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Impact of surgery and adjuvant chemotherapy *versus* chemotherapy alone on the survival of patients with primary gastric diffuse large B-cell lymphoma: a retrospective study

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Introduction. The management of primary gastric diffuse large B-cell lymphoma (DLBCL) remains controversial. Historically, the treatment of localized gastric lymphoma was based on surgery alone or followed by chemotherapy and / or radiation therapy. The aim of this retrospective study was to assess the survival of patients with primary gastric DLBCL after surgery and adjuvant chemotherapy compared with chemotherapy applied alone.

Materials and methods. Fifty-three patients (24 males, mean age 55.1 (range 19–82) years and 29 females, mean age 71 (range 30–82) years) with newly diagnosed primary gastric DLBCL were treated at four main hospitals of Lithuania in 1999–2005 and their treatment outcomes were reviewed. Twenty-one patients underwent primary gastrectomy (9 total and 12 partial gastrectomies), after which nineteen of them received adjuvant chemotherapy. Thirty-two patients received chemotherapy alone. Staging was performed according to Musshoff's criteria. Survival was calculated from the date of diagnosis to patient's death or to the last day known him to be alive. Survival curves were calculated using the Kaplan–Meier method, and the differences between the survival ranges were evaluated by the log-rank test.

Results. Three years' overall survival in patients with localised lymphoma treated by surgery plus adjuvant chemotherapy was 85.2% (52.6%–96.1%) *versus* 78.6% (47.3%–92.5%) in patients treated by chemotherapy alone (p = 0.2904).

There was no significant difference in the overall one year's survival in patients with disseminated lymphoma treated by surgery and adjuvant chemotherapy (14.3% [95%CI 0.7%–46.5%]) compared to those treated by chemotherapy alone (54.4% [95%CI 24.5%–76.8%]) (p = 0.0664).

Conclusion. The results of this study suggest that surgery does not improve the survival of patients with either localized or disseminated primary gastric DLBCL compared to those receiving chemotherapy alone. Patients with advanced disease who undergo surgery may have an inferior outcome.

Key words: DLBCL, surgery and adjuvant chemotherapy, chemotherapy only, survival

INTRODUCTION

The management of primary gastric diffuse large B-cell lymphoma (DLBCL) remains controversial. Historically, the treatment of localized gastric lymphoma was based on surgery alone or followed by chemotherapy and/or radiation therapy (1, 2). Taking in account the high survival rates observed, many authors in surgical series continue to favour surgical resection as the first step of a multimodality approach (3, 4). Some investigators have suggested that surgical resection can perhaps be avoided, sparing most patients the risk and the discomfort related to gastrectomy. Encouraging results have been obtained by using chemotherapy alone or in association with radiation therapy (5, 6). Other studies reported chemotherapy to be the primary choice of DLBCL treatment (7–9). The aim of this retrospective study was to assess the survival of patients with DLBCL after surgical resection plus adjuvant chemotherapy *versus* chemotherapy alone.

MATERIALS AND METHODS

Fifty-three patients (24 males, mean age 55.1 (range 19–82) years and 29 females, mean age 71 (range 30–82) years) with newly diagnosed primary gastric DLBCL treated at four major hospitals of Lithuania between 1999–2005 and their treatment outcomes were reviewed. The diagnostic work-up included patient's history, physical examination, liver enzymes, alkaline phosphatase, creatinine, chest X-ray, radiological and endoscopic evaluation with biopsies of the upper GI tract, abdominal ultrasound evaluation. Pathologists reviewed all the original histopathological material available on slides taken during

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Table. **The overall survival by stage and treatment**

	Chemotherapy alone OS (95% CI)	Chemotherapy and Surgery OS (95% CI)	P, log rank
All stages***	65.5 (43.1–80.8)	60.9 (36.9–78.2)	0.9931
Stage IE–IIE1***	78.6 (47.3–92.5)	85.2 (52.6–96.1)	0.2904
Stage IIE2–IV*	54.4 (24.5–76.8)	14.3 (0.7–46.5)	0.0664

*** Three year estimate.

* One year estimate.

endoscopy or surgery. DLBCL was confirmed morphologically and immunohistochemically using the markers CD20, CD10, BCL2, BCL6, MUM1 and Ki67. Staging was performed according to Musshoff's criteria: IE – lymphoma limited to the stomach, IIE1 – involvement of the stomach and contiguous lymph nodes, IIE2 – involvement of the stomach and non-contiguous subdiaphragmatic lymph nodes, III–IV – involvement of the stomach and lymph nodes on both sides of the diaphragm and one or more extralymphatic organs or tissues. The patients were stratified into two groups: localized disease (gastric lymphoma at stages IE and IIE1) and disseminated disease (gastric lymphoma at stages IIE2–IV). Patients in each group were treated either by surgery and adjuvant chemotherapy or chemotherapy alone. The treatment options were followed according local protocols. The indications for surgery in stage IIE2–IV patients were bleeding and/or obstruction. The protocol required 6 chemotherapy cycles. The chemotherapy plan could not be completed for all the patients due to disease progression or poor performance status.

Twenty-one patients underwent primary gastrectomy (9 total and 12 partial), 19 of them received adjuvant chemotherapy, and two IE stage-patients did not receive any adjuvant chemotherapy. Two patients after surgery received radiotherapy (40 Gy) additionally. Thirty-two patients received chemotherapy alone.

In the localized gastric lymphoma patients, the treatment was as follows: surgery plus 4–7 CHOP (Cyclophosphamide, Doxorubicine, Vincristine, Prednisolone) cycles for 8 patients, surgery plus 1–3 CHOP cycles for 3 patients, and surgery plus 1 CVP cycle for one patient; chemotherapy alone, 6–8 CHOP cycles, for 12 patients, chemotherapy alone, 1–3 CHOP cycles, for 5 patients.

In case of the disseminated disease patients, the following treatment was applied: surgery plus 5–8 CHOP cycles for 4 patients, surgery plus 1–2 CHOP cycles for 3 patients; chemotherapy alone, 6–8 CHOP cycles, for 7 patients, chemotherapy alone, 1–2 CHOP cycles, for 4 patients, chemotherapy alone, 1 CVP cycle, for one patient, chemotherapy alone, 4 doses of Rituximab, for one patient, and other chemotherapy alone for 2 patients.

The median follow-up time was 13.3 months (95% CI 7.2–21.4 months). No patients were lost to follow-up. During the follow-up 18 patients died (6 in the localized and 12 in the disseminated disease group). The majority of the patients (14 patients) died due to lymphoma progression, 2 died from cardio-vascular disorders and 2 died from other diseases. There were no deaths directly related to either surgery or chemotherapy.

Survival was calculated from the date of diagnosis to death or to the last day known to be alive. The survival estimates were carried out using the life-table and the Kaplan–Meier methods. Log-rank test was used to check the survival differences observed as an effect of the treatment.

RESULTS

The overall three years' survival of patients with the localised lymphoma treated by surgery and adjuvant chemotherapy was

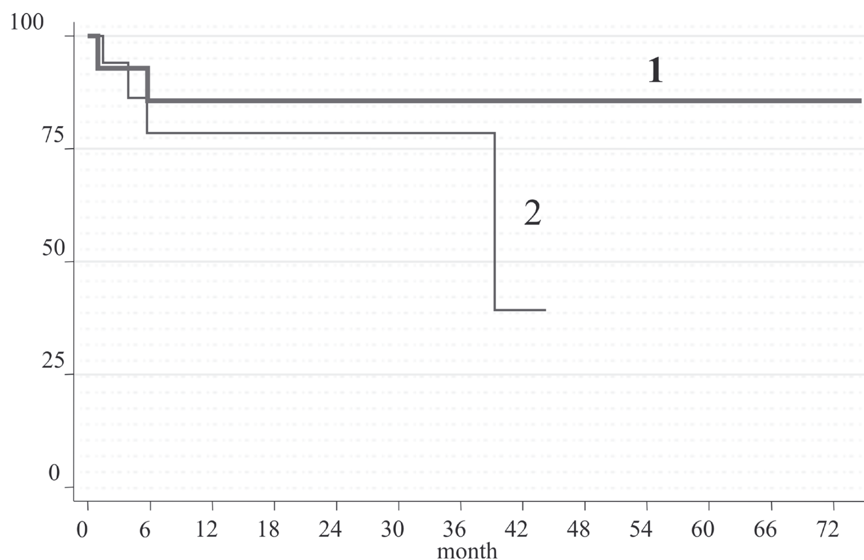

Fig. 1. Survival of DLBCL by treatment at stage IE–IIE1. Surgery + chemotherapy (1), chemotherapy (2). Log-rank p = 0.2904

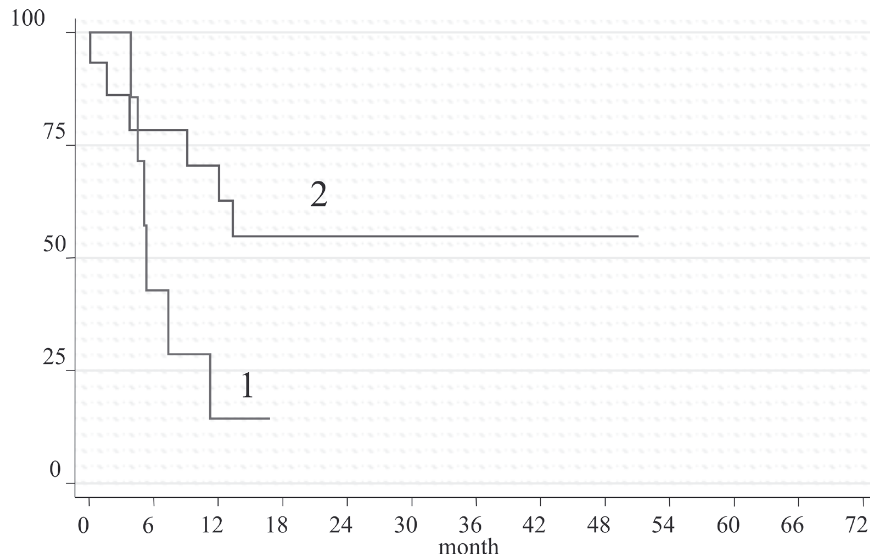

Fig. 2. Survival of DLBCL by treatment at stage IIE2–IV. Surgery + chemotherapy (1), chemotherapy (2). Log-rank p = 0.0664

85.2% (52.6%–96.1%) *versus* 78.6% (47.3%–92.5%) in patients treated by chemotherapy alone (Table) (p = 0.2904) (Fig. 1).

There was no significant difference in the overall one year survival for patients with the disseminated lymphoma treated by surgery and adjuvant chemotherapy (14.3% [95%CI 0.7%–46.5%]) compared to those treated by chemotherapy alone (54.4% [95%CI 24.5%–76.8%]) (p = 0.0664) (Fig. 2).

DISCUSSION

Historically, surgery was a priority option in the treatment of DLBCL. It was mainly used in 3 different settings in DLBCL: as a primary radical treatment, as an emergency treatment for patients presenting with severe bleeding or perforation and as a palliative treatment. Years ago, surgery and adjuvant chemotherapy were considered to be adequate treatment for our patients as the diagnostic examination was lacking the use of the computer tomography and ultrasound endoscopy. The staging was clinical and radiological based on extranodal lymphoma classification. There was no possibility to carry out accurate staging because 60.4% of the patients were not operated. The chance of misclassification was not evaluated in this retrospective study; however, the survival patterns by the treatment make evident the insignificant bias in cases' ascertainment.

Meanwhile the results of the present study show that the 3-year survival rates in patients with localized lymphoma (stage IE–IIE1) treated by surgery and adjuvant chemotherapy *versus* chemotherapy alone are not different (85.2% and 78.6% respectively, p = 0.2904). This fact suggests that surgery does not improve the survival of patients with localized primary gastric DLBCL. Our results are in line with the published reports comparing therapeutical and surgical strategies in the treatment of primary localized gastric DLBCL. Liu et al. (10) found no significant difference in the long-term survival of patients treated by chemotherapy (72.6%) or surgery (77.8%). In the Binn et al. study (11) the overall survival estimate at 5 years was 90.5% for patients treated by chemotherapy alone and 91.1% in the group of patients who underwent primary surgical procedure followed by chemotherapy. Other studies have also supported the feasibility and effectiveness of a non-surgical approach (5–6).

Aviles (12) showed a statistically insignificant 10 years' overall survival difference in primary gastric lymphoma patients treated by surgery and chemotherapy *versus* chemotherapy alone: 91% and 96%, respectively. The same results were found in a German multicentre study. The survival rate at 42 months in patients treated by surgery was 86% compared to 91% in patients treated conservatively (7). The studies by Coiffier and Wohrer (8–9) suggested that combining Rituximab with CHOP regimen increases complete response rate and prolongs event-free and overall survival in patients with DLBCL. These studies confirm DLBCL to be a highly chemosensitive disease and question the appropriateness of the surgical approach.

No significant difference in the survival rates can be explained by a possible staging bias due to the assessment of neoplasia invasion and perigastric lymph nodes. The distressed postoperative condition of a patient is diminishing the opportunity for therapeutic rehabilitation and further chemotherapy. It also suggests the lower range of chemotherapy course in patients after surgery that was urgent or palliative. Other authors have also observed comparable results in the high-risk DLBCL group (13–14). In our patients with disseminated disease, surgery was often performed to control bleeding and/or obstruction. However, there were no cases of death caused by the operating procedure. On the contrary, the large majority of the deaths were caused by lymphoma progression. Thus, the poor condition (a well known risk factor in aggressive lymphoma) in those necessitating surgery rather than the surgical intervention itself may have been the cause of poorer outcome in the surgical group.

CONCLUSION

The results of this study suggest that surgery does not improve the survival of patients with either localized or disseminated

primary gastric DLBCL compared to those receiving chemotherapy alone. Advanced disease patients who undergo surgery may have an inferior outcome.

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DIFUZINE DIDELIŲ B LĄSTELIŲ SKRANDŽIO LIMFOMA SERGANČIŲ LIGONIŲ, GYDYTŲ CHIRURGIŠKAI IR TĘSIANT ADJUVANTINĘ CHEMOTERAPIJĄ, IŠGYVENAMUMAS, PALYGINUS SU LIGONIAIS, KURIEMS TAIKYTA TIK CHEMOTERAPIJA: RETROSPEKTYVI STUDIJA

Santrauka

Įvadas. Difuzinės didelių B ląstelių skrandžio limfomos gydymas išlieka aktualus. Neišplitęs skrandžio limfomos gydymas visada būdavo pradedamas operacija ir tęsiamas taikant chemoterapiją arba spindulinę terapiją. Šios studijos tikslas – retrospektyviai palyginti difuzine didelių B ląstelių skrandžio limfoma sergančių pacientų išgyvenamumą, kai jiems buvo taikytas chirurginis gydymas bei adjuvantinė chemoterapija ir gydymas vien tik chemoterapija.

Medžiaga ir metodai. Atlikta 52 pacientų (24 vyrų (vidutinis amžius – 55,1 metai) ir 29 moterų (vidutinis amžius – 71 metai)), sirgusių difuzine didelių B ląstelių skrandžio limfoma ir gydytų keturiose didžiausiose Lietuvos klinikose 1999–2005 metais, gydymo analizė. Iš šių pacientų 21 buvo operuotas atlikus pirminę gastrektomiją (9 – totalią gastrektomiją ir 12 – dalinę) ir 19 iš jų buvo tęsiama adjuvantinė chemoterapija, 22 pacientai buvo gydyti tik chemoterapija. Limfomų išplitimas buvo įvertintas Musshoffo kriterijais. Pagal Kaplan-Meier metodą ligonių išgyvenamumas buvo apskaičiuotas nuo diagnozės nustatymo iki jų mirties dienos arba paskutinės analizės dienos, skirtumai įvertinti naudojant log-rank testą.

Rezultatai. Pacientų, sergančių neišplitusia skrandžio limfoma ir gydytų chirurgiškai bei adjuvantine chemoterapija, išgyvenamumas trejus metus sudarė 85,2%, o pacientų, gydytų tik chemoterapija, – 78,6% ($p = 0,294$). Pacientų, sergančių išplitusia limfoma ir gydytų tiek chirurgiškai, tiek ir adjuvantine chemoterapija (14%), ir pacientų, kuriems taikyta tik chemoterapija, išgyvenamumas statistiškai patikimai nesiskyrė (54,4%, $p = 0,0664$).

Išvados. Studijos rezultatai rodo, kad chirurginis gydymas ir tęsiama adjuvantine chemoterapija, palyginus su vien tik taikoma chemoterapija, nedidina pacientų, sergančių tiek išplitusia, tiek ir neišplitusia difuzine didelių B ląstelių skrandžio limfoma, išgyvenamumo.

Raktažodžiai: difuzinė didelių B ląstelių skrandžio limfoma, chirurgija ir adjuvantinė chemoterapija, chemoterapija, išgyvenamumas