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PRIMARY GASTRIC NON-HODGKIN'S LYMPHOMA

A retrospective clinico-pathological study

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Prognostic factors and treatment results were analysed in 72 consecutive patients with primary gastric lymphoma treated between 1970 and 1985. There were 37 patients in stage IE, 17 in IIE, 3 in IIES and 15 in stage IV. Histopathological re-evaluation and classification according to the TNM system were performed. We found that disseminated disease (stage IV), serosal penetration (T3), involvement of adjacent organs (T4) and extensive abdominal lymph node involvement (N3) were poor prognostic factors. Neither histological malignancy grading, nor the appearance of lympho-epithelial lesions were significantly associated with relapse-free survival. Forty-six patients with 'limited localized' disease (stage IE, IIE, N3 excluded) received potentially curative treatment (surgery, radiotherapy, chemotherapy or combinations thereof), of whom 85% remained relapse-free. Thirty-four patients did only get local treatment (surgery and/or radiotherapy) with curative potential, the relapse-free survival rate was 85%. We conclude that primary gastric lymphoma stage IE and IIE (N3 excluded) is often a truly localized disease that can be cured with local therapy.

Primary gastric non-Hodgkin's lymphoma represents a relatively uncommon gastric neoplasm, accounting for 1–10% of all gastric malignancies (1–3). However, the stomach is one of the most common extranodal sites for malignant lymphoma (4). Most knowledge on this disease is based on uncontrolled retrospective studies. Therefore, the management of primary gastric lymphoma remains an issue of controversy.

Extranodal lymphomas in the mucosa-associated lymphoid tissue (MALT), i.e. in the gastrointestinal tract, have been described in the literature as diseases with histological and clinical features that differ from nodal lymphomas (5, 6). MALT-lymphomas are difficult to classify according to the commonly used classifications. Special histological features have been identified (5). One objective of the present study was to investigate the prognostic value of malignancy grading and one of the special histological MALT-features, i.e. the appearance of lympho-epithelial lesions (LEL).

Staging according to the Ann Arbor system has been reported to give good prognostic information in gastric lymphoma (7–11). However, a major disadvantage of the Ann Arbor system is that neither local tumor growth, nor extension of the abdominal lymph node involvement are evaluated. One aim of the present study was to investigate whether the use of the TNM classification would add prognostic information to the Ann Arbor staging. Clinically, MALT-lymphomas often remain localized to the primary site and regional lymph nodes for prolonged periods. (5) For this reason they should be curable with local treatment. To what extent localized disease can be cured with local therapy was also evaluated in the present study.

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Material and Methods

Patients. Included in this retrospective study were all 72 patients with a diagnosis of primary gastric non-Hodgkin's

lymphoma (NHL), examined and treated at the Department of Oncology, University Hospital of Lund, Lund, Sweden, during the 16-year period 1970–1985. The lymphoma was considered primary in the stomach if the main symptom, leading to medical attention, was upper gastro-intestinal distress and the bulk of tumor was found in the stomach. Thus, also patients who at investigation were found to have disseminated disease, were included in this series. There were 48 men and 24 women. The median age at diagnosis was 65 years, range 16–80. The median follow-up time was 7.7 years, range 2–16 years.

Staging. The Ann Arbor system for staging was utilized. Locally advanced tumors, without signs of dissemination, were classified as stage IE or IIE, even when involving adjacent organs. Stage IE was found in 37, IIE in 17, IIES in 3 and stage IV in 15 patients. Fifty-three of all 72 patients (74%) were 'adequately' staged (minimum requirements: chest x-ray, bone marrow examination and laparotomy or non-invasive evaluation of abdominal lymph node status). In 19 patients the staging was considered inadequate and the majority of these patients were examined during the early part of the study period, 1970–1976. Non-examined sites were regarded as negative in the staging review. Of 54 patients with localized disease, stage IE-IIE, 40 were 'adequately' staged. Among the 14 'not adequately' staged patients, 4 died of lymphoma, none of them with recurrence in a site not examined at primary staging. Regarding the abdominal staging methods there was a gradual shift from using urography, lymphography, stomach radiography, liver-spleen scintigraphy and fine-needle aspiration in the early years of this study, towards an increased use of CT-scan and gastroscopy during the later part of the study period.

Treatment. The three treatment modalities—surgery, radiotherapy, and chemotherapy—were used and combined in a number of different ways, see Table 1. Laparotomy was performed in 57 cases and 44 of those underwent a surgical resection of the tumor, total or subtotal gastrectomy. External radiotherapy was delivered to 35 patients, in one case with orthovoltage x-ray therapy and to the 34 remaining patients with ^{60}Co or 6–8 MV x-rays from a linear accelerator. The target volume was the stomach including the loco-regional lymph nodes in all but 2 cases where the whole abdomen was irradiated. The majority of cases, 25, were treated with two-field techniques; AP-PA or AP-lateral. The remaining patients received the radiotherapy through one, three or four portals. The absorbed target dose was 30–39 Gy in 4 patients and 40–50 Gy in 26 patients (median 40 Gy). Five patients received lower doses, 12–24 Gy, due to bad performance status or large treatment volumes. A target dose of $\geq$40 Gy will be referred to as 'radical' radiotherapy in the following.

Chemotherapy was included in the initial treatment of 38 patients, 21 with localized disease and 17 with stage IIES or IV disease. The large diversity of chemotherapy regimens used during the 16 years of this study reflects the gradual development of new drugs and combinations towards the chemotherapeutic approach that was up-to-date in the mid 80's. At the early years of the study, most patients received different single drugs (cyclophosphamide, vincristine, etc.) whereas combined drug schedules were used during the later years of the study period. Twenty-four patients received an average of 6 cycles, range 1–11, of CVP (cyclophosphamide, vincristine and prednisone), CHOP (cyclophosphamide, doxorubcin, vincristine and prednisone), CHOP-M (+methotrexate) or MEV (methotrexate, cyclophosphamide and vincristine) in the initial treatment, given with curative intention. In the present study, a minimum of 6 cycles of any of these chemotherapy combinations was, somewhat arbitrarily, considered potentially curative and will be referred to as 'curative chemotherapy' in the following. As the three therapy modalities were combined in so many ways, it was not possible to evaluate and compare in detail the efficacy of the different treatments. Therefore we chose to concentrate on the treatment of patients with 'limited localized' disease (stage IE-IIE, N3 excluded).

Table 1

Treatment by Ann Arbor stage

	Stage IE	IIE	IIES	IV	Total
	No. of patients				
Res	7			1	8
RT	7	2			9
CHT	3			9	12
Res + RT	10	5			15
Res + CHT	5	6	1	3	15
RT + CHT	3		1	1	5
Res + RT + CHT	1	3	1	1	6
No therapy	1	1			2
Total	37	17	3	15	72

Res = Surgical resection
RT = Radiotherapy
CHT = Chemotherapy

TNM classification. In order to evaluate the local extension of the primary lymphoma and the regional lymph nodes, the TNM classification (UICC) designed for gastric carcinomas was utilized. We used the 1982 edition that differentiates between N2 and N3. As T grouping for evaluation of local tumor growth requires a surgical exploration, it could only be performed in the 57 patients who were laparotomized. The N grouping was based on either laparotomy or radiographic findings. Four patients (stage IE: n = 3, stage IV: n = 1) had no adequate assessment concerning abdominal lymph nodes. They were regarded as NX, but still included in the analyses by Ann Arbor stage.

Histopathology. A retrospective histological re-evaluation was performed by our pathologist (MÅ). The specimens were subjected to malignancy grading into high-grade and low-grade malignant lymphomas, according to the Kiel-classification, and the presence of LEL was evaluated. Sixty-five of the 72 cases could be re-examined. New sections were cut from the archival material when the primary sections were of poor quality. Out of those 65 patients, 55 had undergone a laparotomy and 10 were gastrobiopsied only. In the remaining 7 cases re-examination was not possible due to poor quality of the primary sections and insufficient archival material for recutting. In five of these 7 unclassifiable cases, the histological material derived from gastrobiopsy only. Immunohistological staining on archival material was performed in 17 cases; it was used especially if the original diagnosis was 'true histiocytic lymphoma'. The diagnosis of MALT-lymphoma is based on the following histological criteria (5); follicle formation, diffuse infiltrates of centrocyte-like cells, infiltrates of plasma cells in the upper part of the mucosa and lympho-epithelial lesions (LEL). In the present study special interest was paid to the appearance of LEL, a distinctive MALT-feature that was considered the easiest one to identify in this archival material. Evaluation of LEL, which requires presence of gastric glands in the histological specimen, could be done in 48 of the 65 cases.

Statistics. Relapse-free survival was calculated by life-table technique and differences in survival were compared by the generalized Wilcoxon-Gehan's test. Fisher's exact test was utilized for analysis of the clinico-pathological correlations.

Results

Clinico-pathological correlations. The lymphomas were divided into high-grade and low-grade malignant NHL (Table 2a). The high-grade malignant NHLs were localized (stage IE, IIE) in 86% of the cases, while the low-grade NHLs were localized in 68% ($p = 0.09$). Serosal penetration (T3) or involvement of adjacent organs (T4) was found in 65% of the high-grade NHLs and in 41% of the low-grade NHLs ($p = 0.10$). The abdominal lymph node spreading pattern was similar in the two histological groups. High-grade and low-grade NHLs had 'none or regional lymph node involvement' (N0-N2) in equal frequencies, 79% and 81% respectively. In the 48 cases where LEL-status was evaluable, LEL were found in 11/30 (37%) of the high-grade and in 9/18 (50%) of the low-grade malignant lymphomas (Table 2b). This difference was not statistically significant ($p = 0.38$). The proportions of patients with localized disease (stage IE-IIE), locally advanced growth (T3-T4) or 'extensive abdominal lymph node involvement' (N3) were not associated with the LEL-status, within the high-grade and low-grade group respectively.

Survival by histopathology and stage. Relapse-free survival was not significantly associated with histology, nor with the presence of lympho-epithelial lesions (Fig. 1). The

Table 2a

Histopathological and clinical data on 72 patients with primary gastric lymphoma

Histology	n	Ann Arbor stage				UICC stage					
		IE	IIE	IIES	IV	Tx	T1-2	T3-4	NX	N 0-2	N3
High-grade	43	25	12	1	5	6	13	24	2	32	9
Low-grade	22	10	5	1	6	5	10	7	1	17	4
Unclassified	7	2	0	1	4	4	0	3	1	3	3
Total	72	37	17	3	15	15	23	34	4	52	16

Table 2b

Histopathological and clinical data on 48 patients with evaluable LEL-status

Histology	n	Ann Arbor stage				UICC stage					
		IE	IIE	IIES	IV	Tx	T1-2	T3-4	NX	N 0-2	N3
High-grade											
LEL+	11	5	5	0	1	2	3	6	0	10	1
LEL−	19	13	3	1	2	1	7	11	1	14	4
Low-grade											
LEL+	9	5	1	1	2	1	6	2	0	7	2
LEL−	9	4	1	0	4	4	2	3	1	6	2

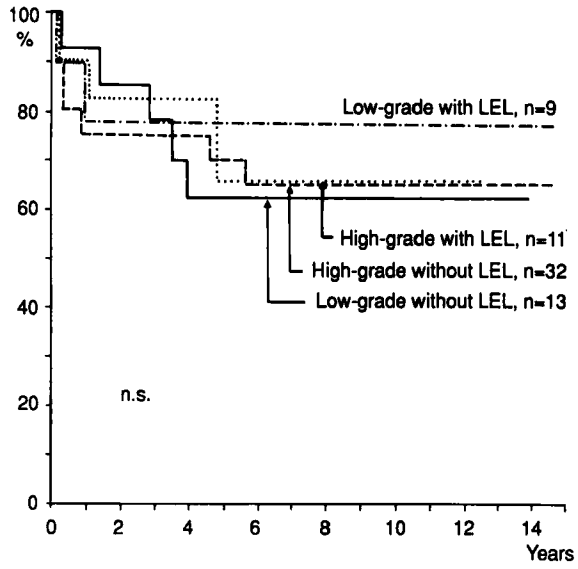

Fig. 1. Relapse-free survival by histological malignancy grading and the appearance of lympho-epithelial lesions, LEL (all stages).

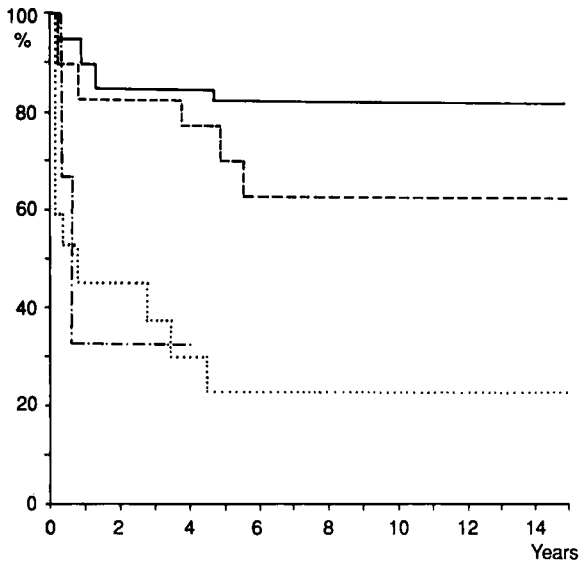

Fig. 2. Relapse-free survival by Ann Arbor stage —— stage IE (n = 36); - - - stage IIE (n = 18); -·-·- stage IIES (n = 3); ····· stage IV (n = 15).

relapse-free survival rate was higher in patients with localized disease (Fig. 2), Ann Arbor stage IE (78%) or IIE (71%), as compared to patients with stage IV (27%). Only three patients had splenic involvement, stage IIES. Two of them died of lymphoma. When analyzing the localized lymphomas, stage IE-IIE, the relapse-free survival rate was higher ($p = 0.01$) in patients with superficial tumor growth (T1-T2) than in patients with locally advanced cases (T3-T4), Fig. 3. Cases with extensive abdominal lymph node spread, N3, had a significantly worse prognosis than the NX, N0-N2 lymphomas ($p = 0.006$), Fig. 4.

Survival by treatment. Table 3 illustrates that 46/48 patients with 'limited localized' disease were treated with one or several of the three treatment modalities with 'curative potential'. Thirty-nine of these 46 patients (85%) remained relapse-free. None of the patients that developed a lymphoma recurrence was rescued. The two patients without treatment with 'curative potential' died. The different therapy modalities seemed to give approximately equal relapse-free survival rates. The small number of cases in each treatment combination group did not, however, permit any statistical comparison. Forty-two patients received adequate local therapy, radical surgery and/or 'radical' radiotherapy. Thirty-six (86%) of those remained lymphoma-free. Out of the 6 patients with recurrent disease, 4 had local abdominal recurrence. When excluding the 8 patients who, besides adequate local therapy, also received chemotherapy with curative potential, the relapse-free survival rate was 85%.

Treatment complications and intercurrent disorders. In the actual series the postoperative mortality rate could not be properly evaluated, since most patients were referred to our department after the postoperative period. No cases of treatment-induced bleeding or perforation were observed. Two patients died of early chemotherapy-related complications; one patient with a pulmonary abscess due to leukopenia after 3 cycles of MEV, and one patient with acute kidney failure 4 days after the start of CHOP treatment. Three patients died of intercurrent disorders several years after radiotherapy. One patient had a pancreatic carcinoma 9 years after 41 Gy, another patient had a bile duct carcinoma 14 years after 40 Gy, and yet another patient developed an extensive abdominal fibrosis 10 years after 40 Gy. Finally, one patient had a multiple myeloma

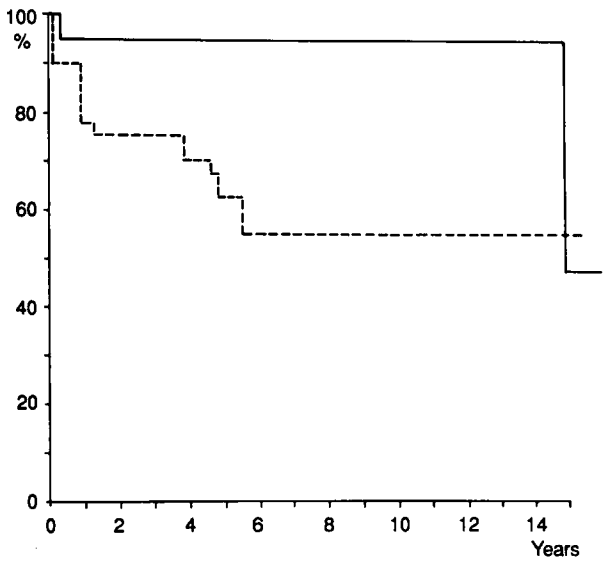

Fig. 3. Relapse-free survival by T category (stage IE and IIE only) —— T1-T2 (n = 21); - - - - T3-T4 (n = 28); p = 0.01.

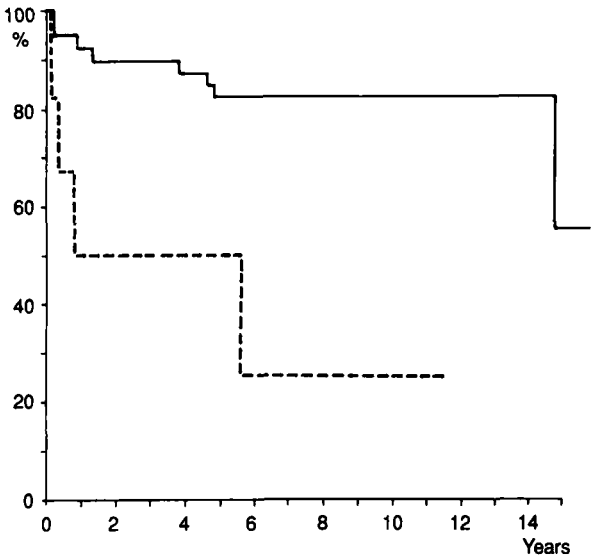

Fig. 4. Relapse-free survival by N stage (stage IE and IIE only) —— NX, N0-N2 (n = 48); - - - N3 (n = 6); p = 0.006.

5.5 years after 7 cycles of CHOP and one patient had a hypernephroma 6 months after lymphoma diagnosis.

Table 3

Recurrence rates by treatment for patients with 'limited localized' disease (stage IE, IIE, NX included, N3 excluded)

	Stage IE	IIE (−N3)	IE + IIE (−N3)
	No. recurrences/No. at risk		
Rad res	1/9	0/0	1/9
Cur RT	0/8	0/2	0/10
Non-rad res + Cur RT	1/2	1/4	2/6
Rad res + Cur RT	2/7	0/2	2/9
Cur CHT + Rad res and/or cur RT	1/5	0/3	1/8
Cur CHT + Non-rad res	1/1	0/0	1/1
Cur CHT	0/3	0/0	0/3
Any potentially curative treatment	6/35	1/11	7/46
No curative treatment	2/2	0/0	2/2
Total	8/37	1/11	9/48

Rad res = Radical surgical resection
Cur RT = Curative radiotherapy, target dose ≥ 40 Gy
Cur CHT = Curative chemotherapy; 6 or more cycles of COP, CHOP, CHOP-M or MEV

Discussion

Identification of reliable prognostic factors is of great importance for guidance of the therapeutic approach. Staging of gastric lymphomas according to the Ann Arbor system has been found to be of prognostic value in most studies (7–11), including the actual series. Two of three patients with splenic involvement died of disease. The limited number of cases does not permit any conclusions, but there are reasons to believe that splenic involvement indicates a disseminated disease with worse prognosis.

A major disadvantage of the Ann Arbor system is the fact that it does not take into account the local tumor growth or the extension of the abdominal lymph node involvement. Many authors have used the Mushoff modification of the Ann Arbor system (12), to subdivide stage IIE according to the site of abdominal lymph node spread and they consistently report a worse survival for stage II2E as compared to stage II1E (7, 13, 14). Others have prefered to use the TNM classification (9, 10). In the present study the TNM system gave valuable information. Extensive abdominal lymph node involvement (N3) showed to be a poor prognostic factor. The TNM system also contains information on the growth depth of the primary lesion. Our study showed a worse relapse-free survival at serosal penetration (T3) or invasion of adjacent organs (T4), in accordance with many other reports (4, 11, 14–18).

Opinions on the prognostic value of histological grading varies considerably in the literature. Using different classifications, some authors have found a worse prognosis for high-grade than for low-grade malignant lymphomas (7, 14, 16, 19). Others report no difference in survival between the high-grade and the low-grade groups (10, 13, 20, 21), nor did the actual study reveal any correlation between malignancy grading and relapse-free survival. However, there was a tendency for the high-grades to be more locally advanced and the low-grades to be more frequently disseminated.

The clinico-pathological correlations of the MALT-concept have only been scarcely studied previously. It has been stated that primary gastric lymphomas express special histological and clinical features (5, 22). Moore & Wright (22) identified lympho-epithelial lesions in 44% in a series of 36 cases of primary gastric lymphomas and the percentage of lesions was highly depending on the types of malignant cells. In 27% of centroblastic, in 61% of centroblastic/centrocytic, and in 29% of centrocytic lymphomas lympho-epithelial lesions were present. A similar tendency of a higher frequency of lympho-epithelial lesions when high-grade and low-grade cellular elements coexist was found also in another study (23). In the present study there was no statistically significant difference regarding the presence of lesions between high-grade (37%) and low-grade (50%) malignant lymphomas. Whether the appearance of these histological features are associated with a more localized disease and a better

prognosis has been the subject of a few studies. MacLennan et al. (24) found that MALT type lymphomas were correlated to a better prognosis, regardless of histological grading. On the contrary, van Krieken et al. (25) reported that introduction of mucosa-associated lymphomas as an entity did not add any prognostic information. Nor did we find any correlation between tumor stage or survival and appearance of one of the histological MALT-features, the lympho-epithelial lesions.

Due to the lack of large prospective studies, the treatment of primary gastric lymphomas still remains a controversial issue. Many authors recommend surgical resection of the gastric tumor (9, 11, 14, 21, 26–29). There are several arguments in favor of primary surgery. The histological diagnosis and subtyping is more reliable when based on large specimens and laparotomy makes the staging procedure regarding serosal penetration and abdominal lymph node involvement much more accurate than different radiographic methods. Bleeding and perforation of an unresected tumor responding to radio- or chemotherapy can be avoided. No instances of bleeding and perforation occurred in the actual series, while the frequencies in the literature vary from 0–25% (3, 11). Another argument in favor of primary surgery is the fact that the patient might be cured with surgery alone. Many authors emphasize the prognostic importance of radical surgery (7, 9, 10, 16, 26, 30). In our study there was no convincing evidence that surgical resection was a superior, or even necessary, treatment modality for curing localized gastric lymphomas. The role of radiotherapy and chemotherapy in the treatment of localized primary gastric lymphoma varies considerably in the literature. Some authors report good results with postoperative chemotherapy, even in stage IE (29, 31), while many others recommend chemotherapy to all patients with stage IIE (27, 29, 31–34). In our study, only three patients had localized disease that received chemotherapy as the only treatment with curative potential, which does not permit us to draw any conclusions on the effectiveness of chemotherapy.

Some authors state that good local control can be achieved with radiotherapy to localized disease, given either as the only treatment or as adjuvant postoperative therapy at target doses of at least 40 Gy (17, 19, 20, 33). Others report poor effect of radiotherapy (11, 27) when using lower doses. Our study confirms that a good local control and high cure rates can be achieved with radiotherapy to the gastric bed and regional lymph nodes at doses in the order of 40 Gy.

In the present study there were four cases (6%) of second malignancies. There are only scattered comments on the occurrence of second malignancies in the literature. Rao et al. (19) reported development of secondary non-lymphomatous malignancies in 6/65 (9%) cases. Two of our patients had secondary carcinomas, in the pancreas and the bile ducts, within the regions of delivered radiotherapy. In those cases the radiotherapy cannot be excluded as an etiological factor. However, this finding might be incidental and there is no evidence in the literature for an increased cancer incidence within regions treated with radiotherapy for gastric lymphomas. The extensive abdominal fibrosis found in one of our patients was probably due to the radiotherapy.

Table 4

Proposed schedule for treatment of localized gastric lymphona

	Treatment after		
	Radical resection	Non-radical resection	Biopsy only
T1-2 N0	—	RT	RT
T3 N0	RT	RT	RT
T4 N0	RT	RT	(CHT)/RT
T1-3 N1-2	RT	RT	RT
T4 N1-2	RT	RT	(CHT)/RT
T1-4 N3	CHT	CHT/(RT)	CHT/(RT)

RT = Radiotherapy, 40 Gy target dose, gastric bed and regional lymph nodes
CHT = Chemotherapy

In conclusion, we believe that primary gastric lymphomas stage IE and 'limited' stage IIE with only regional lymph node involvement are often truly localized diseases and that they can often be cured with local therapy. Possibly, equal results can be achieved in localized gastric lymphomas with chemotherapy but we find it most logical to apply a local treatment approach in these patients.

At present, we have formulated the following principles for treatment of primary gastric lymphoma in our department. The majority of our patients will go through primary surgery for staging and tumor resection (total gastrectomy only when forced by the site and size of the tumor) whenever feasible in view of the general condition of the patient. For additional therapy we use the principles scheduled in Table 4. Patients radically operated on for tumors confined to the mucosa or submucosa (T1-T2) will not get any adjuvant treatment. Chemotherapy will mainly be used in stage IIE N3, and higher stages. Chemotherapy can also be considered when there is involvement of adjacent organs, T4. In all other instances radiotherapy will be used as adjuvant treatment. These principles will be used until further investigations have called for re-evaluation.

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