The aims of this study were to review the clinical presentation of non-Hodgkin’s lymphomas of the large bowel, to analyze the prognostic factors using univariate and multivariate methods, as well as the overall survival. We identified 24 cases at our clinic between 1991 and 2005, based on pathohistological analysis and standard diagnostic criteria established by Dawson et al. They accounted for 1.2% of all cases of the large bowel malignancies (24/2021) during this period. The following clinical information such as age, gender, symptoms, tumor localization, operation performed, histology grade, stage of disease, and adjuvant chemotherapy was obtained. Survival function was expressed by Kaplan-Meier curve and Log-rank test was performed for the difference in survival between two patient groups. Multivariate analysis was carried out using the Cox proportional hazard model. Overall mean survival time was 41.91 months. According to the univariate analysis, the factors influencing overall survival rate was operation type (elective and emergent). Tumor stage and operation type were independent prognostic factors for survival, as determined by multivariate analysis. Our results showed that tumor stage and operation type should be considered as the most important prognostic factors in patients with primary non-Hodgkin’s lymphomas of the large bowel.

Key words: non-Hodgkin’s lymphomas of the large bowel, clinical characteristics, prognostic factors, survival

INTRODUCTION

Primary non-Hodgkin’s lymphomas of the large bowel are rare tumors, and account for 1.4% of human lymphomas, 6-20% of gastrointestinal lymphomas, 0.1-0.5% of all malignant tumors of the large bowel and make 5-10% of all non-Hodgkin’s lymphoma. They are the third most frequent tumors, following adenocarcinomas and carcinoids.1,2

They can occur at any age from 3 to 81 years, but the mean age is 50 years. Men are affected twice as often as women, but recent publication have cited the reverse. The rectum and the caecum seem to be the most common sites for malignant lymphoma due to large amount of lymph tissue in these regions of the large bowel. The most common treatment has been the resection of the primary disease followed with adjuvant chemotherapy, radiation, or both. Although there has been achieved great progress during the last three decades in surgical technique, anaesthesia, and chemotherapy, there is still an impermissibly low level of 40% of five-year survival of the operated patients3,4. Due to various and different attitudes concerning the treatment of primary lymphoma of the colon and rectum, we have decided to present our results of the surgical treatment occupying the period of 15 years, with an analysis of prognostic factors and survival.

MATERIALS AND METHODS

The cases of patients who were diagnosed with primary non-Hodgkin’s lymphomas of the large bowel and operated in the period between 1991 and 2005 were described. For diagnosing the primary lymphomas of the colon and rectum we used pathohistological analysis and standard diagnostic criteria established by Dawson et al.: absence of enlarged superficial lymph nodes, no enlargement of mediastinal lymph nodes, normal values of total and differential white count, existence of secondary deposits only in regional lymph nodes of the colon and rectum, liver and spleen without secondary deposits.5 Out of 2021 patients treated for malignant diseases of the large bowel in the stated period, 24 (1.2%) patients were operated on. The following clinical data were analyzed: age, gender, symptoms, tumor localization, operation performed, pathohistological findings, stage of disease, type of surgical intervention (elective and emergent), method of determining the disease, application of adjuvant therapy, monitor-
ing of patients and treatment outcome. Classification of the World Health Organization was used for determining the histopathological diagnosis; for establishing the clinical stage of the disease, the Ann-Arbor system of categorization of gastrointestinal lymphomas modified by Musshoff was used\(^6\)\(^7\). The type of surgical intervention was expressed with numbers of patients and percentages in parenthesis. The probability curves for survival were calculated according to the Kaplan-Meier method and compared by the Log-rank test. Multivariate analysis was performed using the Cox proportional hazard model. \(P\) was considered as statistically significant. The data were analyzed using SPSS (version 15.0) software.

RESULTS

Of 24 patients, there were 20 males and 4 females, mean age 58.6 ± 16.64 (range 17-82). The most common symptoms were: abdominal pain and weight loss in 17 (70.8%) patients, abdominal mass in 7 (29.2%) patients, constipation in 3 (12.5%) patients and bleeding per rectum in 4 (16.7%) patients. According to tumor localization, caecum lymphoma was diagnosed in 11 (45.8%) patients; 4 (16.7%) patients were diagnosed with lymphoma of ascendant colon; 1 (4.2%) patient was diagnosed with lymphoma in hepatic flexure; lymphoma in transverse colon was diagnosed in 4 (16.6%) patients; 2 (8.3%) patients had lymphoma in sigma; and 2 (8.3%) patients were diagnosed with rectal lymphoma. In 15 (62.5%) patients, the diagnosis was determined by preoperative examinations, whereas 9 operated patients (37.5%) were diagnosed by pathohistological analysis after the operation. Type of surgical intervention depended on tumor localization, and is displayed in Table 1.

All cases were non-Hodgkin B-Cell lymphomas with positive immunohistochemistry on the so-called pan B-cell marker CD-20. B diffuse lymphoma of the large cells was diagnosed in 20 (83.3%) patients; 2 patients (8.3%) had mantle cell lymphoma; 1 patient was diagnosed with Burkitt; and 1 with MALT lymphoma (both accounting for 4.2%). In relation to the clinical stadium of the disease, 11 (45.8%) patients were in II E stadium, whereas 12 (50%) patients were in III E and 1 (4.2%) patient in IV E stadium of the disease. Of the total number of the operated patients, elective surgical intervention was performed on 17 (70.8%) patients, while emergent intervention was performed on 7 (29.2%) patients due to the condition of the ileus, perforations and intraabdominal abscess. After the surgical intervention, 20 (83.3%) patients received adjuvant therapy according to CHOP (cyclophosphamid, doxorubicin, vincristin, prednison) protocols, whereas in 4 (16.7%) patients the administration of therapy was impossible due to patients’ refusal of treatment and death outcome.

The patients were followed up for a mean of 30.3 months (range 2-60 months), while the average survival period was 41.91 months (SE = 4.846; 95% C.I. 32.406-51.404). (Figure 1)

<table>
<thead>
<tr>
<th>TYPE OF SURGICAL INTERVENTION</th>
<th>No of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard right hemicolectomy</td>
<td>15 (62.5%)</td>
</tr>
<tr>
<td>Extended right hemicolectomy</td>
<td>4 (16.7%)</td>
</tr>
<tr>
<td>Palliative right hemicolectomy</td>
<td>1 (4.2)</td>
</tr>
<tr>
<td>Operation in two acts (colostomy+left hemicolectomy)</td>
<td>1 (4.2)</td>
</tr>
<tr>
<td>Left hemicolectomy</td>
<td>1 (4.1)</td>
</tr>
<tr>
<td>Rectal resection</td>
<td>2 (8.3)</td>
</tr>
</tbody>
</table>

FIGURE 1
OVERALL SURVIVAL FUNCTION OF PATIENTS ACCORDING TO THE KAPLAN-MEIER METHOD

During the follow-up period, 9 (37.5%) patients died between 2 and 30 months after making the diagnosis and were in advanced stadium IIIIE or IV. 3 (33.3%) patients of which showed the signs of disease recurrence and 6 (66.7%) patients died of other causes (cardiovascular, respiratory and cerebrovascular diseases). 13 patients (54.2%) had follow up period of 43.5 months with no signs of recurrence of the disease. Two patients were lost during follow-up period, after 20 and 25 months of diagnosis. According to the univariate analysis the factors influencing overall survival rate was type of surgical intervention (elective and emergent) (Table 2). (Figure 2, 3)

The following variables were not of prognostic significance in relation to survival: age, gender, symptoms, tumor localization, operation performed, pathohistological findings, stage of disease, method of determining the disease, application of adjuvant therapy, monitoring of patients and treatment outcome.
Tumor stage and type of surgical intervention were independent prognostic factors for survival as determined by multivariate analysis.

Variables as prognostic factors in Cox proportional hazard method are shown in Table 3.

**DISCUSSION**

Primary colorectal lymphomas are an extra-nodal form of non-Hodgkin’s lymphomas. They are the third most frequent tumors of gastrointestinal system of adults, following lymphomas of the stomach and small intestine, whereas in children intestinal localization is predominant. Etiological factors involved in the development of colorectal lymphomas, as well as of other forms of malignancies, are unknown.

However, high frequency of colon lymphoma has been observed in conditions of immunosuppression such as inflammatory intestinal diseases – ulcerative colitis, HIV infection and conditions following organ transplantation. But, to date, there remains no substantial evidence to confirm the link between IBD and lymphoma. Further evaluation at the molecular level should provide a better understanding of the correlation between IBD and lymphoma.

None of the patients in this series had IBD, or other immune disorders and none were receiving chronic immuno-suppressive therapy of any kind. The disease most frequently appears later in life, after 55 years of age, predominantly in male population.

In our study there were 62.5% of patients over 60 years of age and 83.3% of male sex, median age of 58, 63, which is in accordance with the results of other authors.

The most common symptoms of our patients, which account for 87.5% of the overall number of patients monitored, were pain, weight loss and presence of palpable tumor. Cho et al. reached similar results, but they also added bleeding per rectum to the group of most frequent symptoms which appeared in 82% of patients. Unspecific initial symptoms of the disease often lead to late diagnosis, which is the main cause of high percentage (54.2%) of our patients in advanced stadium of the disease III E and IV, when the possibility of healing is significantly low.

Our study shows the most common localization of primary colon lymphomas on the caecum and the right colon present in 45.8% and 83.3% of the patients respectively, which is in accordance with the results of other authors. However, localization of primary rectal lymphomas in our cases is only 8.3% as compared to the results of other authors, where this frequency is higher.

Colonoscopy is a valuable standard in diagnosing the primary lymphomas of the colon but it is not always possible to determine this type of tumors with the use of endoscopy. The problem could be an inadequate biopsy of the tumor, as well as the need for timely and adequate immunohistochemical staining within processing of the preparations done by the pathologist, which causes correct interpretation of the pathohistological findings impossible. For this reason, only 62.5% of patients were diagnosed by preoperative examinations, which is very similar to the results of some authors.

Histopathological analysis of the preparations determined that all tumors belonged to the group of B cell non-Hodgkin lymphomas, that is, immunophenotype of tumor cells is positive to the so-called pan B cell marker, CD-20. The most common histological form of tumors was B cell lymphoma of the large cells, appearing in 83.3% of the patients, whereas other forms of lymphoma, such as Mantle, Burkitt and MALT types were significantly rare. Other authors have reached similar results, with differences in frequency of certain forms of non-Hodgkin lymphomas depending on the geographical location of the disease.

By the Working Formulation, the majority (83.3%) were intermediate grade lymphoma, comprising twenty diffuse large B-cell types, 4.2% was MALT type as low grade lymphoma and 12.5% were high grade lymphoma.

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**TABLE 2**

**PROGNOSTIC FACTORS EFFECTS ON SURVIVAL (LOG - RANK TEST)**

<table>
<thead>
<tr>
<th>Prognostic factor</th>
<th>Subgroup</th>
<th>Survival Time</th>
<th>SE</th>
<th>95% C.I</th>
<th>Log-rank test (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor stage</td>
<td>IIE</td>
<td>51.91</td>
<td>5.19</td>
<td>41.75-62.07</td>
<td>0.054</td>
</tr>
<tr>
<td></td>
<td>IIIE i IV</td>
<td>30.59</td>
<td>6.31</td>
<td>24.18-36.92</td>
<td>0.152</td>
</tr>
<tr>
<td></td>
<td>Elective</td>
<td>49.35</td>
<td>4.74</td>
<td>40.05-58.65</td>
<td>0.007*</td>
</tr>
<tr>
<td>Operation type</td>
<td>Urgent</td>
<td>19.86</td>
<td>6.79</td>
<td>6.55-33.16</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>&lt;64</td>
<td>50.73</td>
<td>4.79</td>
<td>41.19-59.96</td>
<td>0.061</td>
</tr>
<tr>
<td></td>
<td>≥ 65</td>
<td>26.36</td>
<td>6.09</td>
<td>14.42-38.31</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>male</td>
<td>42.61</td>
<td>5.29</td>
<td>32.25-52.97</td>
<td>0.800</td>
</tr>
<tr>
<td></td>
<td>female</td>
<td>35.60</td>
<td>10.67</td>
<td>24.18-47.07</td>
<td></td>
</tr>
</tbody>
</table>

*Statistically significant
comprising two Mantle types and one Burkitt’s type lymphoma, which correlated well with results of other reports\textsuperscript{23,24}. Depending on the stadium of the disease, 45.8\% of patients were operated in II E stadium using Ann-Arbor system of categorization of gastrointestinal lymphomas modified by Musshoff, which includes primary tumor of the colon or rectum also spread to intermediate and pararectal lymph nodes. 54.2\% of the patients were operated in III E and IV stadium of the disease, which stand for advanced disease stages.

Results of our study differ from the results of other authors with significantly high percentage of the lymphoma in the initial phase, which is a consequence of different criteria on the basis of which the patients were included in the study\textsuperscript{25}. Of the total number of surgical interventions, 70.8\% of patients received elective operation, whereas 29.2\% received emergent intervention due to the condition of the ileus, perforations or intra-abdominal abscess.

Comparing the results of this study to the results of other authors, where frequency of urgent conditions in primary colorectal lymphoma is much higher, we drew the conclusion that different criteria were used in including patients into the study, that is, the frequency of the advanced disease was different in certain studies\textsuperscript{4}. Primary colorectal lymphomas are fast-growing tumors so that late diagnosis, as a rule, leads to urgent condition which demands emergent surgical intervention.

Beside surgical intervention, an adequate treatment of the colorectal lymphomas also includes chemotherapy and sometimes radiotherapy. In our study, the patients who underwent chemotherapy and radiotherapy, in 83.3\% and 8.3\% of the patients respectively, with mean follow up of 30.3 months, of them 54.2\% patients had follow up period of 43.5 months with no signs of recurrence of the disease. Fan et al. displayed statistically significantly longer survival of 117.4 months of the patients in II E stadium of the disease receiving adjuvant therapy, as opposed to the group receiving no chemotherapy where survival was 47.9 months.

Similar results were obtained by other authors who also applied the so-called preventive chemotherapy on patients in I E stadium with 10-year survival of 80\%\textsuperscript{18,26}. Various attitudes towards adjuvant therapy are the results of uneven treatment of colorectal lymphomas, but also of no prospective randomized studies including larger number of patients which would provide scientifically proved results. The univariate analysis of prognostic factors has stated that only type of surgical intervention (elective and emergent) has significant effect.

Advanced disease in stadium III E and IV E often leads to urgent conditions such as obstruction, perforation and intra-abdominal abscesses, with the need for emergent surgical intervention. Severe general condition of the patient and urgency of surgical procedure cause more frequent recurrence of the disease, which was also stated by other authors\textsuperscript{27,28}.

### TABLE 3

<table>
<thead>
<tr>
<th>VARIABLES AS PROGNOSTIC FACTORS IN COX PROPORTIONAL HAZARD METHOD</th>
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</thead>
<tbody>
<tr>
<td>Prognostic factor</td>
</tr>
<tr>
<td>------------------</td>
</tr>
<tr>
<td><strong>Tumor stage</strong></td>
</tr>
<tr>
<td>IIE*</td>
</tr>
<tr>
<td>IIE i IV</td>
</tr>
<tr>
<td><strong>Operation type</strong></td>
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<td>Urgent</td>
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<tr>
<td><strong>Age</strong></td>
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<tr>
<td>&lt; 64</td>
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<tr>
<td>\geq 65</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
</tr>
<tr>
<td>Male*</td>
</tr>
<tr>
<td>Female</td>
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</tbody>
</table>

*Reference category, statistically significant

In the evaluation of surgical treatment, type of operation (elective or emergent) was strongly associated with prognosis in the univariate analysis for survival, and also a significant prognostic factor in the multivariate analysis. Stage of tumor, was a highly superior prognostic discriminator in multivariate studies. In some studies, tumor stage had no influence on survival.

Among the clinical factors, a survival difference was not observed according to the histology type of tumor. However, there are studies which point to histological type of tumor as significant prognostic factor\textsuperscript{18}. Differences in determining the prognostic factors in some studies are the result of small number of patients included in examination.

This study has its limitations. A small number of patients was included, and the study is a retrospective one. The problem lies in the facts that the group is a heterogeneous one; patients with different clinical characteristics of tumor stadium, patients with less advanced and advanced stadium, as well as the electively and emergency operated patients are involved in the study.

The diagnoses are established both by means of preoperative colonoscopy and after surgical intervention as well, making the strategy of proper surgical treatment more difficult.

Due to specific features of the group of examined patients, it is difficult to draw any conclusions about the treatment, valid in clinical practice.
However, already published studies have similar results, and it is a fact that there are no prospective randomized studies which have the greatest significance at qualitative conclusions.

CONCLUSION

Primary colorectal lymphomas are rare type of tumors usually manifested by nonspecific symptoms, such as abdominal pain and weight loss, which complicate timely diagnosis, which further causes urgent conditions of the ileus and perforations with extremely low survival period.

The most significant prognostic factors are type of operation (elective or emergent) and tumor stage. Surgical excision of the tumor with regional lymphovascular structure followed by chemotherapy are the methods of choice in the treatment of colorectal lymphoma.

Overall survival of patients is 41.91 months. Multicentric studies are necessary for analyzing a larger number of patients, which would determine the real significance of the surgical treatment of non-Hodgkin disease of the colon.

SUMMARY

NON-HODGKIN LYMPHOMA OF THE LARGE BOWEL


Ključne reči: Non-Hodgkin limfomi debelog creva, kliničke karakteristike, progostčki faktori, preživljanje

REFERENCES


