Localised gastrointestinal diffuse large B cell lymphomas; Does surgical approach still exist?

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Abstract: Background: Diffuse large B-cell lymphoma (DLBCL) is the commonest pathological type of gastrointestinal lymphoma and its management was changed from surgery to combined chemoimmunotherapy in the last decade; however, this strategy is questionable, especially if rituximab is not available.

Methods: Seventy-nine files were reviewed retrospectively. We divided the patients into two groups; group 1 included 37 patients who underwent surgery followed by chemotherapy and group 2 included 42 patients who received chemotherapy. The indication of surgery was mainly due to obstruction/perforation.

We compared the *outcomes of PFS and OS* between the two groups and according to primary anatomical site.

Results: We found that the outcomes for the surgery group before chemotherapy was superior to chemotherapy alone in terms of DFS, $p = 0.012$ and OS $p = 0.037$. But in the anatomical subgroups analysis, it did not show any significant difference in primary gastric lymphoma (PGL) regarding DFS and OS, $p = 0.706$, $p = 0.858$, respectively; On the contrary, we found significant improvement in PFS and OS, $p = 0.032$, $p = 0.025$, respectively, in primary intestinal lymphoma (PIL) favouring the use of the surgical approach.

Conclusion Surgery is still an important strategy in the case of DLBCL in PIL intestinal lymphoma; however, in the case of PGL, the use of chemotherapy even without rituximab achieves similar results. Our conclusions are limited by the small numbers of the study.

Keywords: Gastrontestinal lymphoma • DLBCL • Surgery • Chemotherapy

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Introduction

Gastrointestinal (GI) lymphoma is the most common form of extranodal lymphoma, accounting for 30–40% of cases. The most commonly involved site is the stomach (60–75% of cases), followed by the small bowel, ileum, cecum, colon and rectum. The most common histological subtypes are diffuse large B-cell lymphoma (DLBCL) and marginal zone B-cell lymphoma of the mucosa-associated lymphoid tissue (MALT) [1].

Treatment strategies for gastric lymphoma have changed dramatically over the last two decades. However, they are still very controversial. The most widely recommended strategy for the management ranged from antibiotic in case of early stage *with positive H. pylori* to radiotherapy and/or systemic therapy in negative *H. pylori* and MALT lymphoma [2]. The role of surgery is now reserved only for those with complications such

as perforation, haemorrhage or obstruction that cannot be treated with other alternative therapies [3]. Recent guidelines for treatment of (DLBCL) of the stomach recommend using aggressive poly-chemotherapy, which is usually combined with rituximab with addition of radiotherapy in early stages [4]. But the same is not true for DLBCL intestinal lymphoma as surgery is still an option in localised disease and a recent study by Kim S. *et al.* [5] recommends surgical resection followed by chemotherapy as an effective treatment strategy for localised intestinal DLBCL. Moreover, their results also showed that addition of rituximab to CHOP failed to show survival benefits in terms of localised disease, regardless of surgery [5]. So their results suggested that inclusion of rituximab in the chemotherapy regimen might not affect the outcome of localised disease as much as it was expected. It also emphasises the importance of surgical resection to the prognosis for patients with localised

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intestinal DLBCL [6,7] in contrast to primary gastric DLBCL; the role of rituximab has been proven by several studies [8, 9]. These data triggered some centres to use surgical resection when rituximab is not available relying on results from earlier studies in late 1990s and early 2000, which showed that surgical resection is mandatory in high-grade primary gastric lymphoma (PGL) [10–12]. Others argue with this conclusion based on results by Koch *et al.* trial [13], which showed equal overall survival between both surgery followed by chemotherapy arm and chemotherapy arm alone, which was in the form of six cycles of CHOP alone without rituximab. This is also supported by a recent study that showed no differences between CHOP and RCHOP in DLBCL of the stomach [14].

In many developing countries, rituximab cannot be afforded by all patients, so we intended to evaluate the role of surgery followed by chemotherapy versus chemotherapy alone without rituximab in our GI DLBCL.

Methods

Study design and patients

We reviewed retrospectively files of 79 patients with DLBCL out of 147 patients with GI lymphoma at South Egypt Cancer Institute and Health Insurance Hospital from January 2003 to 31 December 2012. We divided the patients into two groups; group 1 included 37 patients who underwent surgery followed by chemotherapy and group 2 included 42 patients who received chemotherapy.

All patients at diagnosis underwent oesophagogastroduodenoscopy and/or colonoscopy as a part of the staging evaluation accompanied by both chest and abdomen–pelvis computerised tomography (CT) scans. Patients were staged according to the Lugano staging system specified for GI lymphomas [15]. Stage I is defined as disease confined to the stomach or intestine, stage II is defined as disease extending to local (II-1) or distant (II-2) nodes, stage III-E is defined as disease involving adjacent organs or tissues, and stage IV is defined as disseminated extranodal involvement or concomitant supradiaphragmatic lymph node involvement. Only stage I–II were included in the study.

Biopsy was taken before treatment from all patients by endoscopy. Pathological classification was done according to the Revised European–American Lymphoma. CD20, CD3 and CD30 antibodies were used for confirmation of diagnosis. Only DLBCL were included.

Treatment

Chemotherapy

CHOP (cyclophosphamide 750 mg/m², day 1; vincristine 1.4 mg/m², day 1; doxorubicin 50 mg/m², day 1; and prednisolone 60 mg/m², days 1–5; tri-weekly).

Surgery

Surgical resection of a primary tumour mass, such as gastrectomy, hemicolectomy or segmental resection and anastomosis, was performed with lymph node dissection. The extent of lymph node dissection included regional lymph node dissection equivalent to colon adenocarcinoma or resection only of lymph nodes with suspected lymphoma involvement. All surgical resections were performed via open laparotomy.

In the surgery/chemotherapy group, the median interval between surgery and chemotherapy was 27 days (range, 25–40 days).

Radiotherapy

In PGL, group radiotherapy was given postoperatively in all cases of gastric lymphoma after incomplete surgical resection and after finishing chemotherapy in all cases of gastric lymphoma in chemotherapy group.

Patients underwent CT simulation in a supine position with thermoplastic sheet fixation. Multiple CT cuts at 0.5-cm intervals were obtained throughout the abdomen. CT data was transferred to the XiO treatment planning system (version 4.2). On each axial CT slice, clinical target volume (CTV; defined as the whole stomach plus the perigastric lymph node stations with addition of 1 cm margin). The planning target volume (PTV) was expanded 1 cm in all directions from the CTV and organs at risk (OAR) were contoured. CTV included the entire stomach and perigastric lymph node station and any involved abdominal lymph nodes. PTV was generated with a 1 cm expansion from the CTV to account for the setup errors. Appropriate field weighting and beam modifiers (wedges and blocks) were selected to keep the OAR doses below their tolerance. For beam arrangement in the treatment plans, three-field technique (anterior field and two opposed lateral fields) was used. All patients were treated by a high-energy linear accelerator with photon energies 6 and/or 15 MV. The total dose was: – 40 Gy/20 fractions/4 weeks given to patients with residual disease and 36 Gy/18 fractions/3.5 weeks given after complete response (CR).

Assessment of response

The response was defined according to the World Health Organization criteria as follows [16]:

CR was designated as the disappearance of all lesions and absence of any new tumour lesions. Partial response was defined as a decrease of more than or equal to 50% in each lesion. Stable disease was defined as the state of neither partial response nor progressive disease. Progressive disease was defined as the presence of a newly developed lesion or more than 25% increase in the product of two diameters of at least one tumour. Local relapse, defined as relapse from the primary site or adjacent sites, including regional nodes.

The study was approved by the Local Institutional Review Board Committee and was conducted in accordance with the Declaration of Helsinki.

We compared the clinical features of the two groups, including the Eastern Cooperative Oncology Group (ECOG) performance status, serum lactate dehydrogenase concentration, site of involvement, the International Prognostic Index (IPI), Lugano stage, and the presence of B symptoms with survival in both groups.

Statistical analysis

The X^2 test was used to evaluate the relationships between clinical features and outcomes. Overall survival (OS) was calculated from the date of diagnosis to the date of the final follow-up or death from any cause. Disease-free survival (DFS) was from the date of diagnosis to the date of disease relapse or death from any cause. Survival was estimated from Kaplan–Meier curves [17] and compared using the log-rank test. The Cox proportional hazard regression model was used in the multivariate analysis to identify prognostic factors. P value < 0.05 were considered significant; all P values were two-sided. The statistical software used in this study was SPSS16 (SPSS Inc., Chicago, USA) software.

Results

Characteristics of patients

The characteristics of the 79 enrolled patients at diagnosis are summarised in (Table 1), 43 patients were males and 36 patients were females, with a mean age of 48 years (range, 26–65 years). Fifty-seven patients had PGL while 22 had primary intestinal lymphoma (PIL). The distribution of PGL group was as follows; 27 cases were located in the gastric antrum, 17 in the gastric body and 13 in the gastric fundus, while in PIL group, 6 cases were located in the duodenum, 1 in the jejunum and 15 in the colon.

According to the Lugano stages classification, 40 cases were classified as stage I (33 patients with PGL, 7 patients with PIL) and 39 cases as stage II (24 patients with PGL, 15 patients with PIL). Of 37 patients who

underwent primary surgical resection, the indication of surgery was obstruction in 15 patients (6 patients with PGL, 9 patients with PIL) and perforation in 12 patients (9 patients with PGL, 3 patients with PIL), while missed diagnosis as carcinoma occurred in 10 patients (8 patients with PGL, 2 patients with PIL).

The types of the surgery done were as follows: Of the 15 patients who had intestinal obstruction, 6 of them with PGL had wide local excision and gastrojejunostomy, while 9 patients with PIL had resection and anastomosis. Twelve patients with perforation had wide resection and anastomosis; and of the 10 patients who underwent operation due to missed diagnosis with carcinoma, 5 had proximal radical gastrectomy, 3 had total radical gastrectomy and 2 had right hemicolectomy. Table 1 illustrates that two groups have quite similar distribution regarding the age, sex performance status, LDH level, B symptoms and international prognostic score. However, it showed significant difference between two groups regarding stages and in anatomical sites of the disease.

Treatment outcome

The CR rate was significantly higher in the surgery/chemotherapy group (88%) (Table 2) than in chemotherapy group (74%), $p = 0.001$. After median follow-up duration of 40 months (95% CI, 29–62 months), the relapse rate was lower in the surgery/chemotherapy group (28%) than in the chemotherapy group (34%). However, one patient in surgery/chemotherapy died soon after surgery.

The OS and DFS of the surgery/chemotherapy group were significantly better than those in the chemotherapy-alone group (Figure 1a, b). The 5-year DFS and OS was 72% and 76% in the surgery/chemotherapy group and 68% and 71% in the chemotherapy group ($p = 0.012$, 0.037, respectively).

Because there were significant differences in the distribution regarding the stages and anatomical sites, we performed a subgroup analysis. In PGL, the CR rate was 88% in surgery arm and after median follow-up of 40 months, 7 (33%) patients relapsed, 3 had local relapse while 4 had systemic relapse. While, in chemotherapy arm, the CR was 76% and 11 patients relapsed in the same period of follow-up. Six patients had local relapse and five patients had systemic relapse. Despite the difference in CR rate, no statistical significance was found in 5-year DFS, $p = 0.706$, or in OS, $p = 0.858$ (Figure 2a, b).

On the other hand, in PIL, the CR rate of 13 patients who underwent surgery was 92%; after median 40 months of follow-up, 2 patients had local relapse and 1 patient had systemic relapse.

Table 1. Patients characteristics.

Characteristics	Surgery/Chemotherapy N(%)			Chemotherapy-only N(%)			P value of 2 main groups
	Total N0= 37	PIG N0=24	PIL N=13	Total N0=42	PIG N0=33	PIL N0=9	
Age							
<60	31(84)	20(84)	11(85)	35(83)	30(90)	5(55)	0.771
>60	6(16)	4(16)	2(15)	7(17)	3(10)	4(45)	
Sex							
Male	22(60)	12(50)	10(76)	21(50)	16(48)	5(55)	0.548
Female	15(40)	12(50)	3(24)	21(50)	17(52)	4(45)	
PS							
EGOC 0/1	28(76)	17(71)	11(85)	33(78)	25(76)	8(89)	0.159
EGOC 2	9(24)	7(29)	2(15)	9(22)	8(24)	1(11)	
LDH level							
Normal	10(27)	9(37)	1(7)	14(33)	14(42)	0(0)	0.091
raised	27(73)	15(63)	12(93)	28(67)	19(58)	9(100)	
B symptom							
Present	13(35)	10(42)	3(24)	16(38)	14(42)	2(22)	0.089
Absent	24(64)	14(58)	10(76)	26(61)	19(58)	7(77)	
IPI							
I	8(21)	5(20)	3(24)	10(24)	10(30)	0(0)	0.066
II	10(27)	7(29)	3(24)	14(33)	11(33)	3(33)	
III	19(51)	12(50)	7(53)	18(42)	12(36)	6(66)	
Stage							
I	16(43)	13(54)	3(24)	24(57)	20(60)	4(45)	0.023
II	21(57)	11(46)	10(76)	18(43)	13(40)	5(55)	
Bulky Disease							
Yes	10(28)	6(25)	4(31)	9(21)	5(15)	4(45)	0.056
no	27(72)	18(75)	9(69)	33(79)	28(84)	5(55)	
Location							
Stomach	24(64)			33(79)			0.034
Duodenum	3(8)			3(7)			
Jejunum	1(4)			0(0)			
Colon	9(24)			6(14)			

IPI: international prognostic index, No= number

(a)

(b)

Figure 1. DFS and OS between two groups in gastrointestinal lymphoma (surgery/chemotherapy versus chemotherapy alone).

The chemotherapy arm of PIL included 9 patients, CR occurred in 6 patients (66%). During the follow-up period, 3 patients relapsed (33%), 2 patients had local relapse while 1 patient had systemic relapse. When we analysed the DFS and OS, we found there is higher significant difference between both arms favouring use of surgery $p = 0.032$, $p = 0.025$, respectively (Figure 3a, b).

Analysis of prognostic factors

Analysis of prognostic factor by multivariate analysis, our results showed no significant relation to prognostic factors and OS. Prognostic factors analysed were age more than 60 years $p = 0.056$, performance status more than or equal to ECOG grade 2 $p = 0.097$, increased serum lactate dehydrogenase level $p = 0.721$, and IPI $p = 0.061$.

Table 2. Response and survival between 2 groups.

	Surgery/Chemotherapy N(%)			Chemotherapy alone N(%)			P value of 2 main groups
	Total N0=37	PIG N0=24	PIL N0=13	Total N0=42	PIG N0=33	PIL N0=9	
Response							
CR	33(89)	21(88)	12(92)	31(74)	26(79)	6(66)	0.001
PR	3(8)	2(8)	1(8)	6(14)	4(12)	2(22)	0.001
SD	0(0)	0(0)	0(0)	3(7)	2(6)	1(11)	0.001
Progression	0(0)	0(0)	0(0)	2(5)	1(3)	0(0)	0.001
Death	1(2)	1(4)	0(0)	0(0)	0(0)	0(0)	0.001
Relapse							
local	5(14)	3(13)	2(16)	7(17)	6(18)	1(11)	0.040
systemic	5(14)	4(16)	1(8)	7(17)	5(15)	2(22)	0.040
status							
Alive	28(76)	17(71)	11(84)	30(71)	25(75)	5(55)	0.032
Dead	9(24)	7(29)	2(16)	12(28)	8(25)	4(54)	0.025
5 years DFS total	-(72)	-(69)	-(82)	-(68)	-(72)	-(50)	0.012
5 years OS	-(76)	-(82)	-(92)	-(71)	-(75)	-(55)	0.037

CR: Complete remission, PR: partial remission, SD: stable disease, DFS: Disease free survival, OS: overall survival

Figure 2. DFS and OS between 2 groups in primary gastric lymphoma (surgery/chemotherapy versus chemotherapy alone). **DFS:** Disease-free survival; **OS:** Overall survival.

Tolerance of chemotherapy

We compared the tolerance to chemotherapy between two groups, with total 128 cycles in surgery/chemotherapy group compared to 160 cycles in the chemotherapy groups. We found that fatigue, loss of appetite, diarrhoea and constipation were significantly higher in patients receiving surgery/chemotherapy (write the P value). (Table 3).

Discussion

Treatment strategies for GI lymphoma have changed dramatically over the last two decades. The inclusion of surgery as treatment option has been replaced by chemoimmunotherapy, particularly in gastric DLBCL

[18] but not in intestinal DLBCL [19–22]. Even in gastric DLBCL, the use of surgery is still questionable, especially if rituximab is not available.

Our results showed that using surgical approach in primary GI lymphoma before chemotherapy was superior to chemotherapy alone regarding PFS $p = 0.012$ and OS $p = 0.037$, which was in line with many earlier studies that showed superiority of using surgical approach in GI lymphoma [23–24] in spite of the fact that it badly affected chemotherapy tolerance; this also has been reported in several studies that altered the way of thinking from surgery to organ preservation [25, 26].

This result was also found in intestinal lymphoma patients who underwent surgery as our results showed superior DFS $p = 0.032$ and OS $p = 0.025$. This favourable outcome of surgery/chemotherapy is consistent with

Table 3. Toxicity and tolerance to chemotherapy.

	Total no of cycle =128	Total no of cycle= 160	P value
Fatigue	60%	42%	0.021
N& V	48%	42%	0.679
Loss of appetite	52%	30%	0.001
Diarrhea	44%	16%	0.001
Constipation	32%	10%	0.001

N&V: Nausea and Vomiting

Figure 3. DFS and OS between 2 groups in primary intestinal lymphoma (surgery/chemotherapy versus chemotherapy alone). **DFS**: Disease-free survival; **OS**: Overall survival.

previous results of two prospective studies that reported prolonged survival with a low-relapse rate in intestinal B-cell lymphomas in patients who underwent surgery first. [27, 28]. An explanation of that may be, because intestinal lymphoma has poorer outcome than gastric lymphoma [18], surgical resection in this case is mandatory. Another explanation for the better outcome in the surgery/chemotherapy group might be related to complete resection of the bowel segment, as it would be difficult to discriminate residual lesions in bowel wall thickening, and the underestimation of residual lesions might be another reason for the higher local relapse rate in chemotherapy group and radiotherapy is less suitable in intestine than the stomach [5].

On the contrary, our results showed no significant difference between surgical/chemotherapy arm and chemotherapy alone in PGL regarding PFS and OS, $p = 0.706$, $p = 0.858$, respectively. This could be due to the presence of low-grade lymphoma components that can contribute to local relapse after surgery [22], which could

be managed by radiotherapy after chemotherapy alone. Unlike PIL, the association of low-grade lymphoma is not mentioned among previous studies of intestinal DLBCL [5, 18, 23].

Also, we tried to find if any of the prognostic factor has an effect on the OS using multivariate analysis; our results showed no significant effect of any prognostic factor on survival such as age, performance status, increased serum LDH level and IPI. Also, we did not find any significant effect on survival when we examined them in the anatomical subgroups and this also correlated with the previous studies results, which concludes that prognostic factors in GI lymphoma have no impact on survival outcome [30, 31].

In conclusion, surgery is still an important strategy in case of DLBCL in PIL; however, in case of PGL, using chemotherapy alone even without rituximab achieves similar results. However, our small sample size should be considered.

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