The effect of D3 dissection on postoperative morbidity and early mortality in gastric cancer patients who underwent curative total gastrectomy

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AIM: *The present study presents the factors associated with early complications and mortality in patients undergoing total gastrectomy.*
MATERIAL AND METHOD: *The study included patients who underwent curative total gastrectomy for gastric adenocarcinoma between January 2001 and December 2016 in the General Surgery Department of the Çukurova University Medical Faculty Hospital. The patients were divided into D1, D2, and D3 groups depending on the lymph node dissection width, and the demographic and clinical data and mortality were compared. In addition, mortality-associated factors were analyzed.*
RESULTS: *The study sample included 148 (62.7%) males and 88 (37.3%) females, with a mean age of 65.5±11.4 years. There were 87 patients in the D1 group, 117 in the D2 group, and 23 in the D3 group. As expected, the duration of the operation was longer in the D2 and D3 groups (179 vs. 224 vs. 252; p<0.001), and these groups had also higher numbers of lymph nodes dissected (8 vs. 20 vs. 32; p<0.001) and metastatic lymph nodes (2.6 vs. 7.5 vs. 9.2; p<0.001). The analysis of the operation type in terms of complications revealed a significant relationship only with stump blowout, which was significantly more common after D3 dissection than following D2 and D1 dissections (p:0.01). The male gender (87.5 vs 60.9 p:0.03) was more associated with mortality.*
CONCLUSION: *D1, D2 and D3 Lymph node dissection in gastric cancer surgery can be safely performed with low mortality and morbidity rates by surgeons with sufficient technical knowledge, and in centers with sufficient hospital volume.*

KEY WORDS: Complications, Gastric Cancer, Mortality, Lymph Node Dissection

Introduction

Gastric cancer has one of the highest mortality rates of all cancers worldwide. In recent years, the incidence of gastric cancer has declined, primarily in countries with a high level of development, although it still maintains an important place globally. Each year, 870,000 new cases of gastric cancer and 650,000 deaths are reported [1]. Furthermore, gastric cancer is globally the second most commonly occurring form of cancer in men after lung cancer, and the fourth most commonly occurring cancer in women after breast, cervical and colon cancers. Concerning cancer-related mortality, gastric cancer is the second most common cause of death among men after lung cancer and the third most common cause of death among women after breast and lung cancers [1,2]. The multidisciplinary approaches available for the treatment of the disease include surgery, chemotherapy and radiotherapy. Considering all treatment modalities, the most effective proven treatment for gastric cancer would

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appear to be the complete resection of the tumor and nearby lymph nodes [3,4]. Although D2 constitutes the level of lymph node dissection approved by most surgical societies in their treatment guidelines for gastric cancer, the broader D3 dissection is also performed at several centers in Europe and the Far East to improve oncologic outcome [3,5]. The increased risk of postoperative complications and mortality rates with D3 dissection prevent many surgeons from performing D3 dissection.
The most notable surgical complications in the postoperative period include bleeding, duodenal stump blowout and anastomotic leak, but due to advances in surgical techniques and effective postoperative care, the mortality rate of gastric surgeries is today very low, although an inexperienced surgical team and surgeries under emergency conditions, such as bleeding and perforation, are factors that increase the mortality rate [6].
The present study presents the factors associated with early complications and mortality in patients undergoing total gastrectomy.

Methods

The study was launched after receiving the approval of the local ethics committee of Çukurova University Medical Faculty Hospital (Date: 02.12.2016 and No: 59-3), and included patients over the age of 18 years who had undergone curative total gastrectomy for gastric adenocarcinoma in the General Surgery Department of the Çukurova University Medical Faculty Hospital between January 2001 and December 2016.
The patients were divided into D1, D2 and D3 groups based on the width of the lymph node dissection, and their demographic and clinical data, perioperative blood transfusion, details of the operation, postoperative complications (development of pancreatic fistula, duodenal stump blowout, need for splenectomy due to splenic injury), length of postoperative hospital stay and mortality were compared. Mortality-associated factors were also compared.
The degree of differentiation and type of tumor were analyzed with a histopathological assessment, following the WHO classification, and all patients underwent preoperative endoscopy and abdominal tomography. In the present study, interventions that left no macroscopic tumor behind were considered curative resections. Total gastrectomy and mostly Roux-en-Y esophagojejunostomy anastomosis were performed for proximal tumors, in which the anastomoses were made using circular staplers and polyglactin support sutures.

Statistical Analysis

The statistical analysis was performed using IBM SPSS Statistics (Version 20.0. Armonk, NY: IBM Corp). Between-group qualitative data were compared with a Chi-square test and data were presented as numbers and percentages. The normality of the variables was tested using visual (histogram and probability graphics) and analytic methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). An Independent t-test was used for paired groups with parametric conditions, and a One-Way ANOVA was used for the comparison of three or more groups. Data were presented as arithmetic mean±standard deviation. For statistical significance, the type-1 error level was considered 0.05.

Results

This retrospective study examined the operations performed on 236 patients with gastric cancer in the general surgery department. There were 87 patients in the D1, 117 in the D2 and 23 in the D3 groups. The D1 group comprised older patients (69 vs. 63 vs. 59; $p<0.001$). The male gender was dominant in the D2 and D3 groups ($p<0.001$). Tumor marker levels were similar. The tumor was most often located in the corpus in all groups, with a similar distribution in all groups ($p<0.017$). The comorbidity rates of the patients were also similar in the groups ($p<0.21$). The results are presented in Table I.
The rate of perioperative blood transfusion was similar (p: 0.44). The duration of operation was longer in the D2 and D3 groups, as was expected (179 vs. 224 vs. 252; $p<0.001$), and the D2 and D3 groups also had higher numbers of lymph nodes dissected (8 vs. 20 vs. 32; $p<0.001$) and metastatic lymph nodes (2.6 vs. 7.5 vs. 9.2; $p<0.001$). The length of hospital stay also varied between the groups. The results are presented in (Table II).
An analysis of the types of operation in terms of complications revealed a significant relationship only with stump blowout, which was significantly more common after D3 dissection than D2 and D1 dissections (p: 0.01). Since splenectomy is routinely performed in D3 dissection, D1 and D2 were compared for splenic injury, but no significant difference was identified (p: 0.43). The results are presented in (Table III).
The male gender (87.5 vs 60.9 p:0.03) was associated more with mortality, while age (p: 0.683), tumor localization (p: 0.078) and lymph node dissection width (p: 0.1) were not associated with mortality. The results are presented in (Table IV).

Discussion

Extended lymph node dissection and radical surgery methods, which are well accepted in Far Eastern countries, have attracted the attention of Western researchers, and the first prospective randomized controlled study

Table I - *Demographic and clinical characteristics of the lymph node dissection groups.*

		Type of Operation			
		D1 (n, %)	**D2 (n, %)**	**D3 (n, %)**	**P**
Age, mean+SD (min-max)		69.56+8.47 (29-75)	63.73+6.51 (46-69)	59.28+9.27 (47-66)	0.001 D1>D2 D1>D3
Gender	Male	39 (44.8)	87 (74.49)	22 (68.8)	0.001
	Female	48 (55.2)	30 (25.6)	10 (31.3)	
CEA	High	8 (9.2)	9 (7.7)	4 (12.5)	0.69
	Normal	79 (90.8)	108 (92.3)	28 (87.5)	
Tumor Localization	Cardia	21 (24.1)	24 (20.5)	9 (28.1)	0.017
	Corpus	32 (39.1)	47 (40.2)	13 (50.0)	
	Antrum - Pylorus	31 (35.6)	40 (34.2)	4 (3.1)	
	Linitis plastica	3 (1.1)	5 (4.3)	6 (18.8)	
Comorbidities	Yes	13 (14.9)	14 (12)	6 (18.8)	0.21
	No	74 (85.1)	103 (88)	17 (53.1)	

Table II - *Operative and postoperative characteristics of the lymph node dissection groups.*

		Type of Operation			
		D1 (n, %)	**D2 (n, %)**	**D3 (n, %)**	**P**
Perioperative blood transfusion	Yes	13 (14.9)	15 (12.8)	7 (21.9)	0.44
	No	74 (85.1)	102 (87.2)	25 (78.1)	
Duration of operation (min)		179.71+12.6 (160-200)	224.06+16.58 (190-245)	252.03+25.8 (210-290)	0.001 D2>D1 D3>D1 D3>D2
Total number of lymph nodes (n)		8.02+2.93 (3-14)	20.25+2.06 (16-24)	32.28+2.76 (26-36)	0.001 D2>D1 D3>D1 D3>D2
Number of metastatic lymph nodes (n)		2.64+2.05 (0-8)	7.59+2.27 (2-12)	9.28+1.80 (5-11)	0.001 D2>D1 D3>D1 D3>D2
Length of hospital stay (days)		9.15+ 2.82 (6-16)	8.99+2.52 (6-17)	10.69+2.32 (7-17)	0.005 D3>D1 D3>D2

examining the outcomes of these methods was conducted in the United Kingdom. The study of Cuschieri et al., including 400 cases, made a comparison of D1 and D2 dissections, and it was demonstrated that D2 dissections did not provide any survival benefit, but led rather to increased mortality and morbidity [7]. Considering and fulfilling the limitations of this study, a similar study was conducted in the Netherlands by surgeons who were informed about the surgical technique through videos and libraries before the study, and with the participation of Mitsumura Sasako, an experienced Japanese surgeon, involving a more carefully selected patient sample. This study by Bonenkamp et al. with 711 cases reported no survival advantage of D2 over D1 dissection, and reported high rates of mortality and morbidity [8,9].

Siewert et al.'s study of 1,654 cases, on the other hand, showed a 20% survival benefit of D2 dissection, especially in stage II cases, and reported that extended lymph node dissection by experienced surgeons in high-volume

Table III - *Postoperative complications in the lymph node dissection groups.*

		Type of Operation			
		D1 (n, %)	D2 (n, %)	D3 (n, %)	P
Splenic injury	Yes	6 (6.9)	10 (8.5)	-	0.43
	No	81 (93.1)	107 (91.5)	-	
Anastomotic leak	Yes	5 (5.7)	8 (6.8)	3 (9.4)	0.78
	No	82 (94.3)	109 (93.2)	29 (90.6)	
Surgical site infection	Yes	4 (4.6)	7 (6)	5 (15.6)	0.09
	No	83 (95.4)	110 (94)	27 (84.4)	
Pancreatic fistula	Yes	8 (9.2)	12 (10.3)	6 (18.8)	0.31
	No	79 (90.8)	105 (89.7)	26 (81.3)	
Stump blowout	Yes	7 (8)	8 (6.8)	9 (28.1)	0.01
	No	80 (92)	109 (3.2)	23 (71.9)	

Table IV - *Mortality-associated factors.*

		Mortality (n, %)	No Mortality (n, %)	p
Age (mean ± SD)		64.44 + 11.64	65.65+ 11.49	0.683
Gender	Male	14 (87.5)	134 (60.9)	0.03
	Female	2 (12.5)	86 (39.1)	
Tumor localization	Proximal	6 (42.9)	141 (67.8)	0.078
	Distal	8 (57.1)	67 (32.2)	
Type of lymph node dissection	D1	5 (5.7)	82 (94.3)	0.1
	D2	6 (5.1)	111 (94.9)	
	D3	5 (15.6)	27 (84.4)	

centers could reduce mortality and morbidity, leading to the continuation of the debates on extended lymph node dissection [10].

To bring an end to these discussions, Degiuli from Italy conducted a prospective multicenter study of 118 cases with the participation again with experienced Japanese surgeon Mitsumura Sasako, in which Degiuli et al. performed pancreas-preserving extended lymphadenectomies, and reported a mortality rate of 2.5% and a morbidity rate of 20% [11]. The long-term results of this study showed an overall survival rate of 55%, indicating that operative mortality decreased in parallel with the learning curve [12]. According to the report of a Japanese series, D2 and D3 dissections have better outcomes than D1 dissections in cases where curative surgery can be performed [13,14].

In contrast to Western studies, a study in Turkey reported no significant difference in hospital mortality between D2 and D1 dissections [15]. Furthermore, no significant difference in mortality was identified between D1, D2 and D3 dissections in the present study. A similar situation was observed between the type of operation and the time to mortality.

Gretschel et al. of the University of Berlin divided the patients in their series into "Group 1:75 years old", "Group 2: 60-75 years old", and "Group 3: >75 years old" and found that postoperative 30-day mortality increased significantly with age (0%, 1% and 8%, respectively), while morbidity did not show a significant difference, despite the increasing age (37%, 45% and 48%, respectively). The same study further reported comorbidities to be effective in mortality in the over 75 years of age patient group [16]. Our study revealed no significant relationship between age and mortality.

Saidi and Piso found chronological age alone to be ineffective in the choice of resection for the patient, while biological age and comorbidities were effective [17]. Matsushita et al reported that curative resections contributed to 3-year survival, even in patients over 80 years of age [18]. Our study sample comprised 148 (62.7%) males and 88 (37.3%) females, with a mean age of 65.5±11.4 years. The mean age of the patients was low-

er in the D1 group than in the D2 and D3 dissection groups, and the difference was statistically significant.
The ASCOT trial and the study by Gil-Renda et al. reported gender to adversely affect postoperative morbidity [19,20], and Park et al also reported and increase in operative morbidity in the male gender, along with age and the width of resection [21]. The present study, similar to literature, found mortality to be significantly higher in men.
During the pathological assessment of the material in gastric cancer staging, the localization and number of the lymph node stations and the number of metastatic lymph nodes detected are very important. The studies by Noguchi et al. and Maruyama et al. report that the number of metastatic lymph nodes that can be detected increases as the lymph node dissection width increases. Today, the best-known parameter for the assessment of the radicality of surgery is the number of lymph nodes removed [22,23]. Similar to literature, the present study identified a significantly increased number of LNs and metastatic LNs in the D1 than in the D3 patients.
A retrospective study of 866 patients examined 158 proximal and 708 distal tumors, and found significantly poorer survival in patients with proximal tumors than in those with distal tumors [24]. Other studies have reported no effect of tumor localization on patient survival [23, 25]. In the present study, the tumor was located most often in the corpus and antrum in the D1 and D2 dissection groups, while linitis plastica was observed macroscopically in the D3 dissection group. There was, however, no association between tumor localization and survival, consistent with literature.
The metastatic lymph node detected depending on localization in gastric cancer is absent in the splenic hilar station in proximal T1 and T2 tumors, while the rate rises to 17% in T3 tumors. If spleen-preserving hilar dissection is not possible in a tumor that has grown through the serosa, a splenectomy can be performed, although this should be avoided in early-stage tumors if a hilar dissection is also possible, as the risk of mortality and morbidity associated with splenectomy will be eliminated. In line with these findings, the width of the surgical intervention can be determined by adding the information obtained through a careful preoperative assessment of the patients to the intraoperative findings [23,26].
Deniz İK et al reported that seven patients who underwent a D1 dissection and 13 patients who underwent a D2 dissection were also subjected to organ resection due to invasion, although the difference was statistically insignificant [14]. Similarly, D1 and D2 were compared for splenic injury in the present study, since splenectomy was routinely performed in D3 dissections, although no significant difference was identified. In a study by İbrahim Deniz et al, 10 (17.8%) patients who underwent a D2 dissection, and 14 (24.6%) patients who underwent a D1 dissection required a perioperative blood transfusion, with no statistically significant difference identified between the two groups [14]. In a study in Turkey, postoperative anastomosis or stump blowout occurred in six (10.9%) patients undergoing D2 Dissection, and postoperative fistula or stump blowout in five (8.8%) patients undergoing D1 Dissection [15].
In the present study, when the types of operation were compared for complications, only stump blowout was found to be significantly more common in the D3 dissection group than in the D2 and D1 dissection groups, while there was no significant difference in anastomotic leak, surgical site infection and pancreatic fistula rates. A study comparing the postoperative length of hospital stay reported no difference between two patient groups, with patients who underwent D1 dissection being discharged on an average after 9.2 days, and those who underwent D2 dissection on average after 9.3 days [15]. In the present study, the hospital stay was significantly longer in the patients undergoing D3 dissection than in those who underwent D1 and D2 dissections.
There are many studies from different centers in the literature to evaluate the results in patients who underwent D2 or D3 lymphadenectomy for gastric cancer. Bostancı EB et al. conducted a prospective observational study who underwent gastrectomy with curative intent, lymphadenectomy that was more extensive than D2 did not provide a survival benefit compared to D2 dissection [27]. Although the Japan Clinical Oncology Group (JCOG) 9501 trial did not find that prophylactic D3 lymphadenectomy led to any survival advantage over D2 lymphadenectomy, it did find that the prognosis of subserosal and N0 gastric cancer patients improved [28].
D3 dissection is indisputably a more technically demanding and complicated procedure compared to D1 or D2 as it requires dissection around large vessels located in deep retroperitoneal space. The more extended the dissection the more severe surgical injury and stress. Widespread use of modern hemostatic devices decreased operating time, surgical mortality, and procedural related morbidity 29 Available data suggest that D3 can be performed as safe as D2 procedures in the environment of high volume specialized centers by adequately trained surgeons even in western hemisphere *3*0 Our center is one of the centers in Europe where D3 dissection is performed safely.
We did not analyze long-term oncologic outcomes, as the patient population of our study included the preneoadjuvant treatment period. Further trials should be initiated to test whether a broader lymphadenectomy can be synergistically combined with adjuvant/neoadjuvant therapies to mutually enhance their therapeutic potential and thereby prolong survival.

Conclusion

These findings suggest that extended lymph node dissection can be performed with low mortality and morbidi-

ty rates by surgeons with sufficient technical and anatomical knowledge of gastric cancer surgery in high - volume centers, using pancreas - and spleen-preserving dissection techniques, and under postoperative care conditions.

Riassunto

Questo studio presenta i fattori associati alle complicanze precoci e alla mortalità nei pazienti sottoposti a gastrectomia totale, e si riferisce ai pazienti sottoposti a gastrectomia totale curativa per adenocarcinoma gastrico tra gennaio 2001 e dicembre 2016 presso il Dipartimento di Chirurgia Generale dell'Ospedale della Facoltà di Medicina dell'Università di Çukurova. I pazienti sono stati divisi in gruppi D1, D2 e ™D3 a seconda dell'ampiezza della dissezione linfonodale e sono stati confrontati i dati demografici e clinici e la mortalità. Inoltre, sono stati analizzati i fattori associati alla mortalità.
RISULTATI: Il campione di studio comprendeva 148 (62,7%) maschi e 88 (37,3%) femmine, con un'età media di 65,5±11,4 anni. C'erano 87 pazienti nel gruppo D1, 117 nel gruppo D2 e ™ 23 nel gruppo D3. Come previsto, la durata dell'operazione è stata più lunga nei gruppi D2 e ™D3 (179 vs. 224 vs. 252; p<0,001), e questi gruppi avevano anche un numero maggiore di linfonodi sezionati (8 vs. 20 vs. 32; p<0,001) e linfonodi metastatici (2,6 vs 7,5 vs 9,2; p<0,001).
L'analisi del tipo di intervento in termini di complicanze ha rivelato una relazione significativa solo con la deiscenza del moncone, che è risultata significativamente più comune dopo la dissezione D3 rispetto alle dissezioni D2 e ™D1 (p:0,01).
Il genere maschile (87,5 vs 60,9 p:0,03) è risultato essere maggiormente associato alla mortalità.
In conclusione la dissezione dei linfonodi D1, D2 e D3 nella chirurgia del cancro gastrico può essere eseguita in sicurezza con bassi tassi di mortalità e morbilità da chirurghi con sufficienti conoscenze tecniche e in centri con volume ospedaliero sufficiente.

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