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Authors: Ireneusz Ryszard Pierzankowski, Adam Dmitruk, Sebastian Rybski, Lucjan Wyrwicz, Tomasz Olesiński

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Influence of surgery treatment quality on longtime results gastric cancer combination therapy

Ireneusz Pierzankowski, Adam Dmitruk, Sebastian Rybski, Lucjan Wyrwicz, Tomasz Olesiński

Maria Sklodowska-Curie National Researche Institute of Oncology, Warsaw, Poland

Introduction. The aim of this study was to analyze the influence of surgical center experience on long-term survival of patients with locoregionally advanced gastric adenocarcinoma undergoing primary surgery followed by complementary chemoradiotherapy according to MacDonald's regimen.

Material and methods. 154 patients treated surgically, including 75 (48.7%) at the Maria Sklodowska-Curie National Researche Institute of Oncology (NIO-PIB) in Warsaw, and 79 (51.3%) outside this center, were retrospectively analyzed. The compared groups were statistically homogeneous. The following parameters were analyzed: age, gender, tumor differentiation, TNM VII (2010) staging, nodal index, radicality of surgical treatment, tumor type according to Lauren classification, clinical stage, presence of prognostic factors, overall survival time.

Results. Among the patients operated at NIO-PIB, 71 (94.7%) patients underwent radical resection, 4 (5.3%) cases were microscopically non-radical resection. There were no macroscopically non-radical resections (0%). For patients operated outside NIO-PIB, 60 (75.9%) R0 resections, 15 (19%) R1 resections and 4 (5.1%) R2 resections were performed. The percentage of radical resections was significantly higher at NIO-PIB (p = 0.001). In 77% of patients operated on at NIO-PIB, disease progression in terms of feature n could be established. This percentage for patients operated on outside the NIO-PIB was 54% and was significantly lower (p = 0.001). The probability of 5-year survival was 41.6% in total, with 45.3% for the group of patients operated on in the NIO-PIB and 38.0 % for the group of patients operated on outside the CO-I, respectively (p = 0.628)

Conclusions. The quality of surgical treatment was significantly higher in NIO-PIB. The difference in 5-year overall survival (OS) between the compared groups is not statistically significant. Complementary treatment with chemoradiotheraphy (CRT) according to MacDonald's regimen reduces the shortcomings in the quality of surgical treatment in locoregionally advanced gastric adenocarcinoma.

Key words: gastric cancer, surgery, chemoradiotherapy

Introduction

Gastric cancer (GC), despite a long-term decline in incidence and mortality, remains the fourth most common cancer and the second cause of cancer-related deaths. Differences in

gastric cancer incidence between populations are approximately 10-fold. The incidence is particularly high in East Asia (over 40/100,000), Eastern Europe (about 25/100,000), and Central America (30/100,000) and South America (20/100,000) [1]. The share of gastric cancer in cancer incidence in Poland has decreased almost 3-fold over the last 4 decades. In Poland stomach cancer constitutes about 5% of all cancers in men and about 3% in women. It is the cause of about 7% of deaths in men and 5% in women. The 5-year survival rate in this group of patients increased slightly during the first decade of the 21st century, from 14.6% to 16.4% in men and from 18.2% to 19.8% in women. In total, it currently amounts to 17.6%. In Poland in 2010 the number of deaths due to gastric cancer among men was about 25% higher than the average for the European Union countries (data from 2009), among women about 10%. [1].

Although surgery remains the mainstay of treatment in gastric cancer, in view of its limited efficacy, increasingly more importance is being attached to combined treatment, especially in regionally advanced disease. Currently, the recommended treatment for patients with stage above T1N0 is combination therapy, including perioperative chemotherapy, with the currently preferred quadruple FLOT regimen (fluorouracil, leucovorin, oxaliplatin and docetaxel). This increases the chance of cure of patients by up to 70% [2–4].

Of fundamental importance for the development of combination therapy for gastric cancer was the study by MacDonald et al [5]. The scheme of treatment proposed by the researchers includes 1 cycle of chemoradiotherapy (CRT) consisting of FU at a dose of 425 mg/m^2/day for 5 days and calcium folinate 20 mg/m^2/day for 5 days, followed after 28 days by irradiation to a dose of 45 Gy (fractions of 1.8 Gy) together with CTH according to the scheme: FU 400 mg/m^2 together with calcium folinate 20 mg/m^2/day for the first 4 and for the last 3 days of irradiation – recommendations for the Diagnostic and Therapeutic Management of Malignancies – 2013. 132 irradiation, and one month after completion of radiotherapy (RTH), 2 consecutive cycles of CTH, at doses as in the first course, given one month apart. The irradiation area should include the gastric lobe and regional lymph nodes. Critical of the results of the study, the researchers raised in particular the aspect of poor quality of surgical treatment in most of the analyzed cases (predominantly patients with limited or no lymphadenectomy), which could affect the final results, In our institution complementary treatment according to MacDonald's scheme in the years 2009–2012 was the treatment of choice for locally advanced gastric cancer. Since 2013, it has been used in a selected group of patients as an adjunct to standard combination treatment.

In this study, we retrospectively analyzed the long-term results of combined treatment, which included surgical intervention with the intention of cure and complementary therapy according to the MacDonald regimen. Medical records of 154 patients treated with the MacDonald regimen at the Maria Sklodowska-Curie National Researche Institute of Oncology (NIO-PIB) in Warsaw between 2009 and 2012 were analyzed.

Aim of the study

The aim of this study is to analyze the influence of the experience of the surgical center on the distant results of gastric cancer treatment in a group of patients subsequently undergoing complementary treatment according to the MacDonald regimen.

Material and methods

Between 2009 and 2012, 154 patients, including 55 (35.7%) women and 99 (64.3%) men, after gastrectomy for GER were treated with the MacDonald regimen. The medical records of all patients were retrospectively analyzed. Detailed demographic and tumor type, differentiation degree, type and stage are presented in tables I and II. Two subgroups were distinguished in the analyzed group:

- patients operated in the NIO-PIB,
- patients operated on outside the NIO-PIB.

The following parameters were taken into consideration: age of patients, gender, tumor differentiation degree, tumor stage (according to TNM VII 2010 classification), nodal index, radicality of surgical treatment, tumor type according to Lauren classification, clinical stage, presence of prognostic factors. The overall survival time of the patients was defined as the period from diagnosis of the disease to the end of follow-up in April 2017, using the Kaplan-Meyer estimator.

Results

A group of 154 patients was retrospectively analyzed and divided into two homogeneous subgroups. The first was composed of those operated on at NIO-PIB (75 – 48.7%) and the second was those operated on outside (79 – 51.3%). Patients from both groups then underwent complementary CRT according to the MacDonald regimen. Among patients operated in NIO-PIB, 71 (94.7%) patients underwent radical resection, in 4 (5.3%) cases it was microscopically non-radical resection. There were no macroscopically non-radical resections (0%). For patients operated outside NIO-PIB, 60 (75.9%) R0 resections, 15 (19%) R1 resections and 4 (5.1%) R2 resections were performed.

Thus, the percentage of radical resections was significantly higher in NIO-PIB (p = 0.001). The number of lymph nodes in the evaluated specimen ranged from 2 to 64, with a median of 21 for the entire study group, 25 for patients operated on at NIO-PIB, and 10.5 for patients operated on outside NIO- PIB, respectively. The median number of lymph nodes involved by metastases was 4 for the whole group, with -2 for patients operated in NIO-PIB

and 5.5 for patients operated outside NIO-PIB. In 77% of patients operated in NIO-PIB it was possible to establish the stage of the disease in terms of N feature (number of lymph nodes in the specimen >15). This percentage for patients operated on outside the NIO-PIB was 54% and was significantly lower (p = 0.001). In 19% of patients operated on in the NIO-PIB *vs.* 46% of patients operated on outside the NIO-PIB, the number of evaluated lymph nodes was between 7–15, and for 4% of patients operated on in the NIO-PIB *vs.* 0% of patients operated on outside the NIO-PIB – between 0–6. Angioinvasion was noted in 134 (74%) patients and nerve trunk infiltration in 130 (71%). The median overall survival time was 38.5 (3–104) months, for patients with R1 resection it was 25.5 (7–104) months, and for R2 it was 8.5 (3–31) months (tab. I and II).

The evaluated parameters were statistically analyzed (Levene's test, t-test for equality of means, Pearson's test), which confirmed the homogeneity of the study groups. Based on the collected data, using Log Rank test and Kapplan-Meier estimator, the probability of 5-year survival was estimated for the group of patients studied and for the compared subgroups. It amounted to 41.6% in total, with 45.3% for the group of patients operated in the NIO-PIB and 38.0% for those operated outside the NIO-PIB, respectively (p = 0.628) (fig. 1 and 2).

Discussion

Over the past thirty years, there have been marked advances in the treatment of gastric cancer, which in countries leading in the diagnosis and treatment of this cancer translate into a significantly better prognosis than in the past. In the Far East the 5-year survival rate reaches 70%, in Western European countries it is 25% [1, 4, 6]. Unfortunately, in Poland the 5-year survival rate in this group of patients increased slightly during the first decade of the 21st century, from 14.6% to 16.4% in men and from 18.2% to 19.8% in women. The total is currently 17.6%, and the number of deaths in 2010 due to gastric cancer was, by about 25% in men and 10% in women, higher than the average for European Union countries (data from 2009). Fortunately, the incidence of gastric cancer has decreased 3-fold over the past 40 years [1].

Gastric adenocarcinoma is a disease whose incidence, course and prognosis depend not only on tumor biology and stage, but also on geographic, cultural, economic factors and the organization of the health care system [6]. The best results in the treatment of this cancer are achieved in the highly developed countries of the Far East, where the high incidence has forced certain systemic measures (screening endoscopic examinations, centralization of treatment) to reduce the mortality associated with this disease. A more favorable tumor profile (intestinal type, distal localization), anthropometric parameters of the local population, and thus a significantly lower risk of complications during treatment, related, for example, to obesity and other civilization diseases, as well as a very high quality of surgery, are not without significance for better treatment outcomes [6]. This is also reflected in the different, in relation to European and American, way of combined treatment.

The most common is surgical treatment, involving D2 lymphadenectomy and complementary chemotherapy (CT). The basis for this approach was provided by two randomized, multicenter studies ACTS-GC and CLASSIC [4], which confirmed a significantly higher percentage of overall survival (OS) and disease-free survival (DFS) in patients treated in a combined manner, compared with patients undergoing surgery alone.

The longstanding dominance of treatment based on surgery alone was interrupted by the MacDonald study. The authors presented the results of the study, which showed a significantly higher rate of survival in patients undergoing complementary CRT compared to patients who underwent surgery alone (36 months *vs.* 27 months) [5]. The conclusions of this report, as well as the results of The North American Intergroup – 0116 trial, became the basis for the use of CRT in the United States for the adjuvant treatment of gastric cancer [4, 7]. Critics of the trial emphasized that only 9% of patients had curative surgery with D2 lymphadenectomy, and 54% had less than D1 lymphadenectomy [4, 7].

Thus, complementary CRT may have been primarily to compensate for the shortcomings of surgery. This was confirmed by the retrospective comparative Dutch D1D2 trial, which showed a lower rate of local recurrence after CRT, in patients after gastrectomy and D1 lymphadenectomy. For D2 lymphadenectomy, no benefit was observed [4]. Nevertheless, other reports suggest that patients after optimal lymphadenectomy also benefit from complementary CRT [4]. Studies in this area are currently ongoing. The current indications for complementary CRT are: inadequate extent of surgical treatment, its irreversibility both microscopically (R1) and macroscopically (R2), the presence of locoregional lymph node metastases (especially when the nodal index exceeds 20%), nerve trunk infiltration and angioinvasion [7–9].

According to the ESMO recommendations, the currently recommended treatment is a combined therapy consisting of perioperative chemotherapy starting at stage IB and potentially curative surgery (gastrectomy, subtotal resection) accompanied by D2 lymphadenectomy [4]. This approach was based on the results of the UK MRC MAGIC trial, which demonstrated an improved 5-year survival after perioperative administration of 6 courses of ECF (epirubicin, cisplatin, 5-fluorouracil) compared with patients treated with surgery alone (36% *vs.* 23%). On the other hand, the German AIO study group showed a greater number of complete pathological responses in patients undergoing perioperative CT according to the FLOT4 regimen (5-fluorouracil, leucovorin, oxaliplatin, docetaxel) *vs.* ECF/X (15.6% *vs.* 5.8%), as well as a longer median survival (mOS), 50 *vs.* 35 months. These results have now become the basis for the implementation of the FLOT4 regimen into clinical practice [2, 4]. On the other hand, patients who did not receive preoperative chemotherapy and whose disease stage was determined to be at least IB should undergo complementary treatment with CRT or CT [4, 7–11]. In contrast, the randomized phase III CRITICS trial showed that patients undergoing preoperative CT do not benefit from postoperative CRT over postoperative CT (OS 37 m. *vs.* 43 m., respectively) [12].

Current studies, which aim to optimize the combination treatment, are ongoing. In particular, this concerns the preoperative treatment period. In the multicenter TOPGEAR study patients with resectable adenocarcinoma of the stomach or gastroesophageal junction are randomized to groups receiving, respectively: preoperative CT (3 courses of ECF) or preoperative RT followed by CT (2 courses of ECF), and after surgery in both groups CT (3 courses of ECF). Preliminary results of the study show no significant differences between the groups in terms of operability (90% CT *vs.* 85% CRT), grade III operative complications (according to Clavien-Dindo) – 22% in both groups, grade III toxicity, both hematologic and gastrointestinal, were also similar and were 50% CT *vs.* 52% CRT and 32% CT *vs.* 30% CRT, respectively [13]. In contrast, the phase II CRITICS study focuses on comparing the efficacy of neovjuvant therapy based on, respectively: CT according to DOC regimen (docetaxel, oxaliplatin, capecitabine) – 4 cycles, 2 cycles of CT according to DOC regimen following CRT (45 Gy with paxitaxel and carboplatin) and CRT [14]. Given that 40–50% of patients do not receive postoperative treatment, the results of this study may be extremely

The incidence of severe postoperative complications is also an important prognostic factor that depends directly on the quality of surgical treatment. Peng et al. compared two groups, a total of 239 patients undergoing gastrectomy with D2 lymphadenectomy, combined with neoadjuvant CT. The analysis took into account patient-dependent factors (gender, age, BMI, comorbidities, previous abdominal surgery), tumor-dependent factors, as well as those determined by the surgical process (duration of surgery, blood loss, extent of surgery – e.g. multiorgan resections, type of surgical technique) and the length of hospital stay. The severity of complications was determined according to the Clavien-Dindo classification. Complications were observed in 24.7% of patients, and perioperative mortality was 0.8%. Grade I and II complications occurred in 9.2% of patients, and severe complications (grade III and IV) in 15.5%. The occurrence of postoperative complications was correlated primarily with age >55 years, BMI ≥25, operative time >200 min, and extent of surgery ($p < 0.05$). Both 3-year overall survival and disease-free survival were significantly longer in patients who did not experience complications from groups III and IV ($p = 0.033$ and $p = 0.034$, respectively) [17].

In a study published in 2016, Datta and colleagues analyzed the impact of lymphadenectomy and the results of histopathologic evaluation of the removed lymph nodes on the choice of follow-up treatment. The study group included 3008 patients with gastric adenocarcinoma, grades IB–III treated, surgically and then with complementary therapy, between 1998 and 2006. The analysis concluded that inadequate lymphadenectomy and the presence of lymph node metastases were strong predictors of increased mortality risk. Overall survival after CRT and was significantly longer than after chemotherapy regardless of disease stage (OS CRT *vs.* OS CT 36.1% *vs.* 28.9 m., ($p < 0.0001$). This benefit decreases as the number of evaluated lymph nodes in the specimen increases. CRT improves overall survival in patients with lymph node metastases regardless of the extent of lymphadenectomy (29.8 *vs.*22.2 months, $p < 0.001$). In patients without lymph node metastases, with normal extent

of lymphadenectomy, no benefit of CRT over CT was observed. Patients without lymph node metastases, with inadequate lymphadenectomy, benefited from CRT [18]. In contrast, Dutch researchers took a closer look at the effect of CRT on the prognosis of patients after microscopically non-radical surgery. They compared two groups of patients – 361 patients after R1 resection without complementary CRT and 40 patients undergoing this procedure – using the Cox regression test and the extreme fitting method for statistical analysis. The disease progression in both groups did not show statistically significant differences. However, a significantly longer survival was observed in patients undergoing complementary CRT (24 months *vs.* 13 months) [19].

The retrospective data obtained during the analysis compared two practically homogeneous groups of patients treated in the NIO-PIB with complementary CRT. The factors that differentiated them were:

- percentage of radical operations,
- number of lymph nodes evaluated in the specimen.

It should be added here that in the group of patients treated outside the NIO-PIB, almost all patients were operated in institutions of II and mainly III referral level. Thus, it should have been expected that the parameters determining the quality of surgical treatment and histopathological evaluation, such as the radicality of the surgical procedure and the number of lymph nodes evaluated in the examined specimen, should be similar. Nevertheless, both resection and extent of lymphadenectomy were significantly different. However, the 8.6% higher 5-year OS in the group of patients operated in NIO-PIB did not translate into statistical significance. The authors conclude that the use of adjuvant CRT effectively eliminated the differences in the quality of surgical treatment. Comparing the 5-year OS values with data from foreign centers, it should be noted that the results of surgical treatment of locoregionally advanced gastric cancer supplemented with CRT according to the Mac Donald scheme are similar to those achieved in American and Western European centers and slightly worse than those achieved in the Far East [6, 8, 9, 15, 16].

In summary, improvement in treatment outcomes resulting from advances in gastric cancer therapy will only occur if this cancer is diagnosed early enough [6] and treatment is concentrated in quality-assured facilities. In particular, this applies to the surgical stage of combined treatment and the adherence to protocols for the appropriate preparation of the specimens collected for histopathological examination, as well as the examination itself. A similar opinion is held by researchers gathered around the CRITICS project [20–22]. Much depends also on the awareness of the patients themselves, who should lobby for the introduction of endoscopic screening and avoid institutions where the proposed treatment differs from the commonly accepted one. A hope in this matter is an increasing access to information and a social trend to take active care of one's own health.

Conclusions

- The quality of surgical treatment, expressed both by the percentage of radical operations and the extent of lymphadenectomy, is significantly better at NIO-PIB compared to other centers.
- The difference in 5-year OS between the compared groups is not statistically significant.
- Complementary treatment with CRT according to MacDonald's regimen reduces the shortcomings in the quality of surgical treatment in locoregionally advanced gastric adenocarcinoma.

Conflict of interest: none declared

Ireneusz Pierzankowski

Maria Sklodowska-Curie National Researche Institute of Oncology

ul. Roentgena 5

02-781 Warszawa, Poland

e-mail. i.pierzankowski@gmail.com

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Table I. Parameters of study group

Study group parametres (n = 154)	
age (median, standard deviation)	60 (+/−10.691)
sex: n (%)	
women	55 (35.7%)
men	99 (64.3%)
tumor grade G: n (%)	
G2	37 (24%)
G3	116 (75.3%)
MANEC	1 (0.7%)
anatomic stage of tumor: n (%)	
Ia	0 (0 %)
Ib	18 (11.7%)
IIa	21 (13.6%)
IIb	28 (18.2%)
IIIa	32 (20.8%)
IIIb	39 (25.3%)
IIIc	16 (10.4%)
IV	0 (0%)
primary tumor advanced T: n (%)	
T1a	0 (0%)
T1b	1 (0.6%)
T2	18 (11.7%)
T3	103 (66.9%)
T4a	28 (18.2%)
T4b	4 (2.6%)
regional stage N: n (%)	
N0	26 (16,9%)
N1	39 (25,3%)

N2	33 (21,4%)
N3a	42 (27,3%)
N3b	11 (7,1%)
N3c	1 (0,6%)
tumor type according to Lauren classification: n (%)	
I	17 (11%)
II	127 (82.5%)
III	10 (6.5%)

n – numer of patients; % – percentage of patients characterized by a given parameter

Table II. Comparison of parameters of subgroups: operated in NIO-PIB and operated outside NIO-PIB

Tested parameter	**NIO-PIB operated group n = 75** **n (%)**	**Group operated outside NIO-PIB n = 79** **n (%)**	**Two-sided statistical significance level** **p**
age (median, standard deviation)	62 (+/−10.331)	59 (+/−10,968)	0.181
sex: n (%)			
women	30 (40%)	25 (31.6%)	
men	45 (60%)	54 (68.4%)	
grading: n (%)			
G1	0 (0.00%)	0(0.00%)	
G2	17 (22.7%)	20 (25.3%)	0.540
G3	57 (76%)	59 (74.7%)	
MANEC	1 (1.3%)	0 (0.00%)	
anatomic stage of tumor: n (%)			
Ia	0 (0%)	0 (0%)	
Ib	8 (10.7%)	10 (12.7%)	
IIa	10 (13.3%)	11 (13.9%)	
IIb	17 (22.7%)	11 (13.9%)	0.882
IIIa	15 (20.0%)	17 (21.5%)	
IIIb	17 (22.7%)	22 (27.8%)	
IIIc	8 (10.7%)	8 (10.1%)	

feature T: n (%)			
TIa	0 (0.00%)	0 (0.00%)	
TIb	0 (0.00%)	1 (1.3%)	
TII	5 (6.7%)	13 (16.5%)	0.321
TIII	53 (70.7%)	50 (63.3%)	
TIVa	15 (20.0%)	13 (16.5%)	
TIVb	2 (2.7%)	2 (2.5%)	
feature N: n (%)			
N0	15 (20%)	11 (13.,9%)	
N1	23 (30.7%)	16 (20.3%)	
N2	11 (14.7%)	22 (27.8%)	0.196
N3a	20 (26.7%)	24 (30.3%)	
N3b	6 (8.0%)	5 (6.3%)	
N3c	0 (0.00%)	1 (1.3%)	
tumor type according to Lauren classification: n (%)			
I	8 (10.7%)	9 (11.4%)	
II	60 (80.0%)	67 (84.8%)	
III	7 (9.3%)	3 (3.8%)	

G – grading; T – tumor; N – lymph nodes; n – numer of patients; % – percentage of patients characterized by a certain parameter

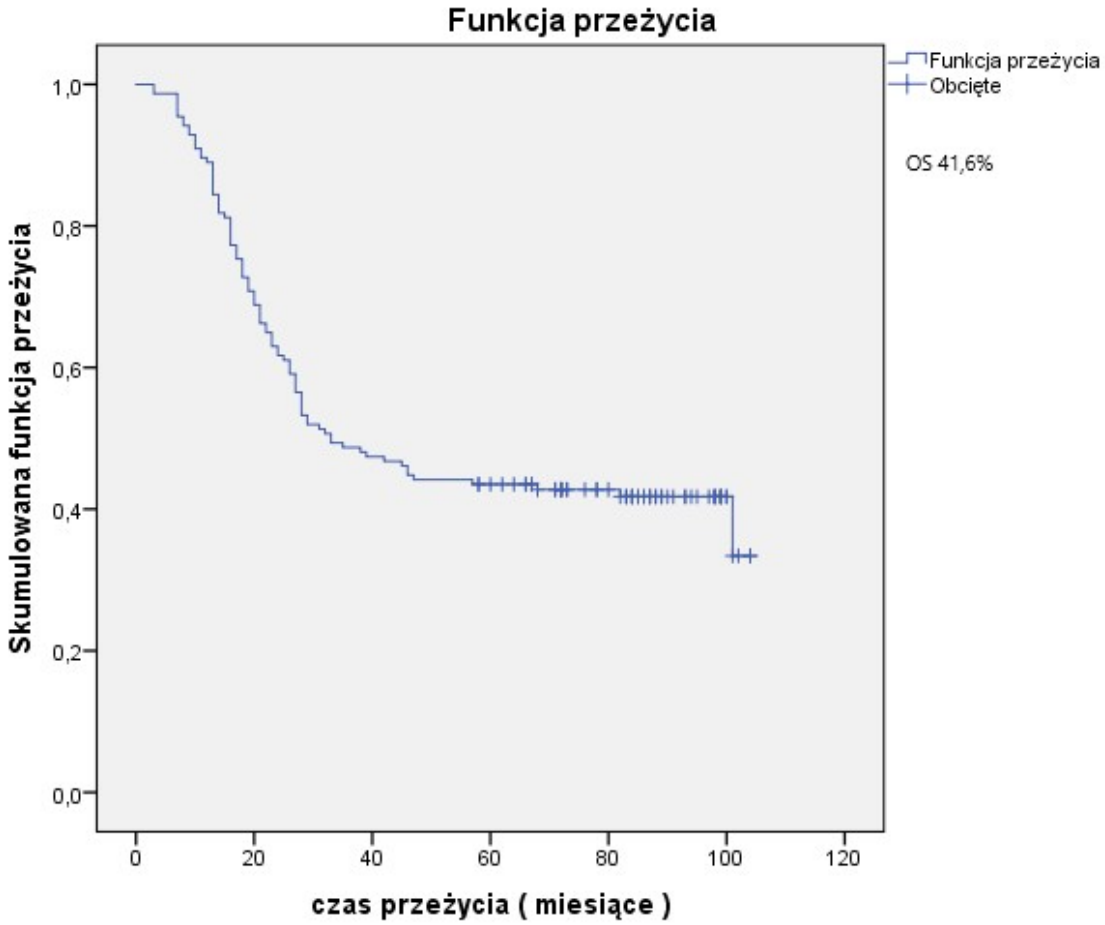

Figure. 1 Survival function

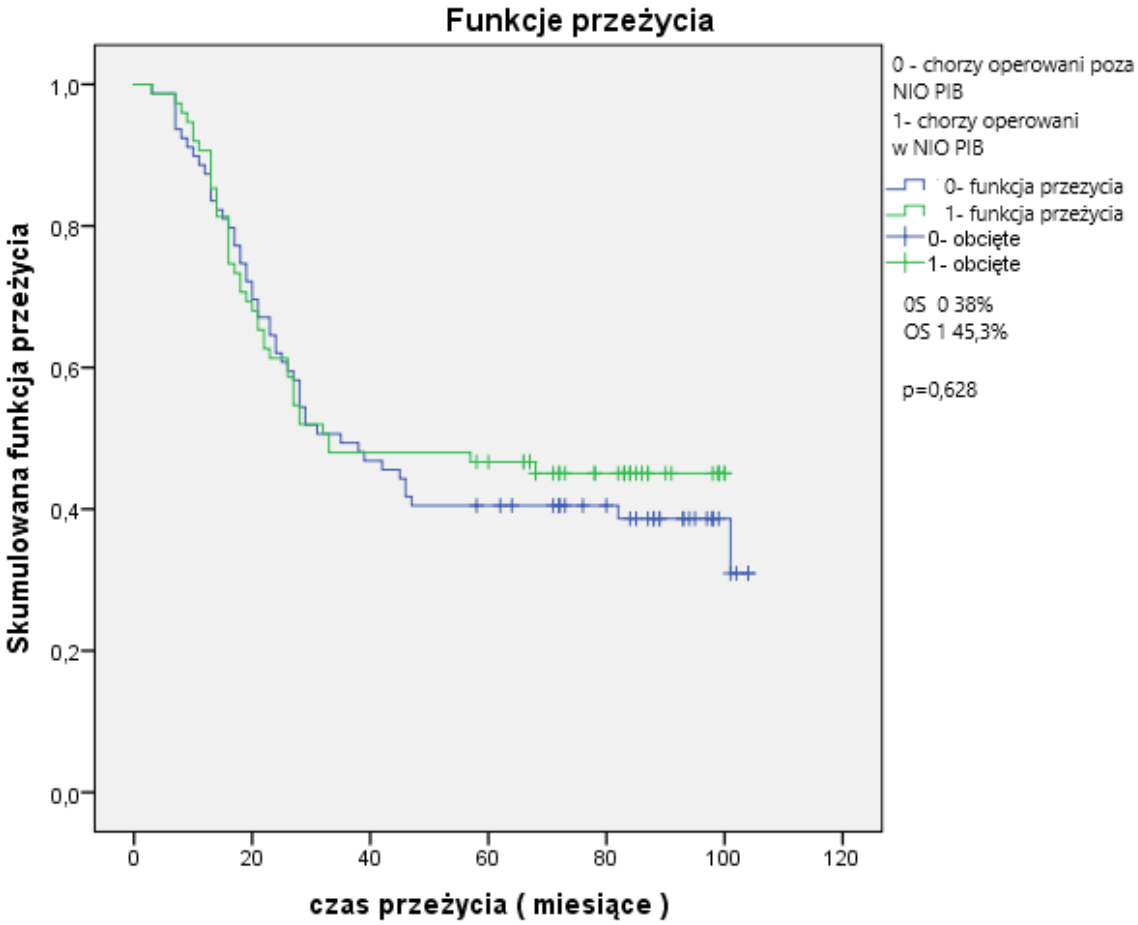

Figure 2. Survival functions by surgical site