Primary Non-Hodgkin's Lymphoma of the Stomach: Changing Aspects and Therapeutic Choices

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Abstract—*Eighty-five consecutive patients, seen between 1970 and 1987, with primary gastric non-Hodgkin's lymphoma were studied to evaluate diagnostic findings and treatment results. At endoscopy three main patterns were recognized: ulceration (n = 21), diffuse infiltration (n = 16) and a polypoid mass (n = 26). Recently, the new technique of endoscopic ultrasonography was used to measure depth of infiltration and regional lymph nodes. Preoperative diagnosis altered the indication of surgery. Since 1978 surgical staging was performed in only 29% of the patients compared to 90% in the earlier period. In the later period stage II was more systematically treated with a combination of chemotherapy and radiotherapy. Over the whole period patients in stage I (n = 52) had a 5 year disease-free survival of 63%. In stage II 38% had a 5 year disease-free survival. Complications were one perforation and one haemorrhage after radiotherapy and two cases of haemorrhage after radiotherapy combined with chemotherapy. Intraabdominal recurrences were found in two cases. Recognition of endoscopic features may lead to early detection and ultimately improved survival.*

INTRODUCTION

PRIMARY non-Hodgkin's lymphoma (NHL) of the gastro-intestinal tract is rare and usually localized in the stomach. It represents only a minority of 1–7% of all gastric malignancies [1, 2]. Whereas the prognosis is favourable in contrast to gastric carcinoma, 5 year survival is still disappointing in stage II. Since endoscopy became widely available [3], the diagnosis of gastric NHL is frequently made preoperatively. Therefore, the role of surgery has been changed and the indication for resection is under discussion. A recent report dealing with endoscopic ultrasonography showed promising results in the staging of gastric NHL; both depth of infiltration and pathological lymph nodes could be visualized [4]. Radiotherapy is an effective treatment for this disease. It is not yet clear whether combination with radical surgery improves the long term results [4]. Chemotherapy alone has not been extensively investigated in gastric NHL.

In the present study several diagnostic aspects and the impact of various treatment strategies have been studied to evaluate the change in therapeutic approach.

MATERIALS AND METHODS

The records of 85 consecutive patients, 52 men and 33 women, presenting with primary non-Hodgkin's lymphoma of the stomach between 1970 and 1987 were studied. Only patients with stage I and II according to the modified Ann Arbor staging system (Table 1) were included [5]. Stage I disease is limited to the stomach, while stage II disease includes patients with involvement of adjacent or regional lymph nodes. Excluded were patients with stage III (involvement of the spleen or lymph nodes above the diaphragm) and stage IV disease (other organ involvement), because primary localization in the stomach is uncertain.

Gastric involvement was established by double contrast radiography, endoscopy and/or laparotomy. The patients were staged by physical examination, detailed inspection of Waldeyer's ring, laboratory studies including haematology and blood chemistry, chest X-ray, bone marrow investigation, lymphangiography and/or computed tomography of the abdomen. In patients seen before 1978 surgical staging was available.

The histological diagnosis was determined by multiple (at least 10) endoscopic biopsies and brush cytology or on surgical material. Pathology was reviewed by one of the authors. In nine cases slides were no longer available. The malignant lymphomas were subdivided according to Lennert's

Table 1. Staging system in non-Hodgkin's lymphoma of the stomach: modification of the Ann Arbor staging

Stage I	Process limited to the stomach
Stage IE	Local extension into the surrounding organs without lymph node involvement
Stage II$_1$	The same with adjacent lymph node involvement
Stage II$_2$	The same with regional abdominal lymph node involvement
Stage III	Involvement of lymph nodes above the diaphragm and/or of the spleen
Stage IV	Involvement of various organs, such as liver, lung parenchyma, bone marrow, kidneys and skin

classification [6], as well as Rappaport's classification [7] and the Working Formulation [8].

For patients where the tumour process was limited to the stomach (stage I or II$_1$) standard radiotherapy was given. This consisted of total abdominal irradiation to a dose of 20 Gy in 3 weeks, five fractions per week. WBC and platelets were checked three times a week and the daily fractional dose reduced if necessary. The whole peritoneal cavity was included in the treatment volume, from the diaphragm to the pouch of Douglas and out to the side wall laterally, with shielding of the right kidney posteriorly. An additional dose of 20 Gy was given in 2 weeks to a total dose of 40 Gy to the whole stomach and para-aortic area to the level of L2-L3, depending on the position of the stomach as found at radiography, endoscopy and/or laparotomy. The left kidney was included in this volume and not shielded. In a few cases, before 1978, adjuvant chemotherapy was given.

For patients with extensive disease (palpable tumours or stage IE or II$_2$), and therefore clinically unresectable, treatment started with induction chemotherapy, after eight courses followed by limited radiotherapy. Chemotherapy consisted of CHVmP: cyclophosphamide 600 mg/m^2 day 1-5, doxorubicin 25 mg/m^2 day 1, teniposide (Vm-26) 60 mg/m^2 day 1 and prednisone 40 mg/m^2 day 1-5 repeated on day 25, with a total of eight courses in case of response. Occasionally teniposide was replaced by vincristine.

A number of patients was not treated according to these schedules, in case of poor general condition or old age. Before 1978 stage II patients did not receive primary chemotherapy. These individualized treatment schedules including mild chemotherapy, palliative radiotherapy only (gastric field only, and/or limited dose) or combinations were coded as 'various treatment'.

Response was assessed according to the WHO classification. Complete response (CR): disappear-

ance of all known disease, determined by two observations not less than 4 weeks apart. Partial response (PR): decrease by at least 50% in the sum of the products of the largest perpendicular diameters of all lesions. No change (NC): neither a 50% decrease in total tumour nor a 25% increase, and no new lesions. Progressive disease (PD): a 25% or more increase of a lesion or the appearance of a new one.

The survival curves were calculated according to the Kaplan–Meier method [7].

RESULTS

Clinical characteristics

According to the modified Ann Arbor system (Table 1), there were 53 patients in stage I and 32 in stage II. The preponderance of male patients was equal in both stages.

Data on the presenting clinical signs, symptoms, laboratory and histologic findings are shown in Table 2. The symptoms were rather non-specific, such as epigastric pain, nausea and vomiting. Night sweats or fever were present only occasionally. Nine patients (11%) presented with haemorrhage; in another five patients anaemia was found without apparent bleeding. Although weight loss was frequently found and the duration of symptoms often prolonged, the vast majority of patients were in a fairly good general condition. The interpretation of the contrast radiography was variable and usually descriptive only. The diagnosis NHL was suggested in only a few cases.

Table 2. Presenting symptoms and signs in primary gastric NHL (n = 85)

	Stage I	Stage II
General:		
age, median (range)	59 years (19–90)	61 years (30–82)
sex	32 m, 21 f	20 m, 12 f
Symptoms:	$n = 53$	$n = 32$
epigastric pain	45	27
nausea	15	11
vomiting	9	10
weight loss	33	26
fever	4	1
haemorrhage	6	3
perforation	1	1
Physical examination:		
Karnofsky index		
80–90%	42	24
60–70%	10	8
≤50%	1	0
no abnormal findings	47	23
mass	3	7
Laboratory:		
Hb ≤6.5 mmol/l	11	2
ESR ≥30 mm	18	15

Histologic types

In Table 3 the histologic classifications are listed. According to Lennert's classification the centrocytic type (34%) and the mixed centroblastic–cytic type (34%) accounted for the majority of cases. Using Rappaport's classification the diffuse histiocytic type and the poorly differentiated lymphocytic type were predominantly found: 51% and 32%. In the Lukes classification most cases consisted of cleaved cells, either large (32%) or small (30%). According to the Working Formulation scheme tumours of intermediate grade of malignancy predominated (73%). No statistical difference was found in histologic type between stage I and II.

Staging

Staging procedures were uniformly performed as summarized in Table 4. In recent years, the computer tomography (CT scan) became available, but has not replaced lymphangiography to detect small lymph node involvement. Although ENT inspection especially of the Waldeyer's ring is highly recommended, this investigation was performed in only 36 cases (42%). Otherwise clinical staging was rather complete. In the period 1970–1977 laparotomy with or without gastrectomy was perfor-

Table 3. Histologic types in primary gastric NHL (n = 85)

	Stage I	Stage II
Lennert's classification:		
lymphoplasmocytic	3	1
centrocytic	20	9
centroblastic–cytic	18	11
centroblastic	6	3
lymphoblastic	2	—
immunoblastic	2	6
unknown	2	2
Rappaport's classification:		
lymphocytic, well differentiated	4	1
lymphocytic, poorly differentiated	22	5
mixed lymphocytic–histiocytic	—	2
histiocytic	22	21
undifferentiated	1	—
unknown	4	3
Lukes classification:		
plasmacytoid lymphocyte	4	1
small cleaved	22	5
large cleaved	11	14
small non-cleaved	1	—
large non-cleaved	7	3
immunoblastic	2	6
unknown	6	3
Working Formulation:		
low malignancy	4	1
intermediate malignancy	40	22
high malignancy	3	6
unknown malignancy	6	3

med in nine out of 10 patients in stage I and 18 out of 20 patients in stage II; overall in 90% of cases. In 1978–1987 these figures were 9/43 and 7/12 cases respectively, overall in 29% of the cases.

Endoscopy

During endoscopy three main patterns could be recognized (see Table 5); extensive ulceration in 21 patients, diffuse infiltration in 16 patients and a polypoid tumour mass in 26 patients. Large superficial or penetrating ulcers connected by stellated branches were a characteristic finding (Fig. 1). Diffuse infiltration with large rigid, sometimes giant, folds must be differentiated from Menetrier's disease and linitis plastica (Fig. 2). A polypoid mass was sometimes hardly distinguishable on contrast röntgenology and should always be differentiated from gastric carcinoma and leiomyoma, but the accompanying abnormal, interrupted mucosal folds suggest malignant lymphoma (Fig. 3). A combination of the different features may be found (Fig. 4) as is also seen in the corresponding endoscopic ultrasonography (Fig. 5) which showed the polypoid lesion, ulceration and depth of infiltration.

The characteristic endoscopic appearance was not correlated with age, grade of malignancy, local control or recurrence. Although the diffuse type was more frequently seen in stage I (Table 5), the difference just failed to reach statistical significance.

Despite suggestive endoscopic features in 10 cases, histology showed only aspecific gastritis. In five patients, however, repeated endoscopy with multiple biopsies revealed the malignant lymphoma leading to a false negative rate of 8%. In the other five cases the final diagnosis was based on resection material. In four other cases histologic biopsy diagnosis was undifferentiated carcinoma: two proved to be NHL after repeated endoscopy and in two cases (3%) the diagnosis was changed in to NHL on the resection material. Most problems occurred in the period before 1978 (7/17 = 41%) and were less in recent years (7/46 = 15%). In addition, the majority of inappropriate diagnoses was seen in the referral hospitals (10 vs. 4).

Resection rate

Among the 30 cases treated before 1978 19 patients (63%) underwent a gastrectomy (nine in stage I, 10 in stage II); in eight cases, all in stage II, the tumour process was inoperable due to infiltration in surrounding tissue; the remaining three cases (one in stage I, two in stage II) were clinically inoperable based on extensive tumour. Since 1978 our policy has been changed and surgery was mainly performed in haemorrhage and deep ulceration.

Among the group of 55 cases in 14 patients a gastrectomy was performed (nine in stage I, five in

Table 4. *Initial staging procedures in primary gastric NHL* (n = 85)

	Stage I n = 53		Stage II n = 32	
Radiology of the stomach	7 ⎫		5 ⎫	
Endoscopy	8 ⎬ 51		3 ⎬ 27	
Radiology + endoscopy	36 ⎭		19 ⎭	
Lymphangiography	15 ⎫		16 ⎫	
CT scan of the abdomen	14 ⎬ 50		6 ⎬ 27	
Lymphangiography + CT scan	21 ⎭		5 ⎭	
Bone marrow aspiration	48		29	
X-chest	53		32	
ENT inspection	30		6	
Laparoscopy	8		0	
Laparotomy	18		25	
1970–1977	9/10	(90%)	18/20	(90%)
1978–1987	9/43	(21%)	7/12	(58%)
Patients				
1970–1977	10		20	
1978–1987	43		12	
Stage I/II				
1970–1977 10/30 = 33%				
1978–1987 43/55 = 78%				

Table 5. *Endoscopic findings in primary gastric NHL*

	Stage I n = 44	Stage II n = 21	Total n = 65	(%)
Main pattern:				
ulcerations	12	9	21	(32)
diffuse infiltration	14	2	16	(25)
polypoid	17	9	26	(40)
not classified	1	1	2	(3)
Diagnosis NHL on				
first biopsies	38	17	55	(85)
repeated biopsies	5	—	5	(8)
resection material	1	4	5	(8)

stage II), in an additional two cases both in stage II the tumour proved to be unresectable. Of the remaining 39 patients the tumour was judged inoperable in 14 cases, while in 12 patients operation was not performed because of old age (greatly over 70 years). In the other 13 cases (33%) the tumour could have been resected, but they were treated according to our new policy avoiding the mutilation of a gastrectomy. Thus, the overall resectability rate would have been 62% (14 + 13/43; excluding the elderly).

Treatment

Among the treatment schedules presented in Table 6 radiotherapy was essential. Up to 1978 gastrectomy was performed followed by standard radiotherapy in 24 patients. Since 1978 surgery was mainly used in bleeding or deep ulceration to avoid perforation and additional standard radiotherapy was given in 26 patients. In a few cases, in the early period of the study, adjuvant chemo-

therapy was given, usually eight courses of CHVmP. Since 1978 CHMvP was used as induction chemotherapy in several stage II_2 patients followed by radiotherapy (six patients). All the other treatment schedules including variable amounts of irradiation and chemotherapy alone or in combination, with or without surgery were included in the various treatment groups (n = 24). These treatments were considered as merely palliative and usually applied in unfit (KI ≤ 60% in three patients) or elderly patients (age ≥ 70 years in 11 cases).

Local tumour control was achieved in approx. 85% in stage I: 41 CR, three PR, one NC and two PD. Six patients are not evaluable, but three of them survived more than 1 year. In stage II, there were 16 CR, six PR, eight PD and two unknown, leading to an overall response rate of 69%. Treatment failure meaning progressive local disease was present in 10 patients: two in stage I and eight in stage II. In three cases the tumour proved to be unresectable at laparotomy. An additional three
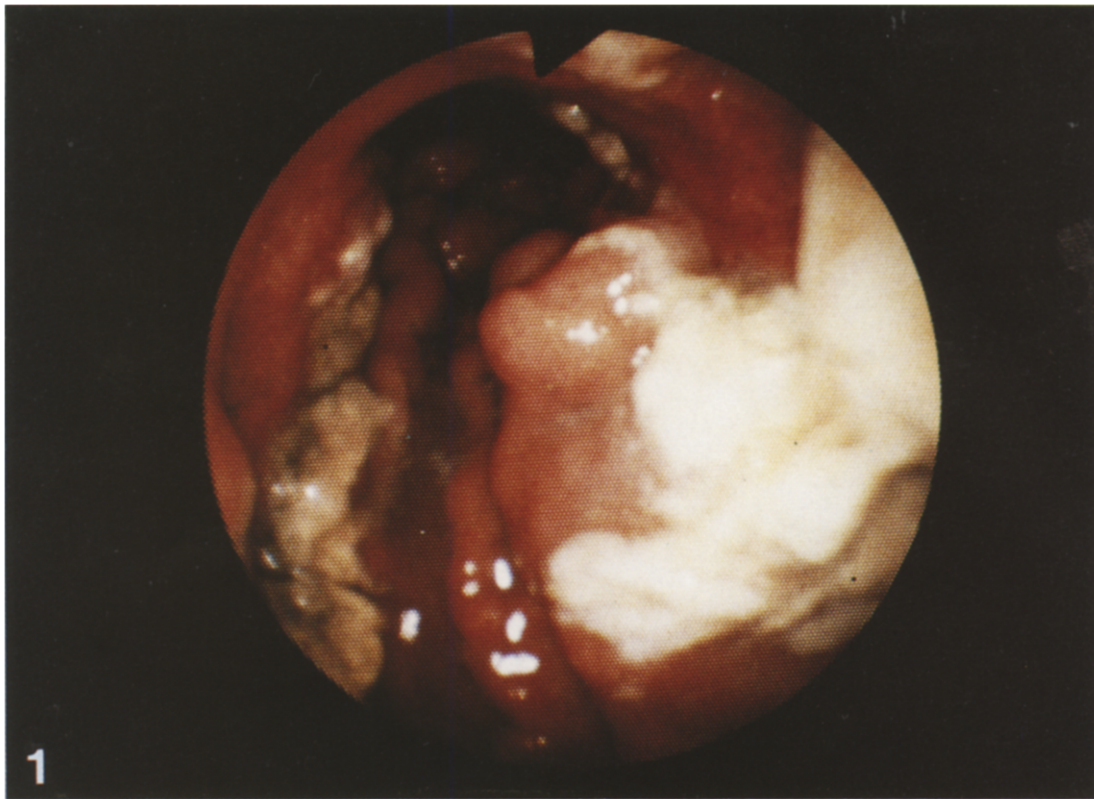
Fig. 1. The characteristic large, irregular and conflating ulcers with thin, stellate and tapered branches.

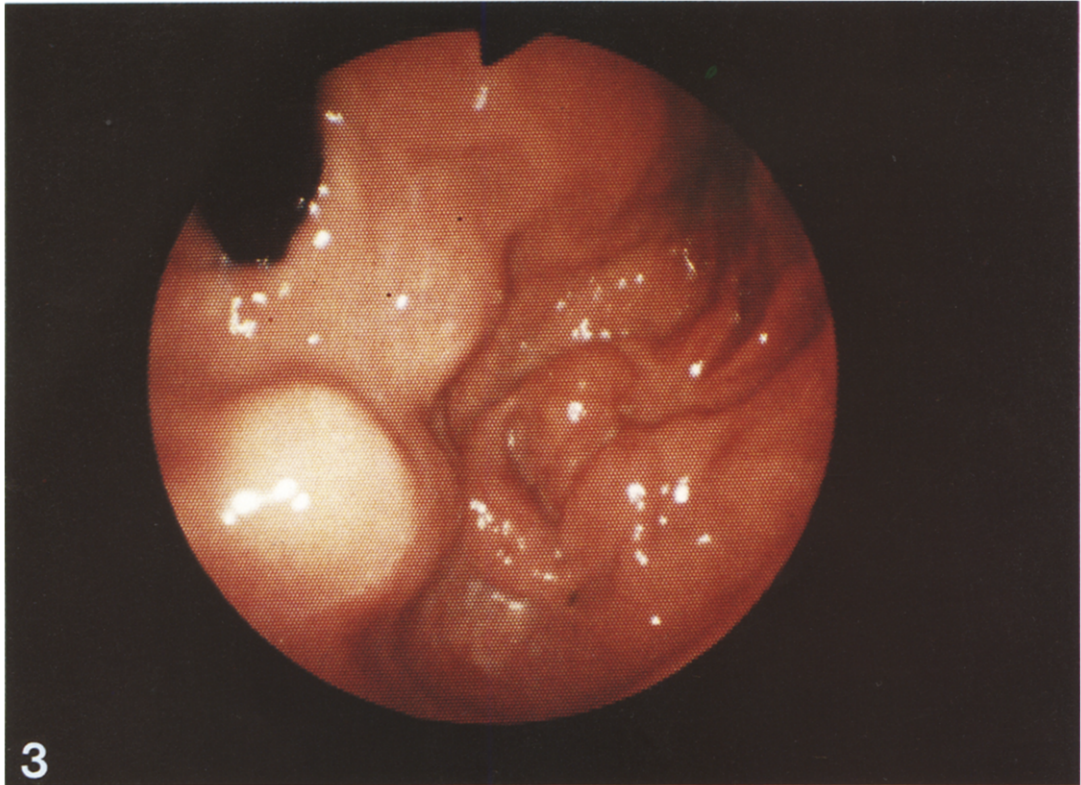*Fig. 2. Giant folds due to submucosal infiltration with oedema, petechiae and superficial erosions.*

Fig. 3. A polypoid mass with a pale and glossy aspect, only seen in U-turn in the gastric fundus.
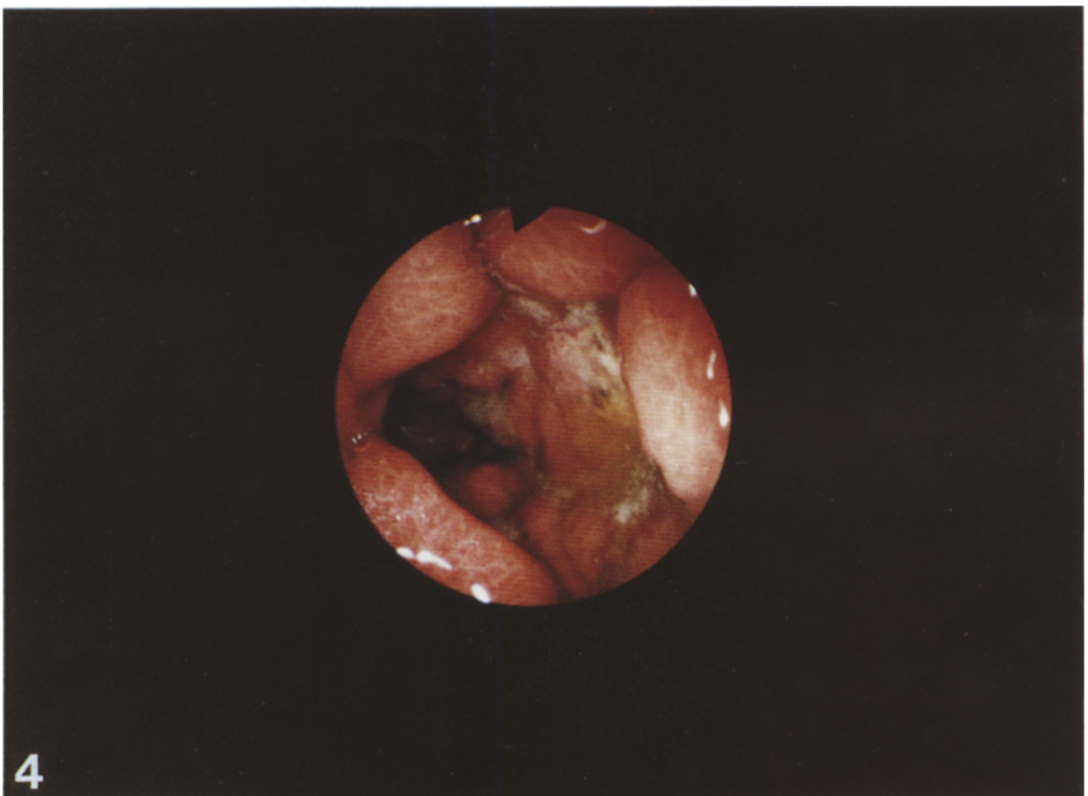

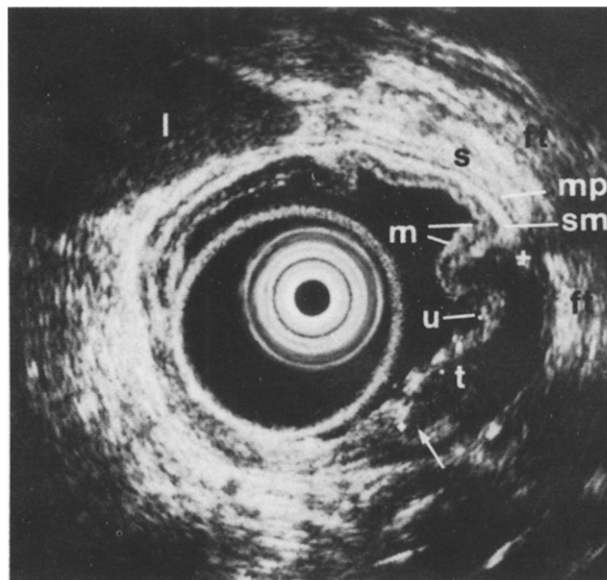Fig. 4. The combination of large polypoid, nodular folds and superficial ulceration.

Fig. 5. Endoscopic ultrasonography, corresponding with Fig. 4, shows the polypoid lesion as a sharply demarcated hypoechoic echo pattern directly adjacent to an ulcerative lesion (U). Note the clear transition between the normal and pathological gastric wall (m = mucosa, sm = submucosa, mp = muscularis propria, s = subserosa, ft = fat tissue and l = liver).

Table 6. *Treatment schedules in primary gastric NHL* (n = 85)

	Stage I n = 53	Stage II n = 32	Total n = 85
Resection + standard RT*	17	7	24
Standard RT only	21	5	26
Standard RT + ad CT† ± resection	3	2	5
Induction CT + st. RT ± resection	0	6	6
Various	12	12	24

*RT = radiotherapy.

†ad CT = adjuvant chemotherapy.

patients were of old age (>70 years) and treated with non-standard schemes or irradiation. No important difference in histologic type was found compared to the whole group.

The 5 year disease-free survival was 63% in the total group of stage I patients and 38% in stage II patients (Fig. 6). According to treatment schedules, patients who underwent standard radiotherapy after resection had a very good disease-free survival at 5 years of 83%. As shown in Fig. 7 the results of standard radiotherapy alone were less favourable: the disease-free survival at 4 years dropped to 64%. Included were a few patients with tumours extending from the cardia to the pylorus, whom we now would consider for induction chemotherapy followed by radiotherapy. Although the follow-up period was shorter, the difference was statistically significant (P = 0.04). The other treatment schedules were less effective.

The treatment schedules were generally well tolerated. Four severe complications, however, were observed. One patient, a women 72 years of age with stage I disease, suffered from a sealed perforation 3 months after the start of radiotherapy (total abdomen 27 Gy, booster 14 Gy). She recovered with conservative treatment; local tumour control was
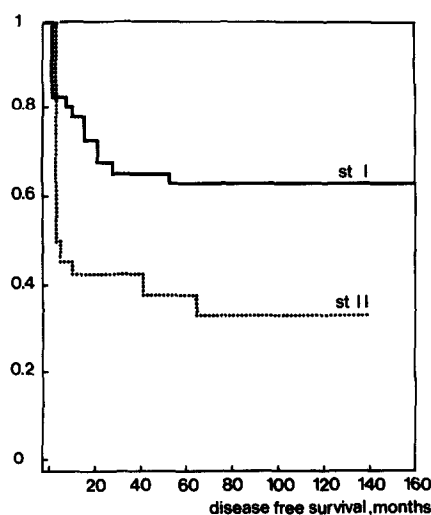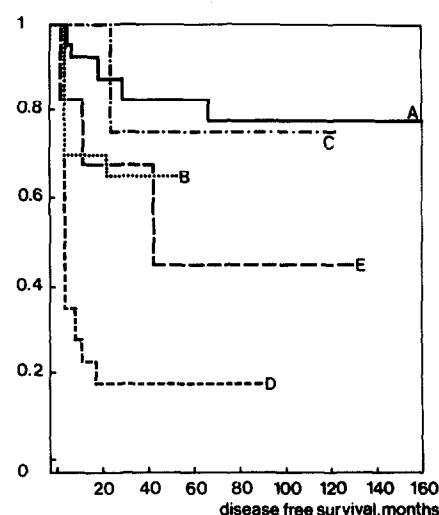

Fig. 7. *Disease-free survival according to treatment: A = resection and standard radiotherapy* (n = 24), *B = standard radiotherapy* (n = 26), *C = standard radiotherapy, adjuvant chemotherapy with or without resection* (n = 5), *D = induction chemotherapy, standard radiotherapy with or without resection* (n = 6) *and E = various treatments; the difference between A and B is statistically significant.*

complete, but she died after 24 months with jaundice due to abdominal recurrence. An additional three patients developed haemorrhage: a 19-year-old boy with extended stage I and high grade malignancy at the end of variable radiotherapy (a large tumour field, 25 Gy); following chemotherapy, he recovered, but died due to new lesions outside the irradiated area after 4 months. In two patients the haemorrhage was fatal: a 72-year-old man in stage I with progressive disease during radiotherapy (23 Gy) developed thrombocytopenia during chemotherapy and died after 2 months, and a 70-year-old man in stage I developed moderate thrombopenia at the end of the standard radiotherapy followed by intractable bleeding (survival 1 month).

Intraabdominal recurrences (small bowel and para-aortic lymph nodes) were found in only two patients as shown in Table 7 with a remarkably large interval as was seen in the extraabdominal recurrences (median 20 months, range 7–54). Extraabdominal recurrences were seen in 13 cases.

Fig. 6. *Disease-free survival in stage I and II: at 5 year 63% and 38%.*

Table 7. Recurrences and secondary tumours after treatment of primary gastric NHL (n = 85)

	Stage I n = 53		Stage II n = 32	
Recurrence:	n, interval months		n, interval months	
terminal ileum	1	16	0	
Waldeyer's ring	2	12, 17	1	17
lymph nodes	1	28	2	12, 64
pleuritis	1	7	1	41
other	3	7, 22, 23	2	6, 6
Total	9		6	
Secondary malignancies:				
stomach	1	128	0	
pancreas	1	54	0	
distal oesophagus	1	48	0	
large bowel	1	48	0	
lung	1	120	0	
prostate	1	44	0	
Total	6		0	

Intercurrent secondary tumours developed in seven cases (Table 7), among which three were localized in the booster field of irradiation (40 Gy) and one in the area of 20 Gy combined with chemotherapy. The bronchial carcinoma was found in a patient treated with partial gastrectomy followed by standard radiotherapy. The association is not clear. The prostate carcinoma was perhaps already present at the first presentation, because rectal examination was not quite normal. The patient with gastric cancer died postoperatively due to septicaemia; in the women with distal oesophageal cancer the tumour was already inoperable at diagnosis and she died 3 months later.

DISCUSSION

Although primary gastric lymphoma is a relatively rare condition, the present series is large and reflects the changes in diagnostic and therapeutic possibilities over the years. The clinical presentation and röntgenography are often non-specific, but since the introduction of endoscopy a preoperative diagnosis of NHL is available with the possibility of recognition in an early stage. Three main patterns were recognized among which the extensive stellated ulcers were characteristic [3, 11]. The endoscopist should keep in mind that the lesions are primarily in the submucosa, therefore multiple and occasionally large forceps biopsies are necessary to prove the diagnosis. With better recognition, the false negative rate of 9% as reported by Maor et al. [12] must be further reduced. In our series the false negative rate of 8% was similar, but primarily in the early period. Gaining experience led to reduction of that figure. The histologic classification revealed frequently a diffuse centrocytic (34%) or centroblastic–centrocytic (34%) type, correspond-

ing to the intermediate grade of malignancy (73%) in the Working Formulation. Similar findings of a small proportion of low grade malignancy and a preponderance of intermediate grade of malignancy have been described in the literature [2, 5]. Immunohistochemical investigations were of great help in distinguishing pseudolymphoma (polyclonal) from NHL (monoclonal).

The clinical staging was uniform in the present series. Since 1978 surgical staging was no longer preferred, in analogy with the therapeutic policy in non-organ NHL, where a preoperative diagosis is obtained. The purpose is both to prevent morbidity and mortality of the operation and to prevent delay in the necessary therapy. The proportion of surgical staging dropped from 90% to 29%. Therefore, staging became less accurate, as regional gastric lymph nodes and local invasion are hard to visualize on CT scan and lymphangiography. Lymph nodes of small size involved adjacent to the stomach leading to stage II on histological examination are particularly missed by non-invasive staging. This explains the shift of 33% to 78% stage I patients in the later period (Table 4). In several series [5, 12] the majority of patients were in stage II, in another the opposite was found [14]. The reason is unclear, whereas a laparotomy was a major part of diagnosis. More accurate staging will be possible in the future with a new non-invasive imaging technique, endoscopic ultrasonography (EUS). Depth of infiltration and pathological lymph nodes can be clearly visualized. Moreover, its use for evaluation of therapy during follow-up will probably become of major importance.

The optimal treatment policy for NHL of the stomach is still under discussion. Most studies are retrospective with a small number of patients in

various subgroups. The role of surgery is unclear. In a large series of 105 patients with gastric NHL Dragosics reported the positive effect of radical tumour resection on survival and local control [12]. These findings were supported by others [13, 14]. In several other studies, surgery did not add to the good results of radiotherapy alone or combined with chemotherapy [1, 12, 15]. Moreover, resection is not always possible due to extensive disease with or without infiltration in the surrounding organs. Based on our previous good results with radiotherapy and also to decrease morbidity, our policy has been changed in 1978 and surgery is no longer routine [16]. Resection, preferably partial, is recommended in case of haemorrhage, deep ulceration or severe obstruction.

In the present series the long term results of partial gastric resection with standard radiotherapy (total abdominal irradiation with a booster to the stomach) were very good with a 5 year disease-free survival of 83%. This figure dropped significantly to 64% at 4 year with radiotherapy alone. This might partly be caused by less accurate staging. In the early years of the new policy we included some 'bulky' lesions which before 1978 might not have come to resection at all, and which since then we included with stage II_2 in the protocol of induction chemotherapy followed by radiotherapy. Therefore, it is not a clear cut conclusion that our new policy gave less favourable results [17]. As regards stage II with extensive lesions, these did better than before 1978 when all these patients were induced in the 'various' treatment groups.

In this respect it is remarkable that there were no recurrences in stomach or lymph nodes which could have been prevented by surgery. Recurrences within the irradiated area were rare: terminal ileum ($n = 1$) and para-aortic lymph nodes ($n = 1$). Also serious complications of radiotherapy were rare: namely one silent perforation and one bleeding;

after combined radiotherapy and chemotherapy two cases of haemorrhage.

Treatment results are better than in gastric carcinoma and comparable to data of the literature [5, 12]. Although local tumour control is frequently achieved (83% in stage I and 69% in stage II), the survival rate still needs to be improved especially in stage II. Since aggressive recurrence outside the irradiated area is the main cause of death, this might only be prevented by a systemic treatment such as chemotherapy. In our series the group treated with induction chemotherapy is too small to draw conclusions. Data on the effect of chemotherapy are all favourable, but the numbers are small and the treated groups not homogeneous [12, 14]. The only prospective study of resection followed by chemotherapy [18] showed a promising disease-free survival rate of 83%, although the numbers are small (23 patients) and the follow-up is relatively short (median 4.6 years).

We feel that it is justified to continue our treatment policy without gastrectomy after non-invasive staging. In stage I non-bulky disease the treatment results with total abdominal radiotherapy, with a booster dose to the stomach are satisfactory. This treatment could also be given to patients between 75 and 85 years. However, for stage II and very large stage I, our current treatment policy of eight courses of CHVmP followed by limited radiotherapy still calls for improvement. The new endoscopic diagnostic procedures are an important step forward in early diagnosis and patient management as it can spare the patient the burden of a laparotomy and a gastrectomy. In patients with extensive tumours the reaction to induction chemotherapy can be watched and treatment accordingly adapted.

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