Primary Gastrointestinal Non-Hodgkin's Lymphoma

A Population Based Study in Central Finland in 1975–1993

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Gastrointestinal lymphomas have been uncommon, but the frequency of their predisposing conditions is increasing. The objective of the present study is to determine the frequency of gastrointestinal lymphomas in the area of central Finland as well as the influence of clinical features and therapeutical approaches on the survival of these patients. All samples of gastrointestinal non-Hodgkin's lymphomas diagnosed of patients living in the province of central Finland in 1975–1993 were re-examined. In central Finland the mean annual frequency of new gastrointestinal lymphomas was 10/1 000 000 in 1975–1984 and 16.0/1 000 000 in 1985–1993. The total incidence of gastrointestinal lymphomas in Finland adjusted for age to the world standard population was 12.5/1 000 000 in 1992. Two patients with peripheric T-cell lymphoma had a coeliac disease. Other predisposing conditions were not found. The stage of distribution of the lymphoma ($p < 0.01$) and radicality of the surgery ($p < 0.01$) were the most influencing factors on the survival of these patients. In conclusion the early distinction of gastrointestinal lymphomas is vital because of an increasing frequency of predisposing factors and a better prognosis due to new combination therapies.

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In the Western countries gastrointestinal lymphomas comprise less than 20% of all non-Hodgkin's lymphomas (1) and less than 5% of all primary gastrointestinal malignancies (2, 3), though there are regional and racial variations. Even in cases of uncommon malignancies the distinction of gastrointestinal lymphomas has become more important due to better awareness and increasing frequency of predisposing conditions (4). The ideal treatment for early stage gastrointestinal lymphomas is still controversial, though the prognosis after treatment is superior to the other gastrointestinal malignancies. Some investigators advocate an aggressive surgical approach and others recommend chemo- and radiotherapy as a primary approach especially for gastric lymphoma (5, 6).

Central Finland is a geographically and administratively well-defined area with a population of 250 000 inhabitants. During the last two decades changes in the population have been minor. In this area there is only one hospital where gastrointestinal malignancies can be treated. The objective of the present study is to determine the annual changes in the frequency of gastrointestinal lymphomas in this area in 1975–1993 and to correlate them to the occurrence of predisposing conditions. Clinical features of gastrointestinal lymphomas, therapeutical approaches as well as the influence of these factors on the survival rate are described.

MATERIAL AND METHODS

The records of patients with a diagnosis of non-Hodgkin's lymphoma of the gastrointestinal tract in the province of central Finland between January 1975 and December 1993 were reviewed. These data were complemented by the nation-wide data of the Finnish Cancer Registry from the same time period (7). The Finnish Cancer Registry is an institution established in 1953 where all physicians and pathologic laboratories in Finland are requested to report all cases of malignancies. During the time period 79 patients who were diagnosed to have gastrointestinal lymphoma and who at the time of diagnosis resided in central Finland were found. Seventy-six of the patients were treated in the Hospital of central Finland, whereas three patients were treated elsewhere.

Pathological samples of the tumours were separately re-examined by two pathologists familiar with gastrointestinal malignancies and lymphomas. Sixty-one of the 79 patients fulfilled the criteria described by Dawson et al. (8): 'non-Hodgkin's lymphoma that originates from the gas-

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Table

Characterisstics of the patients with verified gastrointestinal lymphoma in central Finland in 1975–1993

	Stomach	Small bowel	Colon	Oesophagus	Polyposis	All
Number	30	20	9	1	1	61
Males (%)	15 (50%)	12 (60%)	8 (88%)	1	1	37 (60%)
Mean age (years)	65.2 ± 10.7	61.0 ± 18.4	74.2 ± 13.4*	59	59	65.0 ± 14.3
Range of age (years)	40–82	16–90	45–87			16–90
Grade of malignancy:						
high	83%	85%	67%	–	1	80%
low	10%	10%	33%	1	–	15%
indefinite	7%	5%	–	–	–	5%
Distribution						
stage I	47%	20%	11%	1	–	31%
stage II	23%	60%	33%	–	1	43%
stage III	6%	–	–	–	–	4%
stage IV	24%	20%	56%	–	–	22%
Surgery						
curative	57%	4%	22%	1	–	46%
palliative	23%	55%	56%	–	–	38%
explorative	10%	5%	–	–	–	6%
no surgery	10%	–	22%	–	1	10%

* The patients with lymphoma in the colon were significantly older compared with the other patients with gastrointestinal lymphoma ($p < 0.05$).

trointestinal tract, and no leukemia, no peripheral or mediastinal lymph node enlargement and no hepatic or splenic involvement except direct extension present at the time of diagnosis'. Tumours accepted as gastrointestinal non-Hodgkin's lymphomas were reclassified as high- and low-grade lymphomas (9, 10). The distribution of the lymphomas was graded as stage I if the tumour confined to the gastrointestinal tract, stage II if there was involvement in regional lymph nodes, stage III if there was involvement in lymph nodes other than regional, and stage IV if there was contiguous extension to the other organs within the abdomen (11). Furthermore, in patients with gastric lymphoma tumour-free specimens of the gastric mucosa, if available, were stained for Helicobacter pylori determinations, and in patients with lymphoma of the small bowel tumour-free specimens of the proximal small bowel were examined in order to find villus atrophy.

Most of the patients were primarily sent to surgical treatment and thereafter to an oncological consultation for radio- or chemotherapy. The radicality of the surgery was judged according to histopathological findings of the resection specimen, as well as according to the surgeon's opinion based on the macroscopical appearance. The main principles of the surgical treatment of lymphomas were unchanged during the study period. Radical resection of the tumour was the effort, but if this was not reached, bulcetomy, i.e., unradical resection, was chosen as the second best alternative. Staging examinations including blood cell count and serum chemistry screen, chest radiography, ultrasonography and/or computed tomographic scans, lymphography and bone marrow aspirates were performed on all patients who underwent oncological consultation. Routine laparotomies for staging or evaluation of response were not performed. In the 1970's radiotherapy alone was administered as a complementary therapy after surgery, whereas in the 1980's radiotherapy was replaced by chemotherapy. From 1980 to 1985 the combination chemotherapy regimen used was mostly based on CHOP-bleo-chemotherapy (cyclophosphamide, doxorubicin, vincristine, prednison, bleomycin) and after the year 1985 the combination chemotherapy was mostly based on m-BACOD-chemotherapy (methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, dexametasone).

Statistics. The χ^2-test and Fisher's exact test were used to compare variables in the various patient groups. Differences between the means of the various subgroups were assessed using Student's t-test. The lymphoma specific survival rates were determined using the life-table method (Kaplan–Meier), and statistical differences between the survival curves were assessed by the log-rank test.

RESULTS

Frequency and localization

In 30 patients the lymphoma was situated in the stomach, in 20 in the small bowel, and in 9 in the colon (four lymphomas in the caecum or ascending colon and in the left colon). The patients with lymphoma in the colon were older compared with the patients with another situation of the gastrointestinal lymphoma ($p < 0.05$). The characteristics of the patients with gastrointestinal lymphoma are

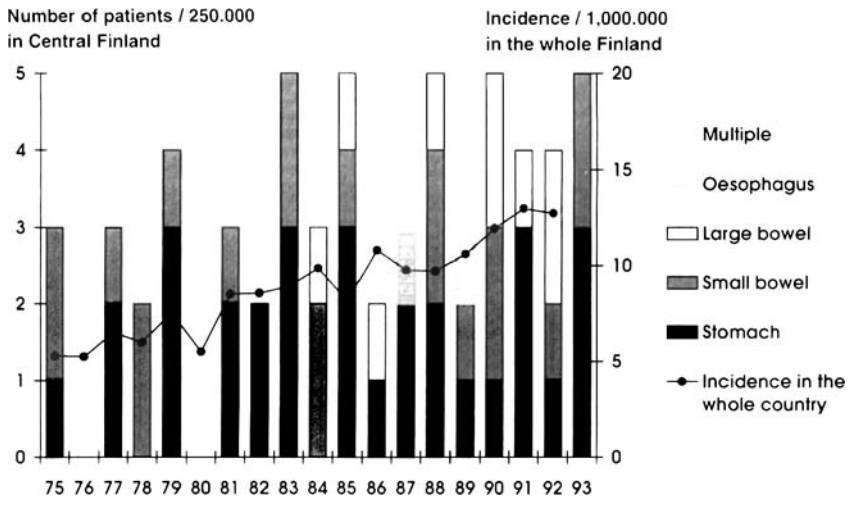

Fig. 1. Annual changes in the frequency of gastrointestinal lymphomas according to site in central Finland (columns) and annual incidence adjusted for age to the world population in the whole Finland (line), as is officially announced by the Finnish Cancer Registry.

shown in the Table. In central Finland the mean annual frequency of gastrointestinal lymphomas was 12.8/1 000 000 inhabitants (10 new cases/1 000 000 annually 1975–1984 and 16 new cases/1 000 000 annually 1985–1993). One contributing factor to the increase seems to be the appearance of colonic lymphoma since 1984. Annual changes in the frequency of new gastrointestinal lymphomas in central Finland are shown in Fig. 1. The figures from central Finland are compared with those of the whole country announced by the Finnish Cancer Registry (7).

Histological type

In 58 (95%) of the 61 patients the type of gastrointestinal lymphoma could be retrospectively classified. Although the diagnosis of the lymphoma could be confirmed, the type of the lymphoma was not possible to classify in three patients due to an insufficient piece of specimen (an edge of perforated gastric ulcer in one patient, only an endoscopical biopsy in another patient and a lymph node in the third patient). Forth-nine (80%) patients were classified to have high-grade lymphoma comprising centroblastic lymphoma in 38 patients, immunoblastic in 5, lymphoblastic in 2, peripheric T-cell in 2, Burkitt in one, and diffuse centrocytic polyposis in one patient. Nine (15%) patients had low-grade mucosa associated lymphoid tissue (MALT) lymphoma.

Predisposing factors

Gastric specimens could be stained for H. pylori in 63% of the 30 patients with gastric lymphoma. Eleven of the 16 patients with high-grade lymphoma were H. pylori positive but none of the three patients with low grade MALT lymphoma. Two of the 20 patients with lymphoma of the small bowel were diagnosed to have villus atrophy at the same time as they were diagnosed to have lymphoma. Both of them had peripheric T-cell lymphoma. No cases with acquired immunodeficiency syndrome, long-standing immunosuppression, chronic intestinal parasite infection or inflammatory bowel disease were observed among the present patients.

Distribution and operability

The distribution of the gastrointestinal lymphomas was stage I in 31%, stage II in 43%, stage III in 4%, and stage IV in 22% of the patients. Fifty-five (90%) of the 61 patients underwent surgery; in the remaining 7 patients the diagnosis and distribution were achieved by endoscopic biopsies, bone marrow aspirates and radiological methods. In 51% of the patients operated on the surgery was judged as curative, in 42% as palliative, and in 7% as explorative. Radio- or chemotherapy was given to 44 (72%) patients of whom 48% were operated on curatively and 41% palliatively. Thirteen (21%) of the patients were judged to need radio- or chemotherapy, but they were in too poor a condition to manage the therapy. Four patients did not receive any additional therapy after curative surgery.

Survival

The lymphoma specific survival rate seemed to be better in the patients with gastric lymphoma compared with those with intestinal lymphoma (N.S.) (Fig. 2). However, the patients with lymphoma in the small bowel and colon had more advanced disease than those with gastric lymphoma, and, furthermore, patients with lymphoma in the colon were significantly older than the others ($p < 0.05$) (Table). On the other hand, the older patients radically operated on did not have a poorer outcome than the others. The survival curves were almost identical in the patients with low- or high-grade lymphomas (N.S.) (Fig. 3). As expected, the patients with stage I lymphoma (Fig. 4), and

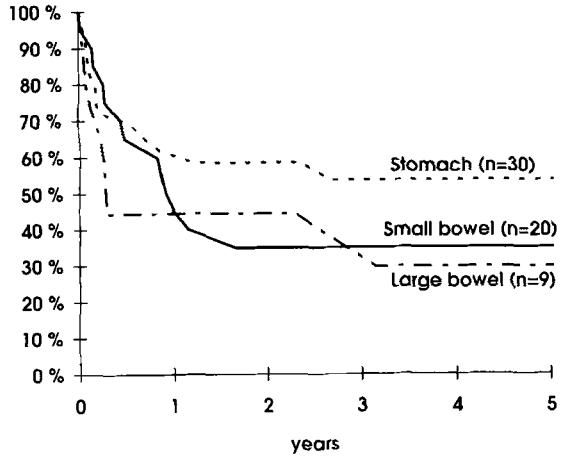

Fig. 2. Lymphoma specific survival of 59 patients with gastrointestinal lymphoma according to the site of the primary tumour. (One patient with lymphoma in the oesophagus and one patient with polyposis are excluded.)

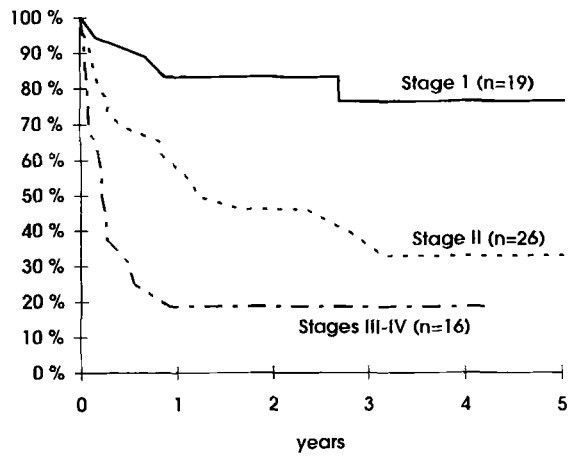

Fig. 4. Lymphoma specific survival of 61 patients according to the distribution of the gastrointestinal lymphoma. Patients with stage I lymphoma had significantly better lymphoma specific survival compared to other stages ($p < 0.01$).

patients operated on curvatively had significantly better prognosis compared with the others (Fig. 5). The influence of different type radio- or chemotherapy on the survival of these patients could not be estimated because the number of patients in each therapy group according to stage was too small.

DISCUSSION

Age-adjusted incidence of gastrointestinal lymphomas in the whole of Finland seems to have had an increasing tendency from 1975 to 1992 (Fig. 1). In central Finland the annual number of new patients increased from 1975 to 1983 and stabilized thereafter. However, figures of increasing incidence of gastrointestinal lymphomas should be handled with cautiousness. Diagnostic facilities improved in the early 1980's; endoscopies were brought into routine use, and pathologists became aware of the modern classifications of non-Hodgkin's lymphomas. Inaccuracies in the diagnosis or announcements of local physicians might also have had a decreasing influence on the figures of the Finnish Cancer Registry, particularly in the early years. However, in the Finnish figures of gastrointestinal lymphomas there seems also to be clear elevation. At the same time as the annual incidence of gastric adenocarcinoma has decreased, the incidence of gastric lymphomas has increased, as has also been reported from other countries (7, 12, 13). The distribution of gastrointestinal lymphomas with respect to site and type was consistent with previous reports (1, 2, 9). An obscure observation was the absence of colonic lymphomas until 1984, whereas during the last 10-year

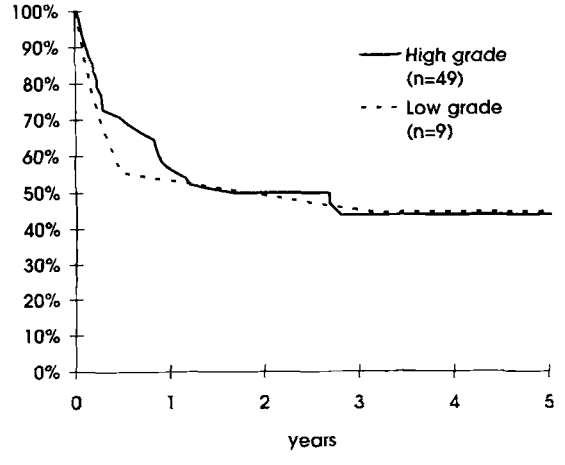

Fig. 3. Lymphoma specific survival of 58 patients according to the grade of malignancy. Three patients with unclassified type and grade of malignancy are excluded.

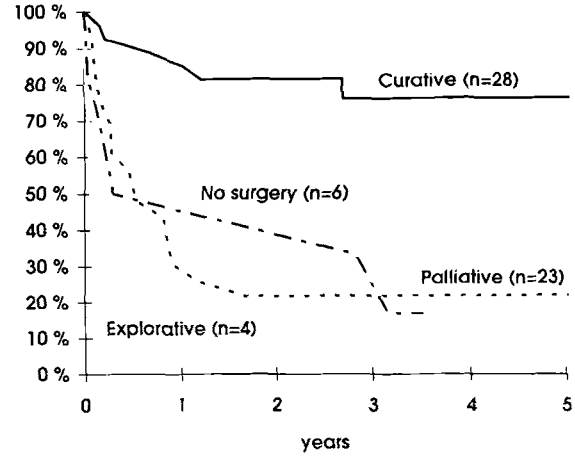

Fig. 5. Lymphoma specific survival of 61 patients according to surgical therapy. The patients had a significantly better survival after curative surger compared to those without curative surgery ($p < 0.01$).

period its average proportion has been 25% of all gastrointestinal lymphomas. In the whole country the proportion of colorectal lymphoma has steadily been about 10% of all gastrointestinal lymphomas (7). The frequency of intestinal lymphomas in Finland seems to be lower than the corresponding figures in the United States, e.g. in 1990 4.5/1 000 000 in Finland vs. 6.3/1 000 000 in the United States (4). This was also expected as the well-known predisposing factors (acquired immunodeficiency, long-standing immunosuppression therapy or inflammatory bowel diseases) were lacking in the present patients. The coeliac disease seems to be a significant predisposing factor for T-cell lymphoma as was also observed by Wright et al. (14). The prevalence of coeliac disease is about 100/100 000 inhabitants in the Scandinavic population (15, 16). Thus, in central Finland the prevalence of coeliac disease ought to be about 250 patients, but in the present series only two patients with villus atrophy and intestinal lymphoma were found. However, according to a recent report from another region of Finland, the number of malignant diseases among 335 adult patients with coeliac disease did not differ from that expected in Finland (17), and no patient with gastrointestinal lymphoma was found.

In the present series there were only three patients with low-grade MALT lymphoma and none of them had a positive finding in the H. pylori staining. However, recent reports have indicated that H. pylori might have an influence on the pathogenesis of low-grade gastric MALT lymphoma. Furthermore, in some patients an eradication of H. pylori has resulted in recovery of the lymphoma (18, 19).

The pathologic stage, patient age, and surgical resection have been found to be the significant independent variables affecting the survival of patients with gastrointestinal lymphomas (6, 20, 21). Recently lactate dehydrogenase and beta-2-microglobulin have been found to be good predictors of response rate and survival in patients with non-Hodgkin's lymphoma (22). In the present retrospective series in which serum samples were not available the stage of distribution and the radicality of surgery were the most influencing factors. According to a recent review, there is no evidence of any substantial benefit of adjuvant radio- or chemotherapy after an apparently radical resection, but in stage II disease the best results are achieved with ablative surgery and complementary therapy (5).

The total 5-year survival of gastric lymphoma was 54% which is on the same level as the figures of several other recent reports (1, 21). In comparison with gastric adenocarcinoma the total 5-year survival rate of gastric lymphomas is significantly better (54% vs. 24–30%) (23). Thus, also palliative resection with chemotherapy is to be considered in patients with gastrointestinal lymphoma (5, 24).

In conclusion, the survival of patients with gastrointestinal lymphomas is superior to that of patients with gastrointestinal adenocarcinoma and it is still improving due to new combination therapies. Furthermore, all over the world the distinction of gastrointestinal lymphomas has been more vital due to an increasing frequency of predisposing factors.

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