Naqvi *et al.* [23], and more recently by Hande *et al.* [11], it became evident to clinicians who have not confined their observations to patients with localized disease, that patients having disseminated NHL with gastrointestinal involvement carry in general a poor prognosis. This observation may be due to a number of concomitant factors such as unfavorable histology, bulky abdominal disease, and lack of primary tumor resection leading to an increased incidence of life-threatening hemorrage and/or perforation. Also some treatment-related complications may adversely influence survival. In particular, when there is involvement of the full thickness of the gastrointestinal wall massive hemorrage and perforation can often be increased by rapid tumor necrosis particularly following intensive primary chemotherapy. This complication occurred in four of five patients given aggressive primary chemotherapy in the series of Fleming *et al.* [24] and accounted for 38% of early deaths in the series of the National Cancer Institute [11]. Also in the experience of Steward *et al.* [4] there were 18 of 36 (50%) patients whose cause of death was due to or strongly suggestive for hemorrage and/or perforation, and in three cases who died in hospital during induction chemotherapy no residual lymphoma was found at post-mortem examination. Thus, today the extreme efficacy of combination chemotherapy for NHL should be added to the classical prognostic variables, unless local control with surgery preceeds drug treatment. In fact, Weingrad *et al.* [17] reported that in patients who had tumor resection as part of their therapy, the rate of the above mentioned complications was nearly half that experienced by patients who received radiation therapy alone (12 vs. 22%).

TREATMENT CONSIDERATIONS

All published reports but that of Steward *et al.*[4] lack uniform and consistent treatment guidelines

for the various stages. Even in recent publications the chemotherapy regimens utilized are different from each other and, at times, also within the same institution.

In spite of different opinions from a few investigators [9, 16], the role of elective surgery remains important for accurate pathological staging, resection of primary neoplasm and to prevent treatment complications related to tumor penetration. The initial surgical approach is particularly valid when effective chemotherapy is indicated as primary treatment since the above reported incidence of massive hemorrage or perforation will require emergency surgery in patients with depressed leukocyte and platelet counts. Depending on the bulky of regional adenopathy, the resection rate ranges from 58 to 64% [9, 24, 25]. As also demonstrated by Steward *et al.* [4], adequate tumor resection has a significant impact on survival.

The role of radiotherapy remains to be clearly defined. If the gastrointestinal tumor is really localized (Stage I_E), abdominal irradiation alone (3000–4000 rad) seems to be as effective as radical tumor resection followed by radiotherapy (Table 1). In these cases almost all authors have observed a few, if any, episodes of hemorrage or perforation. The value of postoperative radiation therapy is difficult to evaluate since most reported series in the literature included patients treated with combined therapy, i.e. resection and radiation. It should be emphasized that if tumor is non-resectable at exploratory laparotomy, primary radiation therapy alone is unable to control the disease. Thus it appears that the role of radiation may be an important adjuvant to resection particularly in patients with Stage II_E and III_E.

The chemotherapy of NHL has rapidly progressed during the past decade and current intensive polydrug regimens can probably cure more than 50% of patients with disseminated high-grade lymphomas (Stage III and IV). Therefore, it is not surprising that combination chemotherapy has been administered also in patients with Stage I–I_E and II–II_E disease. In prospective randomized studies, combined radiotherapy and chemotherapy (CVP and BACOP regimens) were found superior to radiotherapy alone [6] but also intensive chemotherapy alone (mainly the CHOP regimen) was reported to yield relapse-free and survival results which were superior to radiation therapy also in patients with gastrointestinal NHL [26]. Our current approach for Stage I–II high-grade nodal and extranodal lymphomas utilize first an Adriamycin-containing regimen followed by involved-field radiation therapy, particularly in patients with initial bulky disease, to ensure maximum local tumor control [6].

As far as the role of primary chemotherapy in gastrointestinal lymphomas is concerned, the findings derived from recent case series would indicate that excellent 5-yr relapse-free survival can be obtained in Stage I_E and II_E by tumor resection followed by drug therapy (Table 1). This sequential approach also yielded good survival results in small series with either Stage III_E or Stage IV disease [3, 19].

CONCLUSIONS

Published reports fail to indicate that treatment results and patterns of recurrence clearly distinguish NHL of the gastrointestinal tract from those arising in other nodal or extranodal sites. A similar conclusion was reached about NHL of the Waldeyer's ring [6]. However, without representing a distinct clinico-pathological entity, gastrointestinal lymphomas deserve specific diagnostic and therapeutic approach which takes into account topography and abdominal extent of the tumor. Initial diagnostic investigations should include barium roentgenographic studies as well as endoscopic studies. Once the diagnosis is made, further investigations, such as lymphography and bone marrow biopsies, must be carried out to document or rule out the presence of distant tumor involvement. If laparotomy is indicated to establish tissue diagnosis, the above mentioned procedures should be performed following surgery and before starting systemic therapy.

The extensive published material strongly supports that surgical tumor resection is crucial in all clinical stages to enhance the cure rate and to avoid life-threatening complications. This appears to be true even if the resection margin is involved by lymphoma microscopically. Recent data indicate that a combination of surgery plus one of the modern drug combinations is a promising new approach, and is capable of producing long-term remission and cure in both localized and advanced gastrointestinal lymphomas. Therefore, this sequential approach should be adopted in all stages as the treatment of choice. In patients with complete tumor resection the indicative duration of chemotherapy should not exceed 6 monthly cycles. In patients with residual measurable tumors, as many treatment cycles of chemotherapy should be delivered to achieve complete remission (minimum 6 cycles) followed by two consolidation cycles. Current line of evidence would exclude that in complete responders maintenance drug therapy is required to prolong relapse-free and/or total survival, even in the presence of follicular lymphomas. The assumption that the routine use of post-operative radiotherapy may improve prognosis of gastrointestinal lymphomas, particularly when adequate chemotherapy follows surgery, remains

to be proven through controlled studies considering tumor stage and histologic type. Short-term radiotherapy may precede chemotherapy in clearly inoperable patients to reduce bulky disease and minimize the above mentioned complications following rapid tumor destruction by drugs.

REFERENCES

1. Paryani S, Hoppe RT, Burke JS *et al.* Extralymphatic involvement in diffuse non-Hodgkin's lymphoma. *J Clin Oncol* 1983, **1,** 682–688.
2. Non-Hodgkin's Lymphoma Pathologic Classification Project. National Cancer Institute sponsored study of classification of non-Hodgkin's lymphoma: summary and description of a working formulation for clinical usage. *Cancer* 1982, **49,** 2112–2135.
3. Sheridan WP, Medley G, Brodie GN. Non-Hodgkin's lymphoma of the stomach: a prospective pilot study of surgery plus chemotherapy in early and advanced disease. *J Clin Oncol* 1985, **3,** 495–500.
4. Steward WP, Harris M, Wagstaff J, Scorffe JH, Deakin DP, Todd IDH, Crowther D. A prospective study of the treatment of high grade histology non-Hodgkin's lymphoma involving the gastrointestinal tract. *Eur J Cancer Clin Oncol* 1985, **21,** 1195–1200.
5. Nassar VH, Salem PA, Shahid MJ *et al.* "Mediterranean abdominal lymphoma" or immunoproliferative small intestinal disease: Part II. Pathological aspects. *Cancer* 1978, **41,** 1340–1354.
6. Bonadonna G. Management of stage I and II non-Hodgkin's lymphomas in adults. In: Rees J, Bennett JM, eds. *Lymphomas.* Borough Green, Butterworth, 1986 (in press).
7. Spinelli P, Lo Gullo C, Pizzetti P. Endoscopic diagnosis of gastric lymphomas. *Endoscopy* 1980, **12,** 211–214.
8. Dragosics B, Bauer P, Radaszkiewicz T. Primary gastrointestinal non-Hodgkin's lymphomas. A retrospective clinicopathologic study of 150 cases. *Cancer* 1985, **55,** 1060–1073.
9. Maor MH, Maddux B, Osborne BM *et al.* Stages IE and IIE non-Hodgkin's lymphomas of the stomach. Comparison of treatment modalities. *Cancer* 1984, **54,** 230–237.
10. Lewin KL, Ranchod M, Dorfman RF. Lymphomas of the gastrointestinal tract. A study of 117 cases presenting with gastrointestinal disease. *Cancer* 1978, **42,** 693–707.
11. Hande KR, Fisher RI, De Vita VT, Chabner BA, Young RC. Diffuse histiocytic lymphoma involving the gastrointestinal tract. *Cancer* 1978, **41,** 1984–1989.
12. Filippa DA, Lieberman PH, Weingrad DN, Decosse JJ, Bretsky SS. Primary lymphomas of the gastrointestinal tract: Analysis of the prognostic factors with emphasis on histological type. *Am Surg Path* 1983, **7,** 363–372.
13. Henry K, Farrer-Brown G. Primary lymphomas of the gastrointestinal tract. I. Plasma cell tumors. *Histopathol* 1977, **1,** 53–76.
14. Blackledge G, Bush H, Dodge OG, Crowther D. A study of gastrointestinal lymphoma. *Clin Oncol* 1975, **5,** 209–219.
15. Rao AR, Kagan AR, Potyk D *et al.* Management of gastrointestinal lymphoma. *Am J Clin Oncol* 1984, **7,** 213–219.
16. Herrmann R, Panahon AM, Barcos MP, Walsh D, Stutzman L. Gastrointestinal involvement in non-Hodgkin's lymphoma. *Cancer* 1980, **46,** 215–222.
17. Weingrad DN, Decosse JJ, Sherlock P, Straus D, Lieberman PH, Filippa DA. Primary gastrointestinal lymphoma: a 30-year review. *Cancer* 1982, **49,** 1258–1265.
18. Gospodarowicz MK, Bush RS, Brown TC, Chua T. Curability of gastrointestinal lymphoma with combined surgery and radiation. *Int J Radiat Oncol Biol Phys* 1983, **9,** 3–9.
19. Paulson S, Sheehan RG, Stone MJ, Frenkel EP. Large cell lymphomas of the stomach: improved prognosis with complete resection of all intrinsic gastrointestinal disease. *J Clin Oncol* 1983, **1,** 263–269.
20. Mittal BB. Gastric lymphoma. Proc Second International Conference on Malignant Lymphoma 1984, Lugano, Switzerland (Abstract P73).
21. Lim FE, Hartman AS, Tan ECG, Cady B, Meissner WA. Factors in the prognosis of gastric lymphoma. *Cancer* 1977, **39,** 1715–1720.
22. Fu YS, Perzin KH. Lymphosarcoma of the small intestine: a clinicopathologic study. *Cancer* 1972, **29,** 645–659.
23. Naqvi MS, Burrows SL, Kark AE. Lymphosarcoma of the gastrointestinal tract. Prognostic guides based on 162 cases. *Ann Surg* 1969, **170,** 221–231.
24. Fleming ID, Mitchell S, Dilawari RA. The role of surgery in the management of gastric lymphoma. *Cancer* 1982, **49,** 1135–1141.
25. Connors J, Wise L. Management of gastric lymphomas. *Am J Surg* 1974, **127,** 102–107.
26. Miller T, Jones SE. Initial chemotherapy for clinically localized lymphomas of unfavorable histology. *Blood* 1983, **62,** 413–418.