The value of resection of primary tumor in gastric cancer patients with liver metastasis

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Abstract

Purpose Surgery for gastric cancer with synchronous liver metastasis is applied for palliation. The aim was to determine whether surgical removal of the primary tumor provides a better survival and disease progression

Methods Sixty-two patients are classified according to the primary tumor were removed or not. Patients and tumor characteristics, removal of the primary tumor are examined as the factors that were affecting overall survival and metastatic progression-free survival.

Results The mean follow-up time was 243 ± 23 days. The mean survival of the resection and nonresection groups were 422 ± 50 and 170 ± 16 days ($p = 0.0001$), respectively. After adjustment for other covariates, resection was associated with a trend toward improvement in overall survival ($p = 0.003$; relative risk RR: 0.34; 95% confidence interval (CI): 0.17–0.66) and improvement in metastatic progression-free survival ($p = 0.07$, RR = 0.51; 95% CI: 0.25–1.07).

Conclusions Excision of the primary tumor has an effect on metastatic progression-free survival and overall survival.

Keywords Palliative gastrectomy · Liver metastasis · Survival

Introduction

Surgery is the dominant curative treatment method for gastric cancer. Palliative resection relieves symptoms as well as maintains survival benefit in advanced gastric cancer. There are several studies that indicate the importance of palliative gastrectomy in Stage IV gastric cancer [1–6]. Stage IV gastric cancer is defined according to the American Joint Committee on Cancer (AJCC, 6th edition), as M_1 , all N_3 , or $T_4 N_{1-3} M_0$ (AJCC, 2003) [7]. In this heterogeneous group, subgroup analyses are necessary to determine the patients that can benefit from surgery. In this study, we examined the role of palliative resection of the primary in the gastric adenocarcinoma patients who had liver metastasis at diagnosis but did not have extra-abdominal disease.

Patients and methods

Sixty two patients with gastric cancer who had liver metastasis at diagnosis, treated at Ankara Oncology Education and Research Hospital between January 2005 to January 2008 were included in the study. Patient's follow-up lasted until death or until cut-off date of July 31, 2008. Patients were grouped whether resection of the primary tumor was performed or not. The patient's performance status was evaluated according to Eastern Cooperative Oncology Group (ECOG) criteria's and ECOG 0, 1 and 2 patients were included in this study. The indications of palliative gastrectomy were decided according to the patient's symptoms and general health, performance status,

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extent of the disease, and feasibility of resection. Some surgeons did not believe in the benefit of the primary tumor resection in stage IV gastric carcinoma, and they prefer other palliative techniques. The primary tumor was removed in 18 patients who were considered as resection group (RG). In the nonresection group (NRG), 12 of 44 patients were treated with a bypass procedure, where three only had exploratory laparotomy. Twenty-nine of 44 patients the patients were not subjected to any operation. Overall, the mean follow-up time were 243 ± 23 days (82–855 days).

Patients were selected according to following criteria: (i) histopathologically proven gastric adenocarcinoma; (ii) presence of liver metastasis at the time of diagnosis; (iii) absence of extra-abdominal disease; (iv) the patients whose performance status is suitable to receive chemotherapy are included. The patient data is collected prospectively and is approved by our institutional ethical committee. All patients were treated with some form of systemic 5-fluorouracil based chemotherapy regimens. None of the patients received postoperative adjuvant radiotherapy.

Follow-up examinations were performed in 3-week intervals during the chemotherapy schedules, in every three months for the first two years, and every six months for the years thereafter. The follow-up program included clinical examination, hematological analyses, liver function tests, and tumor marker assay (carcinoembryonic antigen (CEA) and CA19-9) at each checkup; abdominal ultrasound and chest x-ray is performed in every 6 months; and endoscopy of the upper digestive tract once a year. Abdominal and/or thoracic computed tomography was performed in cases of suspected recurrence. Only for the chemotherapy patients, abdominal ultrasonography was performed after the third cycle to determine the effectiveness of chemotherapy.

The age, gender, serum tumor marker (CEA, CA19-9) levels, localization of the tumor in liver and stomach, number of metastasis in liver, existence of ascites, peritoneal dissemination, existence of krukentberg tumor, and primary tumor resection are examined as the factors that were affecting the overall survival (OS) of the patients.

Statistical analysis

Univariate analyses of categorical values were defined using the Chi-square test or Fisher's exact test. Survival curves were estimated according to the method of Kaplan-Meier and compared to log-rank test. The factors that might be significant parameters which can affect the OS are fitted in Cox stepwise proportional risk regression model. P values $< .05$ were considered to be statistically significant. Statistical analysis was performed using SPSS 13.0 software (Statistical Software, Chicago, USA).

Results

There were 45 male and 17 female patients and mean age was 58 years (range, 22–77). Demographics and tumor characteristics of patients for the RG and NRG are compared in Table 1. The two groups were similar in respect to age, gender, serum tumor marker levels, localization of tumor in liver and stomach, number of metastasis in liver and peritoneal dissemination. The mean follow-up time was 243 ± 23 days. The mean survival of the resection and nonresection groups were 422 ± 50 and 170 ± 16 days ($p = 0.0001$), respectively. At the end of the study, all of the patients died because of the disease.

Table 1 The parameter of comparison in RG and NRG

		RG (n=18, pts %)	NRG (n=44, pts %)	P
Age	<65	12 (66.7%)	33 (75%)	0.72
	≥ 65	6 (33.3%)	11 (25%)	
Gender	Female	3 (16.7%)	14 (31.8%)	0.36
	Male	15 (83.3%)	30 (68.2%)	
The levels of tumor marker	Normal	6 (33.3%)	7 (15.9%)	0.33
	High	9 (50%)	28 (63.6%)	
	Unknown	3 (16.7%)	9 (20.5%)	
Localization of tumor	Upper third	8 (44.4%)	7 (16%)	0.06
	Middle third	6 (33.4%)	13 (29.5%)	
	Lower third	4 (22.2%)	24 (54.5%)	
Isole liver metastasis	Unilobar	8 (53.3%)	7 (29.2%)	0.13
	Bilobar	7 (46.7%)	17 (70.8%)	
Isole liver metastasis	Solitary	4 (26.7%)	3 (12.5%)	0.48
	Multiple	11 (73.3%)	21 (87.5%)	
Liver metastasis with peritoneal dissemination	Present	3 (16.7%)	16 (36.4%)	0.12
	Absent	15 (83.3%)	28 (63.6%)	

RG: Resection group NRG: Nonresection group

Vomiting and/or fatigue were the general symptoms of all the patients. In this study, there wasn't any perforated tumor or serious bleeding attributable to tumor itself. In general, resection was performed if there was an obstructive complaint in the proximal region tumors where by-pass procedure was preferred in the distal region tumors. In 18 (29%) of 62 patients the primary tumor were removed (distal gastrectomy in four and total gastrectomy in 14) where 44 (71%) of them were not removed. Based on the surgery records, although tumor is resectable in the 6 of the 12 patients bypass surgery was performed since there were multiple metastases in liver. No patient had undergone liver resection. Resection of the primary tumor was preferred in patients who did not have ascites and krukenberg tumor. Comparison of the resection and nonresection groups according to tumor involvement and outcomes are given in Table 2. It was observed that resection increased the survival of the patients (Fig. 1). The factors affecting OS in 62 gastric cancer patients who had liver metastasis are given in Table 3. Related risk factors based on the univariate analysis were serum tumor marker levels ($p = 0.03$), localization of liver metastasis ($p = 0.0002$), existence of ascites ($p = 0.0001$), peritoneal dissemination ($p = 0.009$), type of operation ($p = 0.0001$), and primary tumor resection ($p = 0.0001$). These factors were analyzed with Cox regression analysis and results are given in Table 4.

Table 2 Comparison of survival in RG and NRG according to tumor involvement

		Pts no	MOS (days)	P value
Isole liver metastasis	RG	15	364	0.001
	NRG	24	173	
Isole solitary liver metastasis	RG	4	364	0.01
	NRG	3	223	
Isole multiple liver metastasis	RG	11	254	0.01
	NRG	21	173	
Isole unilobar liver metastasis	RG	8	563	0.02
	NRG	7	223	
Isole bilobar liver metastasis	RG	7	254	0.04
	NRG	17	151	
Liver metastasis with peritoneal dissemination	RG	3	327	0.02
	NRG	16	110	

MOS: Median overall survival RG: Resection group
NRG: Nonresection group

The mean of metastatic progression-free survival of the resection and nonresection groups were 7.2 ± 1.1 and 3.1 ± 0.3 months ($p = 0.001$). In univariate analysis, metastatic progression-free survival seemed to be associated with localization of liver metastasis ($p = 0.001$), the number of liver metastasis ($p = 0.004$), existence of ascites ($p = 0.02$), peritoneal dissemination ($p = 0.01$), and primary tumor resection ($p = 0.001$). Kaplan-Meier curves are

Fig. 1 Survival curves gastric carcinoma patients with liver metastasis. RG: resection group, NRG: nonresection group

demonstrating the difference between the RG and NRG in metastatic progression-free survival which is shown in Fig. 2. On multivariate analysis the effect of primary tumor resection and the other parameters on metastatic progression-free survival ($p = 0.07$, $RR = 0.51$; 95% CI: 0.25–1.07) were not significant as well.

Evisceration developed in one of the patients of the resection group; thus the patient was reoperated. Furthermore, one of the patients underwent ultrasound-guided drainage due to intra-abdominal abscess. No complication was observed in patients in whom bypass/ostomy or laparotomy alone was applied. All patients were examined by a medical oncologist after their histopathological investigation and were discharged from hospital after their chemotherapy schedule was determined. The median hospital stay of the resection and nonresection group patients was 12 and 8 days, respectively ($p = 0.0002$).

Discussion

In the stage IV gastric carcinomas primary tumor can easily result in gastric obstruction, perforation, bleeding, or excessive ascites. The aim of the palliative procedures is to manage those symptoms. Increased survival may be a secondary goal of a palliative procedure. The benefits of palliative surgery in the survival of the patients who

Table 3 Univariate survival analysis for gastric cancer patients who had liver metastasis

		No of patients	Mean (day)	Median (day)	P
Age	<65	45	225	173	0.47
	≥65	17	268	254	
Gender	Female	17	243	207	0.5
	Male	45	291	173	
The levels of tumor marker	Normal	13	332	258	0.03
	High	37	209	150	
	Unknown	12	221	190	
Localization of tumor	Upper third	15	292	254	0.47
	Middle third	19	225	151	
	Lower third	28	216	173	
Localization of liver metastasis	Unilobar	18	366	282	0.0002
	Bilobar	44	184	150	
The number of metastasis in liver	Solitary	7	353	338	0.1
	Multiple	55	222	180	
Ascites	Present	11	122	115	0.0001
	Absent	51	261	223	
Peritoneal dissemination	Present	19	164	129	0.009
	Absent	43	269	222	
Krukenberg	Present	3	135	143	0.08
	Absent	59	242	207	
The type of the operations	No operation	29	186	151	0.0001
	Laparotomy	3	168	149	
	Bypass/ostomy	12	132	85	
	Resection	18	402	338	
Resection of primary tumor	RG	18	402	338	0.0001
	NRG	44	170	145	

Table 4 Cox regression analyses for gastric cancer patients who had liver metastasis

	P	RR	95%CI
Ascites	0.03	2.31	1.06 – 5.07
Resection of primary tumor	0.003	0.34	0.17 – 0.66

RG: Resection group NRG: Nonresection group

have stage IV metastasis were indicated in several studies [1–4, 8–13]. The effect was not identified in only a few of these studies [14–16]. The reason of the different results in the series is poor prognosis in the stage IV gastric carcinomas as the estimated survival time is too short and performing resection or not may have different clinical features. However, performing the same conditions is clinically impossible. This study was carried out to determine whether surgical removal of the primary tumor provides a better survival and disease progression. To prevent the problem in the patient selection, patients are evaluated according to the place and number of metastases. As a result survival increased in the resection group when subgroup analysis considered.

No hepatic resection is done and all the patients received chemotherapy. Preoperatively determined hepatic metastases are also controlled postoperatively and progression of these metastases was observed later (7.2 versus 3.1 months) in the resection group. Tumor load reduction diminishes the metabolic demand by the tumor. In addition, because the tumor itself can produce immunosuppressive cytokines, reducing the tumor load may also have an immunologic benefit [17]. However, if a significant proportion of the tumor load is removed perhaps the disease may be more responsive to adjuvant treatment [18].

Analyses were done based on both the number and the localization of the liver metastasis. The effect of the presence of solitary or multiple metastases on the survival was not significantly different. However, bilobar metastasis was determined as an important factor that affects survival in all patient groups and in RG by cox regression analysis. In literature there were studies supporting [4, 10, 13] and contradicting [2, 11] these findings. The presence of ascites was a negative factor and resection was not applied to such patients.

In some studies, four signs of incurability are noted: irresectable tumor, hepatic metastasis, peritoneal metastasis, and distant lymph node metastasis [1, 9, 12].

Fig. 2 Kaplan-Meier curves show metastatic progression-free survival. RG: resection group, NRG: nonresection group

The resectability rate decreases as the number of sites of tumor spread increases. Survival advantage of resection procedure disappeared when more than two sites of tumor spread were present. In the study of Kikuchi et al. [19], the benefit of resection in the survival was not presented in the patients who have both hepatic metastasis and peritoneal dissemination. In the present study, all the patients had hepatic metastasis. Peritoneal dissemination was observed only in three resected patients. The survival of the patients that had peritoneal dissemination in the resection group was better when compared to the NRG. When the resected and nonresected patients were examined according to OS, univariate analysis revealed peritoneal dissemination as a negative factor whereas multivariate analysis did not.

Neither in this study nor in the others, the age of the patient was determined as a factor that significantly affects survival [2, 3, 11]. On the other hand, Hartgrink et al. [1] indicated that resection was not effective in patients who are older than 70 years of age with multiple metastases. Increased tumor marker levels at the time of diagnosis negatively affect the prognosis [20]. Results of the present study supported this finding. However, there was an opposing study [4]. Localization of the tumor in the stomach did not affect the survival [2, 3]. Although the size of the tumor is considered as an important parameter in the study

of Kunisaki et al. [2], neither present study nor the study of Kim et al. [11] supports this finding.

The most strict argument about palliative resection versus other palliative procedures is the increased ratio of postoperative mortality, morbidity, and time of hospitalization [1, 2, 12]. We didn't consider the mortality rates of the applied surgery because chemotherapy receiving patients were selected at first in the patient selection. Complication was observed only in two patients in RG. One of these was evisceration and the other was intra-abdominal abscess. The hospital stay in the RG, was significantly longer than the other palliative procedure applied ones. (12 versus 8 days). There were studies indicating that palliative resection did not have a negative effect on the mortality and morbidity [14].

In conclusion, despite stage IV patients have poor prognosis, removal of the intact primary tumor for gastric cancer with synchronous liver metastasis at diagnosis is associated with improvement in metastatic progression-free survival and overall survival.

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