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RESEARCH

DOES PRIMARY TUMOR RESECTION AFFECT SURVIVAL IN ELDERLY PATIENTS WITH METASTATIC GASTRIC CANCER?

ABSTRACT

Introduction: In this study, the effect of primary tumor resection (PTR) on the survival of patients with metastatic gastric carcinoma (mCG) aged over 65 years was aimed to be searched.

Materials and Method: In total, 98 patients with mCG from the Akdeniz University, Necmettin Erbakan University, and Antalya Training and Research Hospital databases who were aged over 65 years were retrospectively evaluated. The patients were divided into two groups based on PTR: PTR (+) and PTR (-).

Results: The median progression-free survival in the PTR (+) group was 10.2 months (95% confidence interval [CI] 6.6–13.7) and in the PTR (-) group was 5.9 months (95% CI 2.6–9.3) (p=0.054). When we evaluated the overall survival (OS) of the groups, the median OS was significantly higher in the PTR (+) group (11.5 months, 95% CI 8.4–14.6) than in the PTR (-) group (7.2 months, 95% CI 4.3–10.0) (p=0.001). In the final multivariate analysis, none of the parameters studied were independent prognostic factors.

Conclusion: PTR may be beneficial for the survival of patients with mGC aged over 65 years.

Kew Words: Stomach Neoplasms; Geriatrics; General Surgery; Mortality.

ARAŞTIRMA

PRİMER TÜMÖR REZEKSİYONU YAŞLI METASTATİK GASTRİK KANSERLİ HASTALARDA SAĞKALIMI ETKİLER Mİ?

ÖZ

Giriş: Bu araştırmada 65 yaş üstü metastatik gastrik kanserli (mGK) hastalarda tanıda primer tümör rezeksiyonunun (PTR) sağ kalıma etkisinin araştırılması amaçlanmıştır.

Gereç ve Yöntem: Altmış beş yaş üstü mGK'lı 98 hasta verisi Akdeniz Üniversitesi, Necmettin Erbakan Üniversitesi ve Antalya Eğitim ve Araştırma Hastanesi veritabanlarından retrospektif olarak incelendi. Hastalar PTR'ye gore PTR (+) ve PTR (-) olarak iki gruba ayrıldı.

Bulgular: PTR (+) grupta medyan progresyonsuz sağkalım 10.2 [95% CI 6.6-13.7] ay iken, PTR (-) grupta 5.9 [95% CI 2.6-9.3] aydı (p=0.054). Genel sağkalım açısından incelendiğinde PTR (+) grubun sağkalım süresi anlamlı olarak daha yüksek bulundu (p=0.001). PTR (+) grubun sağkalımı 11.5 [95% CI 8.4-14.6] ay iken, PTR (-) grubun sağkalımı 7.2 [95% CI 4.3-10.0] aydı. Çok değişkenli analizde hiç bir parametre bağımsız prognostik faktör olarak bulunamadı.

Sonuç: Altmış beş yaş üstü tanıda MGC hastalarda primer tümörün cerrahisinin sağ kalıma faydası olabilir.

Anahtar Sözcükler: Gastrik Neoplaziler; Geriatrik, Cerrahi; Sağkalım.

Introduction

The incidence and mortality of gastric cancer (GC) has decreased in the last two decades. However, 40% of all GC cases are stage IV cancers (1). The 5-year survival in patients with metastatic gastric cancer (mGC) rarely exceeds 5%, and the prognosis for these patients is poor (2). Palliative chemotherapy is the treatment of choice for mGC, although the effect of non-curative gastric resection remains contentious, apart from in emergency surgical treatment.

The effect of primary tumor resection (PTR) on survival is currently being researched and has been shown to increase survival in patients with advanced-stage colon, breast, and renal cancers (3-5). Some studies on mGC have also shown that PTR has a positive effect on survival (6-10).

The incidence of GC increases with age, with the median age being 70 years for men and 74 years for women (11). Despite incidence increasing with age, most GC studies focused on patients under 70 years. Although the role surgery in patients with mGC is a matter of debate, it is known that age is an important factor for morbidity and mortality, even in the setting of curative GC surgery (12). Therefore, we studied the effect of PTR on the survival of elderly patients with mGC.

Materials and Method

Between February 2008 and March 2015, 98 patients with mGC from Akdeniz University, Necmettin Erbakan University, and Antalya Training and Research Hospital were retrospectively evaluated. Ethical approval was obtained from Akdeniz University Medical Faculty Clinical Investigations Ethics Committee. The patients were divided into two groups based on PTR: PTR (+) and PTR (-). Patients in the PTR (+) group received emergency or elective surgery due to tumor-related complications. Metastases were detected preoperatively, intraoperatively, or postoperatively in these patients.

All patients had histologically confirmed gastric adenocarcinoma, aged over 65 years, with ECOG performance ≤2, without any organ dysfunction, and were diagnosed with stage IV carcinoma (any T, any N, or M1; as listed in the American Joint Committee on Cancer, 7th ed.) by imaging or laparotomy. Gastric resections were total, subtotal, or distal gastrectomy without the removal of other metastatic lesions. Patients who had underwent non-resectional operations such as bypass surgery, jejunostomy, and gastrostomy; patients receiving neoadjuvant chemotherapy, radiotherapy, combination therapy, or who had relapsed or recurrent gastric carcinomas, and other synchronous tumors were excluded from analysis.

We retrospectively obtained patients' age, sex, comorbidities, smoking status, tumor grade, cerbB2 status, metastatic area, first-line chemotherapy, and radiologic M-stage from the medical archives of the participating hospitals. The date of diagnosis, date of progression under first-line chemotherapy, and date of death for the patients were also obtained. Overall survival (OS) was defined as the time from the beginning of treatment to death.

Statistical analyses were performed using SPSS version 16.0 (SPSS for Windows, Version 16.0. Chicago, SPSS Inc.). To determine the properties of the groups and compare patient and tumor characteristics between them, frequency analysis, chi-square tests, and two independent samples *t*-tests were used. The effect of PTR on the OS of patients with mGC was investigated using a log-rank test. Kaplan–Meier survival estimates were calculated. Multivariate analysis was performed with a Cox proportional hazards regression model. Factors with p values of <0.150 were included in the multivariate analysis. A p value of <0.05 was considered statistically significant.

Results

Patient Characteristics

A total of 98 patients with mGC (aged over 65 years) from the Akdeniz University, Necmettin Erbakan University, and Antalya Training and Research Hospital were included in the analysis. The PTR (+) group comprised 32 patients who underwent PTR and the PTR (-) group included 66 patients who did not undergo surgery. Patient characteristics are presented in Table 1. The mean age of patients in the PTR (+) group was 74.1 years (±5.7 years) and that of patients in the PTR (-) group was 71.8 years (±4.6 years). Both groups had male predominance, and 50% of those in the PTR (+) group had other comorbid diseases. Both PTR (+) and (-) patients had similar histological grades (p=0.038) and metastatic areas (p=0.237). Cerb-B2 positivity was dominant in the PTR (-) group, but this was not statistically significant (p=0.800). More patients in the PTR (+) group had not received first-line chemotherapy, although this was not statistically significant (p=0.187).

Survival Analysis

Patient clinic and pathological characteristics were similar for the two groups. Some patients (18.8%) were diagnosed radi-

Table 1— Properties of the Patients According to Primary Tumor Resection (PTR)

	PTR (-) (n:66)	PTR (+) (n:32)	P value
Age (mean)	71,8±4,6	74,1±5,7	0.038
Sex			0.330
Female	24,2% (16)	15,6% (5)	
Male	75,5% (50)	84,4% (27)	
Comorbidity			0.672
Yes	54,5% (36)	50% (16)	
No	45,5% (30)	50% (16)	
Smoking			0.866
Yes	42,4% (28)	40,6% (13)	
No	57,6% (38)	59,4% (19)	
Grade			0.038
1	12,5% (5)	19,2% (5)	
2	20% (8)	34,6% (9)	
3	27,5% (11)	38,5% (10)	
Unknown	40% (16)	7,7% (2)	
CerbB2 Positivity			0.800
Yes	10,4% (5)	5,3% (1)	
No	29,2% (14)	31,6% (6)	
Unknown	60,4% (29)	63,2% (12)	
Metastatic area			0.237
Only Liver	45,5% (30)	28,1% (9)	
Only Lung	0% (0)	6,2% (2)	
Only Peritoneal	19,7% (13)	28,1% (9)	
Only Bone	1,5% (1)	3,1% (1)	
Other	10,6% (7)	12,5% (4)	
≥2 organs	22,7% (15)	21,9% (7)	
First-line CT			0.187
Yes	83,3% (55)	71,9% (23)	
No	16,7% (11)	28,1% (11)	
Radiologic M stage			0.002
Local Disease	1,5% (1)	18,8% (6)	
Metastatic Disease	98,5% (65)	81,2% (26)	

ologically as having localized disease; however, they were intraoperatively diagnosed with stage IV gastric carcinoma.

The median progression-free survival (PFS) was 10.2 months (95% confidence interval [CI] 6.6–13.7) in the PTR (+) group, and 5.9 months (95% CI 2.6–9.3) in the PTR (-) group (p=0.054). The PFS curves are shown in Figure 1. We also found that the median OS was significantly higher in the PTR (+) group at 11.5 months (95% CI 8.4-14.6) than the PTR (-) group (7.2 months, 95% CI 4.3-10.0) (p=0.001). The OS curves are shown in Figure 2.

Patient age, sex, comorbidities, smoking status, grade, cerbB2 status, metastatic area, first-line chemotherapy, radiologic M-stage, and PTR were included the univariate analysis. The p values for these factors are presented in Table 2. Following this factors with p values of <0.150 were included in the multivariate analysis: cerbB2 status, first-line chemotherapy, radiologic M-stage, and PTR. In the final multivariate analysis, none of the parameters were found to be independent prognostic factors.

Discussion

Patients with stage IV GC are treated with palliative chemotherapy, and survival rates are low. Surgery in these patients is reserved for tumor related complications such as blee-

Table 2— Results of Univariate Analysis

	p value
Age	0.657
Sex	0.319
Comorbidity	0.749
Smoking	0.930
Grade	0.542
CerbB2	0.026
Metastatic area	0.523
First-line CT (yes or no)	0.087
Radiologic M Stage	0.008
Primary Tumor Resection	<0.001

ding, perforation, and obstruction. Approximately 50% of patients with mGC receive surgery for these complications during their disease course (13). However, survival benefits obtained with gastrectomy for the remaining 50% of patients with mGC have been reported recently.

The hypothesis for the survival benefit of PTR in patients with mGC is a reduction of tumor load, which may also act as an immunosuppressant, removal of the main source for further metastases, and alleviation of symptoms related to gastric tumor.

Some previous studies have shown the importance of an increased risk of postoperative mortality in palliative surgery for patients aged over 70 years (14-16). The effect of PTR on survival of older adult patients, are available only as subgroup analyses in retrospective or prospective trials.

A retrospective Dutch gastric cancer trial (17) evaluated 285 patients with metastatic GC. The median survival of patients who underwent tumor resection (partial or total) was 8.1 months versus 5.4 months for surgery without resection (explorative or gastroenterostomy) ($p < 0.001$). Prognostic factors such as unresectable tumor, hepatic metastasis, peritoneal metastasis, and distant lymph node metastasis were evaluated, median survival was in favor of resection in the presence of one factor (10.5 months vs. 6.7 months) ($p=0.034$). However, in the presence of two or more factors, statistically significant survival benefit was not observed. Survival benefit of tumor resection did not differ in age stratification of the resection group (8.0 months in younger than 70 years old vs. 8.1 months in older than 70 years old). Significantly higher surgical morbidity and longer hospital stay was reported in resection group. Although mortality was also higher (20% vs. 9%), difference was not significant ($p=0.06$). The trial results revealed that age is an important factor, together with the metastatic site in patients undergoing PTR. Authors hypothesized that PTR is potentially beneficial for patients younger than 70 years with limited metastatic disease (17).

We found a two-fold increase in PFS and an increase in the median OS of 4.5 months in patients who underwent PTR; even though the mean age of patients who underwent PTR was over 70 years. In addition, there were no differences in metastatic areas between the two groups in our study; however, there was a relatively high proportion of patients with two or more visceral organ metastases (21.9%). Although our patients had more metastatic sites, survival was 3.5 months longer when compared with the Dutch gastric cancer trial.

In a retrospective trial with 63 patients with mGC who received palliative gastrectomy (18), the median age at diagnosis was 64 years (range 21–7 years), and the median survival was 12 months in patients aged over 60 years. This result is consistent with our results for median survival (11.5 months), although the patients who received PTR in our study were older (mean age 74 years, ±5.7 years). In addition, peritoneal metastases were present in 48% of the patients in the previous trial, whereas 56% of our patients had visceral metastases inappropriate for surgery (28.1% hepatic, 6.2% lung, 21.9% two or more). Only 28% of our patients had peritoneal metastases.

In a multicenter study that reported survival of non-curative surgery for mGC (19), the median survival of patients aged over 70 years (n=183) was 5.5 months; our patients survived two-fold longer. However, the previous analysis included both PTR and non-resectional surgery, whereas our analysis did not include non-resectional surgery.

In another study including 48 patients with mGC undergoing surgery (13), non-curative resection was shown to increase survival when compared with non-resectional surgery (15 months vs. 5 months). Our results showed similar benefits; however, that study was conducted with a relatively younger patient group (aged over 50 years). Survival was not affected by sex, peritoneal carcinomatosis, or hepatic metastatis but was effected by postoperative chemotherapy and multiple visceral metastases. We did not find that any of these factors affected survival in our study.

In a Turkish study with 236 patients receiving non-curative gastrectomy (20), the PFS results for patients who received surgery versus patients who did not were similar to those in our study (10 months vs. 6 months). In that study, the OS was 14 months for those who received surgery and 9 months for those that did not. However, in the surgery group, 20 pa-

tients underwent metastasectomy; patients who had surgery predominantly had peritoneal metastases, whereas patients who did not receive surgery predominantly had visceral metastases. Single hepatic metastasis was common in the surgery group ($p<0.001$), and first-line chemotherapy was higher in the non-operative group ($p=0.01$). The mean age of patients in that study was 56 years; however, no differences in PFS and OS were seen when patients aged over 50 years were compared with patients younger than 50 years. In our study, none of the patients received metastasectomy, there were no differences in metastatic sites between the groups, and both groups had similar percentages of first-line chemotherapy.

There were some limitations in our study. In particular, access to technical surgery data, and data for surgical mortality and morbidity, hospital stay, quality of life, total tumor load in metastatic areas, primary tumor localization, and regimen of first-line chemotherapy was either limited or inaccessible. Even so, the two study groups were evenly distributed, and we found a survival benefit of PTR (PFS of 10.2 months and an OS of 11.5 months) in older adult patients with mGC (aged over 65 years). Further prospective randomized studies with larger sample sizes are needed to confirm these findings.

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