



# Early and late outcomes of patients who underwent en-bloc multiorgan resection in locally advanced gastric cancer and factors affecting the results

Lokal ileri mide kanserlerinde en-blok multiorgan rezeksiyonu yapılan hastaların erken ve geç dönem sonuçları ve bu sonuçlara etki eden faktörler

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**Background and Aims:** The aim of this study is to examine the early and late results of patients with adjacent organ invasion (cT4b) who were operated for locally advanced gastric cancer in a high-volume center and to investigate the factors affecting survival. **Material and Methods:** Patients who underwent gastrectomy and en-bloc adjacent organ resection due to locally advanced gastric cancer between 2015 and 2019 were included in the study. **Results:** Radical gastrectomy and en-bloc additional organ resection were performed in 54 patients out of 435 patients who were operated for gastric cancer due to clinical T4b tumors. The mean age of all patients was 61.87 ± 12.67 years. The median survival was found to be 16.5 (1 - 72) months. First-year survival was achieved in 37 (68.5%) patients, three-year survival in 11 (20.3%) and five-year survival in only 4 (7.4%) patients. Considering the factors affecting long-term survival, it was seen that postoperative complications affected survival significantly (p = 0.04). We found that performing R1 resection (p = 0.001), large tumor diameter (p = 0.02), presence of lymphovascular invasion (p = 0.024) and presence of perineural invasion (p = 0.024) adversely affected long-term survival. **Conclusion:** Adequate lymph node dissection and en bloc R0 resection with adjacent organ are important for long-term survival in patients with clinical T4b gastric cancer. Surgery should be performed regardless of the T-stage of the tumor. In this respect, surgery performed with adequate R0 resection can be considered as an independent prognostic factor affecting survival. Other factors affecting long-term survival are lymph node metastasis, tumor size, post-operative complications, and vascular and perineural invasion.

**Key words:** Locally advanced gastric cancer, en-bloc multiorgan resection, results

**Giriş ve Amaç:** Bu çalışmanın amacı, yüksek volümlü bir merkezde lokal ileri mide kanseri nedeniyle opere edilen komşu organ invazyonu (cT4b) olan hastaların erken ve geç sonuçlarını incelemek ve sağkalımı etkileyen faktörleri araştırmaktır. **Gereç ve Yöntem:** 2015-2019 yılları arasında lokal ileri mide kanseri nedeniyle gastrektomi ve en-blok komşu organ rezeksiyonu yapılan hastalar çalışmaya dahil edildi. **Bulgular:** Klinik T4b tümörü nedeniyle mide kanseri nedeniyle ameliyat edilen 435 hastanın 54'üne radikal gastrektomi ve en-blok ek organ rezeksiyonu uygulandı. Tüm hastaların yaş ortalaması 61.87 ± 12.67 idi. Ortanca sağkalım 16.5 (1 - 72) ay olarak bulundu. 37 (%68.5) hastada birinci yıl sağkalım, 11 (%20.3) hastada üç yıllık sağkalım ve sadece 4 (%7.4) hastada beş yıllık sağkalım sağlandı. Uzun dönem sağkalımı etkileyen faktörlere bakıldığında postoperatif komplikasyonların sağkalımı anlamlı olarak etkilediği görüldü (p = 0.04). R1 rezeksiyon (p = 0.001), büyük tümör çapı (p = 0.02), lenfovasküler invazyon (p = 0.024) ve perinöral invazyon (p = 0.024) varlığının uzun dönem sağkalımı olumsuz etkilediğini bulduk. **Sonuç:** Klinik T4b mide kanserli hastalarda yeterli lenf nodu diseksiyonu ve komşu organla en-blok R0 rezeksiyonu uzun dönem sağkalım için önemlidir. Tümörün T-evresi ne olursa olsun cerrahi yapılmalıdır. Bu açıdan yeterli R0 rezeksiyon ile yapılan cerrahi, sağkalımı etkileyen bağımsız bir prognostik faktör olarak değerlendirilebilir. Uzun süreli sağkalımı etkileyen diğer faktörler, lenf nodu metastazı, tümör boyutu, ameliyat sonrası komplikasyonlar ve vasküler ve perinöral invazyondur.

**Anahtar kelimeler:** Lokal ileri mide kanseri, en-blok multiorgan rezeksiyonu, sonuçlar

## INTRODUCTION

According to the 8th edition of the American Joint Committee on Cancer (AJCC), tumors that invade the subserosa but do not reach the visceral peritoneum are defined as T3 and tumors that invade the visceral peritoneum (T4a) or adjacent organs (T4b) are defined as T4 tumors (1). The definition of locally advanced gastric tumors is used for tumors that adhere to or infiltrate adjacent organs (2). Preoperative staging and neoadjuvant treatment in advanced gastric cancer require multidisciplinary management. Today, in addition to imaging methods such as endoscopy, computed tomography (CT), and positron emission tomography (PET), laparoscopy also plays an important role in the evaluation of occult metastases (3). Longer survival is achieved with the addition of neoadjuvant therapy, understanding the importance of the number of lymph nodes removed, and developing immunotherapies (4). Currently, the accepted curative treatment option for locally advanced gastric cancers with adjacent organ invasion is D2 lymph node dissection and radical gastrectomy with adjacent organ resection, which is performed to provide R0 resection margin (5,6). There are few comparative studies and cases in the literature on advanced gastric tumors undergoing multiorgan resection. Studies are generally retrospective and include a small number of patients. Considering these studies, presence of lymph node metastasis, R1 resection, advanced age, and the number of organs included in en-bloc resection seem to decrease survival and increase post-operative complications (7,8).

The aim of this study is to examine the early and late results of patients with adjacent organ invasion (cT4b) who were operated for locally advanced gastric cancer in a high-volume center and to investigate the factors affecting survival.

## MATERIALS and METHODS

Ethics committee approval dated 26/05/2021 and numbered E1-21-1818 was obtained from the Ethics Committee of our hospital for this study. Patients who underwent gastrectomy and en-bloc adjacent organ resection due to locally advanced gastric cancer between 2015 and 2019 were included in the study. The data of prospectively enrolled gastric cancer patients were evaluated retrospectively. Patients with distant organ metastases, positive peritoneal implants or cytology and patients who underwent palliative procedures were excluded from the study. Regardless of lymph node metastasis, gastric tumors invading clinically adjacent organ or multiple organs were considered clinical T4b. Radical total or radical subtotal gastrectomy and en-bloc resection of the adjacent organs were performed in all patients with clinical T4b in order to provide a clear surgical margin according to the localization of the gastric tumor. D2 lymph node dissection was performed in all patients in accordance with the recommendations of the IV. Japanese Gastric Cancer guideline, 2014 (9). Adjacent organ resection was performed en-bloc with the stomach and providing clear macroscopic margins away from the tumoral mass. All patients who underwent colon resection underwent anastomosis, and none required a colostomy. The remnant pancreatic stump of all patients who underwent distal pancreatectomy was closed with single or continuous non-absorbable sutures. Patients who could not undergo curative resection were excluded from the study. Patients who did not have metastases but were treated with prophylactic intraperitoneal chemotherapy were also excluded from the study. All patients were operated by the same clinicians and preoperative, perioperative and postoperative data of the patients were recorded prospectively. Demographic data of patients, neoadjuvant treatments, surgery notes, pathology reports, pre- and post-treatment radiological imaging reports, re-

currence information, follow-up notes and survival information were examined.

Patients with pathology other than adenocarcinoma were excluded from the study. Patients with an The Eastern Cooperative Oncology Group (ECOG) performance score above 3 were not included in the study (10). Post-operative complications were evaluated using complication grading performed according to the National Cancer Institute Common Terminology Criteria for Adverse Events scoring version (NCICTCAE) 3.0 ([http://ctep.cancer.gov/protocoldevelopment/electronic\\_applications/docs/ctcaev3.pdf](http://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcaev3.pdf)) (11). The pathological examination was re-evaluated according to the 8th edition of AJCC (1).

### Statistical Analysis

The Statistical Package for Social Sciences version 16 software (SPSS Inc.; Chicago, IL, USA) was used in this analyses. The variables were expressed as mean  $\pm$  standard deviation, and they were compared with the Student-t test. The categorical variables were expressed in frequencies and percentages, and were compared with Fisher test or chi-square test. A P value less than 0.05 was accepted as statistically significant.

### RESULTS

Radical gastrectomy and en-bloc additional organ resection were performed in 54 patients out of 435 patients who were operated for gastric cancer due to clinical T4b tumors. Thirty eight (70.4%) of the patients included in the study were male and 16 (29.6%) were female, and the mean age of all patients was  $61.87 \pm 12.67$  years. The number of patients who were operated after receiving neoadjuvant treatment was 37 (68.5%), while the number of patients operated without neoadjuvant treatment was 17 (31.5%). Considering the pre-operative ECOG scores of the patients, 4 (7.4%)

patients were ECOG -0, 18 (33.3%) patients were ECOG -1, 24 (44.4 %) patients were ECOG -2 and 8 (14.8%) patients were ECOG -3. When we look at the additional organ resections performed, 20 (37%) patients had distal pancreatectomy + splenectomy, 14 (25.9%) patients had colon, 9 (16.7%) patients had only splenectomy, 5 (9.3%) patients had segmental or wedge liver resection, 5 (9.3%) patients had distal pancreatectomy + splenectomy + transverse colon resection and 1 (1.9%) patient had distal pancreatectomy + splenectomy + segmental liver resection. Radical total gastrectomy was performed in 42 (77.8%) patients and radical distal gastrectomy was performed in 12 (22.2%) patients. Considering the number of organs resected en bloc with gastrectomy; One organ resection was performed in 28 (51.8%) patients, two organ resections were performed in 20 (37.1%) patients and three organ resections were performed in 6 (11.1%) patients.

**Table 1** Postoperative complications in all patients

Postoperative Complications	Total (54 Patients)
<b>Minor (grade 0, 1, 2)</b>	46 (85.18%)
<b>Major (grade 3, 4, 5)</b>	8 (14.81%)
<b>Wound infection</b>	7 (12.95%)
<b>GIS complications</b>	
Anastomotic leak	4 (7.4%)
Ileus	1 (1.85%)
Intraabdominal collection, abscess	3 (5.5%)
Chylous fistula	1 (1.85%)
Pancreatic fistula	6 (11.1%)
Grade A	5 (9.25%)
Grade B	1 (1.85%)
Reoperation	1 (1.85%)
<b>Pulmonary complications</b>	
Atelectasis	1 (1.85%)
Pneumonia	2 (3.7%)
Pleural effusion	2 (3.7%)
<b>Cardiac complications</b>	2 (3.7%)
<b>Nephrotoxicity and acute renal failure</b>	1 (1.85%)
<b>Early mortality</b>	2 (3.7%)

The median length of stay of the patients was 13.5 (6-56) days. When evaluated in terms of post-operative complications, no complications were observed in 27 (50%) patients, while 9 (16.7%) patients were grade 1, 10 (18.5%) patients grade 2, 4 (7.4%) patients grade 3, 2 (3.7%) patients had grade 4 complications and 2 (3.7%) patients died after sepsis due to anastomotic leakage in the early postoperative period (grade 5). Complications according to their frequency are shown in Table 1.

Considering the pathological examination; R0 resection was performed in 49 (90.7%) patients and

R1 resection was performed in 5 (9.3%) patients. The median value of macroscopic tumor size was 6 (2 - 14) cm. The median value of total removed lymph nodes was 24 (5 - 88) and the median value of positive lymph nodes was 5 (0 - 78). When evaluated according to their differentiation, 23 (42.6%) patients had poor, 16 (29.6%) moderate, 8 (14.8%) good differentiation and 7 (13%) patients had signet ring cell pathology. When we look at the depths of invasion, 22 (40.7 %) patients had T4b tumor with single organ invasion, 5 (9.3%) T4b with two-organ invasion, 13 (24.1%) T4a tumors and 14 (25.9%) T3

**Table 2** Clinicopathological characteristics of the patients operated for T4b gastric cancer.

Variables (n, %)	Number of Patients	Variables (n, %)	Number of Patients
Age (Mean ± SD)	61.87 ± 12.67	Age (Mean ± SD)	61.87 ± 12.67
Gender		Resection	
Male (n, %)	38 (70.4%)	R0 (n, %)	49 (90.7%)
Female (n, %)	16 (29.6%)	R1 (n, %)	5 (9.3%)
Neoadjuvant treatment		Differentiation	
Yes (n, %)	37 (68.5%)	Mild - Moderate (n, %)	24 (44.4%)
No (n, %)	17 (31.5%)	Undifferentiated - signet cell (n, %)	30 (55.6%)
ECOG		Diameter	
0 (n, %)	4 (7.4%)	≤ 6 cm (n, %)	29 (53.7%)
1 (n, %)	18 (33.3%)	> 6 cm (n, %)	25 (46.3%)
2 (n, %)	24 (44.4%)	pT stage	
3 (n, %)	8 (14.8%)	T3 (n, %)	14 (25.9%)
Gastrectomy		T4a (n, %)	13 (24.1%)
Total	42 (77.8%)	T4b single organ invaded (n, %)	22 (40.7%)
Subtotal	12 (22.2%)	T4b double organ invaded (n, %)	5 (9.3%)
Number of organs resected		Lymphovascular invasion (LVI)	
1 (n, %)	29 (53.7%)	LVI - (n, %)	6 (11.1%)
2 (n, %)	19 (35.2%)	LVI + (n, %)	48 (88.8%)
3 (n, %)	6 (11.2%)	Perineural invasion (PNI)	
Postoperative complication grade		PNI- (n, %)	6 (11.1%)
0 (n, %)	27 (50%)	PNI+ (n, %)	48 (88.8%)
1 (n, %)	9 (16.7%)	N Stage	
2 (n, %)	10 (18.5%)	0 (n, %)	8 (14.8%)
3 (n, %)	4 (7.4%)	1 (n, %)	11 (20.4%)
4 (n, %)	2 (3.7%)	2 (n, %)	13 (24.1%)
5 (n, %)	2 (3.7%)	3a (n, %)	7 (13%)
		3b (n, %)	15 (27.8%)

tumors. In this study in which all patients were operated with clinical T4b tumors, the number of patients with pathological T4b was only 27 (50%).

Considering the survival analysis of the patients, the median survival was found to be 16.5 (1 - 72) months. First-year survival was achieved in 37 (68.5%) patients, three-year survival in 11 (20.3%) and five-year survival in only 4 (7.4%) patients. Considering the factors affecting long-term survival, it was seen that postoperative complications affected survival significantly ( $p = 0.04$ ). We found that performing R1 resection ( $p = 0.001$ ), large tumor diameter ( $p = 0.02$ ), presence of lymphovascular invasion ( $p = 0.024$ ) and presence of perineural invasion ( $p = 0.024$ ) adversely affected long-term survival. The factors affecting the survival are as given in Table 2.

## DISCUSSION

Even today, the only curative treatment modality in locally advanced gastric cancer is surgery. The surgery to be performed should be R0 and with appropriate lymph node dissection. In our study, we examined the results of curative resection in patients who were operated for clinical T4b gastric cancer. We found that R1 resection, large tumor size, development of early postoperative complications, and perineural and lymphovascular invasion are poor prognostic factors for long-term survival.

In locally advanced gastric cancers with adjacent organ invasion, the preferred treatment modality is radical lymph node dissection along with en-bloc resections with the adjacent organs providing clean surgical margins away from the tumor (5,12). In 28-80% of adhesions, adjacent organ invasion (pT4b) is found in the pathological evaluation, while a desmoplastic reaction is found in the rest (12,13). Clinical and pathological correlations occur only in 35% of patients (14). For this reason, the orientation of the pathological specimen and

correct examination has importance (14). In our study, we found that patients with clinically T4b had a 50% rate of malignant adhesion by pathological evaluation. We found that 25% of the patients were T3. In studies with T4b colorectal tumors, it was emphasized that en-bloc resection should be performed regardless of whether the adjacent organ adhesions are desmoid reaction or malignant invasion (15). It has been shown that attempting to separate the adhesion increases the risk of tumor dispersal into the peritoneum and increasing local recurrence, and reduces the 5-year survival from 53% to 21% (16). Although there is no similar study in the literature for T4b gastric tumors, the authors recommended en bloc resection without adhesiolysis (17,18). We performed en-bloc resection and D2 LND with clean surgical margins in all patients, regardless of whether the adhesion was malignant or benign. When we evaluated the pathology results, we found that patients with T4b in terms of survival were not different from patients with T4a and T3 tumors. Consistent with the literature, we can say that T stage does not affect survival in R0 resections (19,20). Today, prophylactic hyperthermic intraperitoneal chemotherapy (HIPEC) treatment has come to the agenda due to the potential of tumor cells to spread peritoneally and increase recurrence in patients with invasion depth of T3 and above (21). In our study, the group that underwent prophylactic HIPEC was not included in the study because it may affect the results. When we look at the additional organ resections performed, distal pancreatectomy + splenectomy (37%) was the most common, followed by transverse colon (16.7%) resection, and liver wedge and splenectomy were performed in 5 patients each. Consistent with the literature, the most common additional organ resections are distal pancreas and colon (2,7). Complications are accordingly seen as pancreatic fistula, anastomotic leakage and intra-abdominal abscess and wound infection (22).



In this study, the most common postoperative complication was pancreatic fistula, which was seen in 6 (11.1%) patients. The majority of patients who developed pancreatic fistulas were grade-A fistulas that did not require intervention. Performing en-bloc distal pancreatectomy with gastrectomy increases post-operative complications in patients, but does not change mortality rates (23,24). In the literature, mortality ranges from 1 to 7.3 in series with multiorgan resection (19,23,25). In our study, early mortality was observed in 2 (3.7%) patients, which is consistent with the literature.

The 1, 3, and 5-year survivals of the patients were found to be 37 (68.5%), 11 (20.3%) and 4 (7.4%), respectively, in accordance with the literature (26,27). Although chemotherapy regimens vary, there are studies showing that neoadjuvant therapy reduces local recurrence in locally advanced gastric tumors, increases R0 resection rates, and increases 5-year overall and disease-free survival rates (28-30). In our study, 37 (68.5%) patients received neoadjuvant therapy while 17 (31.5%) did not. We received neoadjuvant treatment as a general approach to patients with T3 and above and lymph node positive tumors, but there is a group of patients who can not receive neoadjuvant treatment because of low toleration and who have acute bleeding or obstructive tumors. There was no difference in survival between the two groups (p: 0.96). This may be due to the fact that the group is heterogeneous and few in number. Adequate number of lymph nodes should be removed for accurate staging and long survival (31). Presence of lymph node metastasis also shortens life expectancy and is considered an indication for neoadjuvant therapy. In the literature, if the number of dissected lymph nodes is over 16, survival increases (32). We

found the median value of the total lymph nodes removed as 24 in the patients included in the study. Lymph node positivity is an independent poor prognostic factor for survival, and 5-year survival is 11% in lymph node positive patients, while it increases to 35-80% if lymph node is negative (20,27). According to our results, survival decreases as the stage of lymph node metastasis increases (p: 0.022). In addition, the presence of lymphovascular and perineural invasion was found to be a poor prognostic factor in our study in accordance with the literature (26). Studies have shown that tumor size greater than 7 - 10 cm is a poor prognostic factor (33,34). Tumor size was found to be another poor prognostic factor in our study. Survival decreases with increasing tumor size.

In conclusion, adequate lymph node dissection and en-bloc R0 resection with adjacent organ are important for long-term survival in patients with clinical T4b gastric cancer. Surgery should be performed regardless of the T-stage of the tumor. In this respect, surgery performed with adequate R0 resection can be considered as an independent prognostic factor affecting survival. Other factors affecting long-term survival are lymph node metastasis, tumor size, post-operative complications, and vascular and perineural invasion.

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**Conflict of Interest:** There is no conflict of interest with any institution or person. No financial support was received.

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