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Outcomes of Locally Advanced Gastric Cancer Treated with D2 Gastrectomy and HIPEC

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Abstract

Background-Aims:

D_2 gastrectomy followed by adjuvant chemotherapy is considered the potentially curative treatment for locally advanced gastric cancer. The addition of hyperthermic intraperitoneal chemotherapy (HIPEC) is a promising adjuvant treatment intending to reduce the incidence of loco-regional recurrences. The aim of the study is to evaluate the effect of HIPEC in locally advanced gastric cancer by comparing patients who underwent D_2 gastrectomy and HIPEC (HIPEC group) with D_2 gastrectomy alone (CON group).

Methods:

Overall survival, morbidity, in-hospital mortality, and recurrence were correlated to clinical and histopathological variables.

Results:

Overall survival in HIPEC and CON group was 68% and 48% respectively but the difference was not statistically significant (p=0.091). The groups were similar for in-hospital mortality although the morbidity rate was higher in HIPEC group (p=0.032). The recurrence rate was similar in both groups even though the rate of locoregional recurrence in CON group was considerably higher (p=0.003).

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Conclusions:

HIPEC may safely be used as an adjuvant in gastric cancer despite the higher risk of complications although it is not an independent indicator of morbidity. HIPEC does not increase the in-hospital mortality and the rate of distant metastases; it appears to reduce the rate of loco-regional recurrence. Further studies are required to investigate the role of HIPEC in locally advanced gastric cancer.

Keywords D_2 gastrectomy, HIPEC, survival, morbidity, mortality, recurrence

Introduction

Gastric cancer is the fifth most common cancer and the third most common cause of cancer-related death for approximately 800000 deaths annually [1]. It is diagnosed twice more frequently in men than in women. The majority of patients are over 60 years of age [1, 2]. D_2 gastrectomy combined with perioperative systemic chemotherapy is considered the potentially curative treatment achieving 36-45% 5-year overall survival rate in Eastern Asian countries [3, 4, 5], even though it has been criticized or largely questioned in regard to its oncological effect in Western countries [6, 7, 8, 9]. Despite initial disappointing results, D_2 gastrectomy has demonstrated significant survival advantage compared to D_1 gastrectomy after 15 years of follow-up [10]. Comparative and prospective randomized studies from Japan have not shown any difference between D_2 and D_3 or D_4 gastrectomies [11, 12, 13]. D_2 gastrectomy is considered the single potentially curative method of gastric cancer despite contradictory opinions [14] even though the comparison between D_1 and D_2 gastrectomy is rare in international literature and has not definitely proved the superiority of D_2 gastrectomy [8, 11-13, 15]. In Asia D_2 gastrectomy has been accepted as the standard treatment for locally advanced gastric cancer [16]. Despite the demanding and time consuming surgical technique no reduction in recurrence has been reported even in patients without nodal involvement. The recurrence rate has remained as high as 40-70% [17]. Complete mesogastric excision has been strongly advocated [18] and has been in use by many specialized centers. The superiority of the method is still under investigation even though the Asian surgeons recommend it as the gold standard in the treatment of gastric cancer [19, 20].
HIPEC in combination with D_2 gastrectomy has been proposed as an adjuvant treatment in locally advanced gastric cancer with promising results especially for patients at high risk to develop peritoneal carcinomatosis [21, 22].

The purpose of the study is to evaluate the effect of HIPEC in patients with locally advanced gastric cancer by comparing D_2 gastrectomy alone (CON group) to D_2 gastrectomy combined with HIPEC (HIPEC group).

Patients-methods

The files of patients with locally advanced gastric cancer who were treated from 2000 until 2015 with R_0 D_2 gastrectomy were retrieved and analyzed retrospectively. The diagnosis of the disease

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was established by physical examination, hematologic-biochemical examinations, tumor markers (CEA, CA 19-9, CA-125), endoscopic examination, and biopsy. Staging was possible by thoracic and abdominal CT-scan. MRI and PET-CT scan were rarely used if staging was doubtful. Patients over 16 years of age, capable to undergo major surgery, with acceptable performance status (>70% according to Karnofsky performance status), without distant and unresectable metastases or positive peritoneal cytology, who had no history of previous neoplastic disease at risk for recurrence (except for basal cell carcinoma or carcinoma of the cervix adequately treated) were selected for surgery. Patients with poor performance status (<70% according to Karnofsky performance status), with distant and unresectable metastases, with recent history of heart attack, recent pulmonary or urine infection, and pregnant women were excluded from surgery. All patients selected to undergo D_2 gastrectomy in combination with HIPEC signed an informed consent. The Ethical Committee of the Hospital approved the publication of the study.

Treatments

A vertical midline incision extending from the xiphoid process to the pubic symphysis was always used for maximal abdominal exposure. After resection of the round and falciform ligaments, peritoneal cytology was received from the left upper abdominal cavity and the pelvis. Patients with tumors of the antrum underwent sub-total gastrectomy. Patients with tumors of the body, fundus, and Siewert I esophagogastric tumors underwent total gastrectomy. D_2 lymphadenectomy consisted of the en-bloc resection of the greater and lesser omentum, the stomach and the first part of the duodenum, the sub-pyloric lymph nodes, and the lymph nodes of stations 7, 8, 9, 11, 12a, and 10 (if splenectomy needed to be performed) [23, 24]. Patients with Siewert II and III esophagogastric tumors were excluded from the study. HIPEC was administered after the tumor resection and before the reconstruction of the gastrointestinal tract by the open abdominal (Coliseum) technique [25] implemented at 42.5-43^{o}C for 90 min with Mit-C (15mg/m^2) and Doxorubicin (15mg/m^2). A heater circulator with two roller pumps, one heat exchanger, one reservoir, an extracorporeal system with two inflow and two outflow tubes, and 4 thermal probes was used for HIPEC (Sun Chip, Gamida Tech, Paris, France). A prime solution of 2–3 L of normal saline or Ringer's lactate solution was instilled into the abdomen prior to the administration of the cytostatic drugs. As soon as the mean abdominal temperature reached 40◦C, the cytostatic drugs were administered in the abdomen. During HIPEC, the patients received concomitantly intravenous 5-FU (400mg/m^2) and Leucovorin (20mg/m^2). Bi-cavitary HIPEC was performed if the diaphragm had been opened. The reconstruction of the continuity of the gastrointestinal tract was always performed after the completion of HIPEC and was possible by performing Roux-en-Y gastro-jejunal anastomosis at 60 cm after sub-total gastrectomy, or Roux-en-Y esophago-jejunostomy at 60 cm after total gastrectomy. All anastomoses were hand-made.

The age, gender, tumor anatomic location and size, as well as the type of gastric resection were all recorded in detail. The depth of gastric wall invasion, the number of the resected lymph nodes, the number of the infiltrated lymph nodes, the classification according to Lauren, Ming,

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WHO, and Bormann, the stage of the disease (according to the Japanese classification of Gastric Carcinoma) [26], as well as the degree of differentiation were recorded in detail. The complications and the in-hospital deaths were also recorded. The severity of the complications was classified according to Clavien-Dindo classification [27]. All patients were scheduled to receive adjuvant systemic chemotherapy.

Follow-up

All survivors were followed-up with physical examination, hematologic-biochemical examinations, tumor markers (CEA, CA 19-9, CA-125), endoscopic examinations, abdominal and thoracic CT-scans every 4 months during the first year after surgery, every 6 months for the first 5 years, and once a year later. The recurrences and the sites of recurrence were recorded in detail. MRI, or whole body bone scanning or PET-CT was used if the results of the other radiologic examinations were inconsistent.

Statistical analysis

Statistical analysis was possible using the SPSS (Statistical Package for Social Sciences version 17). The proportions of patients with a given characteristic were compared using the x^2 or the Fisher's-exact-test. Survival curves were obtained using the Kaplan-Meier method, and the comparison of curves was possible using the log-rank-test. Cox's regression analysis and logistic regression analysis were used for multiple analyses. A p value < 0.05 was considered statistically significant.

Results

From 2000 until 2015, 45 patients, mean age 70.3 ± 8 (47-85) underwent D_2 gastrectomy in combination with HIPEC (HIPEC group) and 76 patients, mean age 68.4 ± 10.5 (35-89) underwent D_2 gastrectomy alone (CON group).

The groups were comparable for age, gender, type of operation, TNM stage, Lauren, and WHO classification, degree of differentiation, in-hospital mortality, recurrences, tumor depth, tumor size, and tumor anatomic location, performance status, and ASA class ($p>0.05$). They were different in Ming and Bormann's classification, morbidity, treatment with adjuvant chemotherapy, and sites of recurrence ($p<0.05$) (Table 1). Although all stage II and III patients were recommended to receive adjuvant chemotherapy only 8 patients from the HIPEC group and 33 from the CON group accepted to receive systemic chemotherapy.

The overall 5- and 10-year survival for all patients was 52%. The median survival was not reached (Figure 1). The overall 5- and 10-year survival rate for HIPEC and CON group was 68% and 48% ($p=0.091$) respectively (Figure 2). The median survival in HIPEC group was not reached whereas in CON group was 53 months.

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Univariate analysis demonstrated that the overall survival was related to stage, nodal involvement, ASA class, degree of differentiation, Lauren and Bormann's classification ($p<0.05$). Multivariate analysis demonstrated that the stage, the ASA class, and the Lauren classification were identified as the independent variables of survival (Table 2).

During hospitalization 37 patients (30.6%) were recorded with complications and 2 (1.7%) of them died. One patient died because of myocardial infarction and the other because of acute renal failure. There were 6 patients (4.9%) with pulmonary complications (atelectasis, pneumonia), 1 (0.8%) with myocardial infarction, 3 (2.4%) with cardiac arrhythmias, 1 (0.8%) with acute renal failure, 7 (5.8%) with urine infection, 1 (0.8%) with duodenal stump failure, 5 (4.1%) with anastomotic failure, 2 (5.4%) with dehiscence, 10 (8.2%) with wound infection, and 1 patient (0.8%) with postoperative hemorrhage. There was no patient with Grade I complications. There were 14 (11.6%) patients with Grade II, 15 (12.4%) with Grade IIIA, 6 (3.8%) with Grade IIIB patients, no patient with Grade IV, and 2 (1.7%) patients with Grade V complications. Severe complications were recorded in 23 patients (19%) and the re-operation rate was 3.3% (4 patients). Univariate analysis showed that Bormann's classification, the ASA class, and the use of HIPEC were related to morbidity ($p<0.05$). Multivariate analysis showed that Bormann's classification was the single independent variable of morbidity (Table 3).

With a median follow-up time 24 months recurrence was recorded in 47 patients (38.8%). Loco-regional recurrences were identified in 26 (55.3%) patients and distant in 21 (44.7%). Univariate analysis showed that the stage, the Lauren classification, the degree of differentiation, and the nodal involvement were related to recurrence ($p<0.05$). The stage and the Lauren classification were identified as the independent variables of recurrence in multivariate analysis (Table 4). There distant and the loco-regional metastases were found in 12 (75%) and 4 (25%) patients respectively in the HIPEC group, and 9 (29%) and 22 (71%) patients respectively in the CON group (Table 1).

Discussion

Despite advances in surgery which resulted in survival improvement the prognosis is still unfavorable in gastric cancer [28]. The results of our study showed that the 5- and 10-year overall survival for HIPEC and CON group was 68% and 48% respectively. This difference was not significant ($p=0.091$). Similar results have been shown by other investigators using HIPEC (21, 22). Radical D_2 gastrectomy with or without complete mesogastric excision is associated with approximately 40% recurrence rate in Asian countries [29]. The majority of recurrence is loco-regional which develops either pre-operatively spontaneously or intra-operatively iatrogenically. Cancer cells exfoliated from the surface of a tumor that has infiltrated beyond the serosa are implanted at the adjacent peritoneal surfaces resulting in proximal random peritoneal carcinomatosis. On the other hand during surgical manipulations cancer cells from traumatized interstitial tissues or from transected lymphatic network or even from venous blood loss are entrapped with fibrin and blood clots at the adjacent raw peritoneal surfaces and during wound healing promoted by growth factors are transformed to recurrent tumors [30]. Pharmacokinetic

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studies have shown that cytostatic drugs administered intraperitoneally may remain for long at the peritoneal surfaces acting intensively their pharmacologic properties because of the peritoneal-plasma barrier and may eradicate peritoneal nodules that have maximal diameter < 3mm [31, 32]. The initial clinical reports using HIPEC as an adjuvant treatment in locally advanced gastric cancer have been particularly promising in regard to the oncological result [33]. The reports were disappointing because of the high incidence of complications (50%) while the re-operation rate exceeded 30% [34]. In our study the morbidity rate has been shown to be 30.6% but severe morbidity has been restricted to 19% and the re-operation rate to 3.3%. Morbidity in the HIPEC group has been considerably higher.

Later studies showed that the morbidity, the in-hospital mortality, the overall survival, the disease free survival, and the recurrences were all improved compared to older studies [34, 35]. Recent studies demonstrate that HIPEC is effective in preventing the development of peritoneal carcinomatosis after curative resection of advanced gastric cancer and is indicated for patients with tumor infiltrating beyond the serosa or with positive peritoneal cytology and nodal involvement [36, 37].

One prospective randomized trial comparing radical gastrectomy with HIPEC or systemic chemotherapy has shown that the disease free survival and the development of peritoneal carcinomatosis are reduced in patients treated with HIPEC [21]. One retrospective study has shown that peritoneal carcinomatosis is reduced while the overall survival is improved in T_4 gastric tumors treated with radical gastrectomy and HIPEC [22]. Another randomized trial with a small number of patients has confirmed that the incidence of peritoneal carcinomatosis is reduced and the overall survival is improved [38]. In our study recurrence has been recorded in 38.8% of the patients. Although no difference between the groups has been identified, a significant difference at the sites of recurrence has been identified. The loco-regional recurrence in the HIPEC and the CON group has been recorded in 25% and 71% of the patients respectively. It is likely that adjuvant chemotherapy has not affected the HIPEC group significantly because only 8 patients (6.6%) accepted to be treated by receiving systemic chemotherapy. In the CON group in which 33 patients (27.3%) have received systemic chemotherapy the rate of the loco-regional recurrences has been considerably high. It appears that the intraperitoneal chemotherapy may effectively reduce the rate of peritoneal carcinomatosis.

The type of operation (sub-total or total gastrectomy) has not had any effect on overall survival, morbidity, and the recurrence rate in our study even though the data from meta-analyses are conflicting [39, 40].

Perioperative chemotherapy is considered the standard treatment for resectable localized gastric cancer. The MAGIC trial and its modifications is a significant advancement in the treatment of resectable gastric cancer [41]. Adjuvant chemotherapy is recommended for patients undergoing primary surgery for stage II and III patients. Adjuvant chemoradiotherapy is not recommended

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for patients with R_0 resection and D_2 gastrectomy [42]. Neo-adjuvant chemotherapy followed by radical surgery has been shown to be associated with reduced recurrence in esophagogastric tumors but morbidity and perioperative mortality are not influenced [43]. The role of perioperative targeted therapy or as an adjuvant as well as the role of immunotherapy in resectable gastric cancer is unclear and under investigation [42].

In our study no patient received postoperative chemo-radiotherapy as adjuvant treatment. Neo-adjuvant chemotherapy has not been used because it has been widely implemented in clinical practice after 2015. Only 8 patients (6.6%) of the HIPEC group, and 33 (27.3%) of the CON group accepted to receive adjuvant chemotherapy. All the others denied treatment with systemic chemotherapy.

The study as every retrospective study includes biases. The number of the patients was small and the time of the study long. Excluding the surgical part of the treatment, the other parts had not been performed as scheduled. A small number of the included patients completed the adjuvant chemotherapy protocol. The two groups were not identical. As a consequence, definitive conclusions cannot be drawn, although all patients underwent surgery by the same surgical team.

Conclusions

HIPEC appears to be an effective and safe treatment as an adjuvant in gastric cancer despite the higher risk of complications. However, HIPEC is not a possible prognostic indicator of morbidity. HIPEC does not influence the in-hospital mortality but it appears to reduce the rate of loco-regional recurrences even though it has no effect on the development of distant metastases. Further prospective randomized studies are required to investigate the role of HIPEC in the treatment of locally advanced gastric cancer.

Author Contributions: A.A.T. was responsible for designing and supervising the study, collecting the data, and writing the manuscript. D.K. and A.K. contributed to the writing of the manuscript. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: This study was conducted in accordance with the Declaration of Helsinki. Ethical review and approval by Ethical Committee of the Hospital.
Informed Consent Statement: All patients were required to sign a consent form and were provided with complete information regarding their medical condition, including the proposed treatments, potential risks, and benefits.

Data Availability Statement: The datasets used and analyzed in the current study are available from the corresponding author upon reasonable request.

Conflicts of Interest: The authors declare no conflict of interest

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Legends

Figure 1: overall survival of patients with D_2 gastrectomy
Figure 2: overall 5- and 10-year survival for HIPEC (blue line) and CON group (green line)

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Table 1: clinical and pathologic characteristics of radical gastrectomy

Variable	HIPEC group	CON group	P value
Age	70.3+-8 (47-85)	68.4+-10.5 (35-89)	0.508
Age (<75/>75)	32/13	57/19	0.639
Gender (M/F)	33/12	46/30	0.153
Operation			0.335
SG	16	30	
TG	29	43	
TNM stage			0.86
II	7	19	
IIIA	10	28	
IIIB	18	19	
IV	10	10	
Lauren classification			0.352
Intestinal	27	39	
Diffuse	14	24	
Mixed	0	3	
Ming classification			0.007
Expanding	0	11	
Invasive	44	62	
Bormann's classification			0.035
Polypoid	0	3	
Fungative	13	7	
Ulcerated	27	51	
Infiltrative	4	9	
G (G1/G2/G3)	0/12/28	4/10/49	0.081
In-hospital mortality	0	2	0.273
ACT	8	33	0.004
Recurrence	16	30	0.668
Sites of recurrence			0.003
Distant	12 (75%)	9 (29%)	
Loco-regional	4 (25%)	22 (71%)	
Morbidity	19	18	0.032
T (T3/T4)	40/5	69/7	0.735
Anatomic location			0.858
Upper third	6	13	
Middle third	19	30	
Lower third	19	33	

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Tumor size <5cm >5cm	 17 23	 31 33	0.555
N (N0/N1/N2)	7/11/27	21/27/28	0.045
ASA (I/II)	27/17	50/26	0.626
Performance status 90-100% 70-80%	 38 7	 68 8	0.417

Explanations: SG=subtotal gastrectomy, T=total gastrectomy, G=degree of differentiation, ACT=adjuvant chemotherapy

Table 2: analysis of survival

	Univariate analysis	Multivariate analysis		
Variable	P value	HR	P value	95% CI
Gender	0.985			
TNM stage	0.001	5.719	0.017	1.098-2.561
Operation	0.323			
Lauren classification	0.025	8.062	0.005	1.327-4.09
Ming classification	0.055			
WHO classification	0.937			
Bormann's classification	0.002			
Degree of differentiation	0.014			
Adjuvant chemotherapy	0.17			
Age	0.508			
Morbidity	0.948			
Tumor depth	0.871			
Tumor anatomic location	0.853			
Tumor size	0.72			
Nodal involvement	0.002			
ASA class	0.006	12.279	<0.001	1.906-9.8
Performance status	0.088			

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Table 3: analysis of morbidity

	Univariate analysis	Multivariate analysis		
Variable	P value	HR	P value	95% CI
Gender	0.239			
TNM stage	0.626			
Operation	0.475			
Lauren classification	0.119			
Ming classification	0.432			
WHO classification	0.937			
Bormann's classification	0.009	6.025	0.014	0.215-0.842
Degree of differentiation	0.733			
Adjuvant chemotherapy	0.17			
HIPEC	0.032			
Age	0.29			
Tumor depth	0.659			
Tumor anatomic location	0.785			
Tumor size	0.467			
Nodal involvement	0.412			
ASA class	0.041			
Performance status	0.805			

Table 4: analysis of recurrence

	Univariate analysis	Multivariate analysis		
Variable	P value	HR	P value	95% CI
Gender	0.439			
TNM stage	0.006	8.215	0.004	0.295-0.795
Operation	0.605			
Lauren classification	0.019	8.495	0.004	0.106
Ming classification	0.249			
WHO classification	0.831			
Bormann's classification	0.095			
Degree of differentiation	0.003			
HIPEC	0.668			
ACT	0.576			
Age	0.081			
Morbidity	0.401			
Tumor depth	0.725			
Tumor anatomic location	0.989			

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Tumor size	0.206			
Nodal involvement	0.003			
ASA class	0.553			
Performance status	0.461			

Figure 1

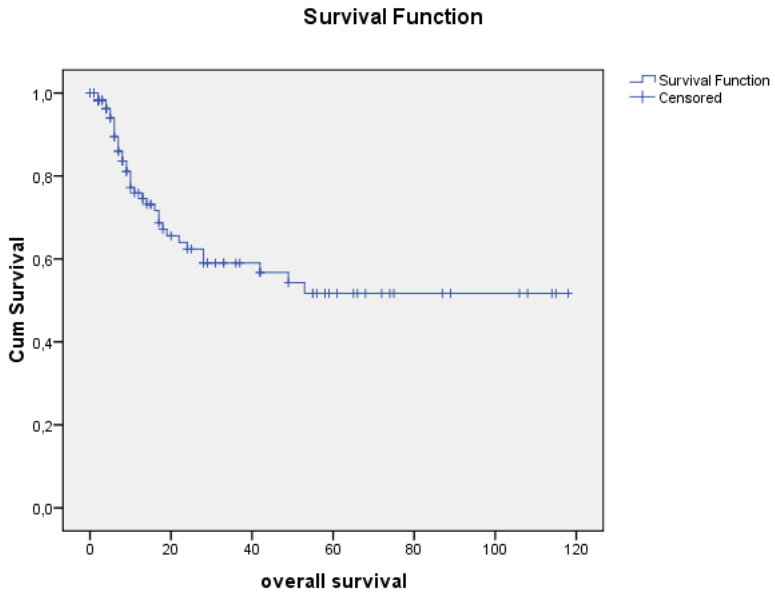

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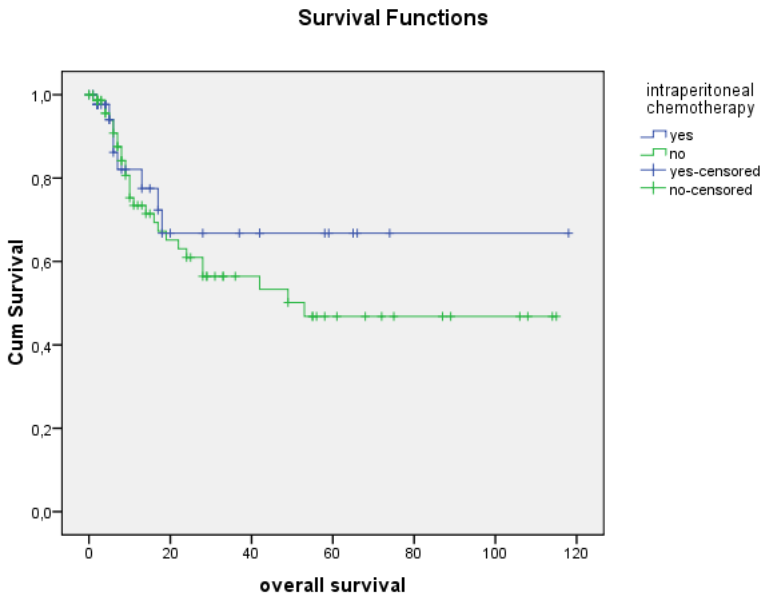
Figure 2



Cover Letter

The manuscript "OUTCOMES OF LOCALLY ADVANCED GASTRIC CANCER TREATED WITH D_2 GASTRECTOMY AND HIPEC" has not been published nor has it been for consideration in any other journal. If accepted it will not be published elsewhere in the same or similar form in English or in any other language without the written consent of the publisher. All authors agree with the results and have equally participated in the preparation of the manuscript. The research has received no external funding. The authors declare no conflicts of financial, professional, personal interest or relations with other people or organizations.