Prognostic Effect of Peritoneal Metastasis in Patients with Metastatic Gastric Carcinoma

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ABSTRACT

Objective: The aim of this study is to evaluate of prognosis of the patients with peritoneal carcinomatosis in metastatic gastric carcinoma.

Methods: Eighty-seven patients diagnosed with metastatic gastric adenocarcinoma between January 2005 and August 2014 were retrospectively reviewed. The effect of peritoneal metastasis on overall survival and progression-free survival was assessed.

Results: In univariate analysis, Eastern Cooperative Oncology Group (ECOG) performance status (p=0.04), histologic type (p=0.04) and site of metastasis (p=0.02) were significant prognostic factors for overall survival; favoring ECOG performance status 0-1, histopathologically without mucinous component, patients without peritoneal metastasis respectively. Patients with peritoneal metastasis (HR, 1.681; 95% CI, 1.032-2.739; p=0.037) had worse overall survival in multivariate analysis. ECOG PS≥2 predicted inferior PFS in both univariate (8.1months versus 5.5 months, p=0.001) and multivariate analysis (HR, 2.228; 95% CI, 1.397-3.553; p=0.001).

Conclusion: The presence of peritoneal metastasis in patients with metastatic gastric carcinoma is associated with significantly shorter overall survival compared to patients without peritoneal metastasis.

Keywords: Metastatic gastric cancer, peritoneal metastasis, prognosis

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INTRODUCTION

Gastric carcinoma is the fourth most commonly diagnosed cancer and the second leading cause of death globally (1). It represents one of the most common gastrointestinal cancers and is associated with a poor prognosis (2, 3). Currently, gastrectomy remains the only curative therapeutic option, and 40% to 60% of the patients relapse despite surgery (4). Furthermore, most patients with gastric carcinoma have advanced disease at the time of diagnosis.

The peritoneum represents the most common site of metastasis and recurrence (5). In a previous study involving a total of 1,172 gastric cancer patients treated surgically, 29% of the patients relapsed, with development of peritoneal metastasis (6).

Peritoneal metastasis is frequently indicative of advanced disease, either due to progression of the existing disease or due to recurrence (7), and it also predicts a poor survival. According to the published literature, the median survival in gastric cancer patients with peritoneal metastasis is 3 to 11 months (8-10). In such patients, the mainstay of treatment is systemic chemotherapy using agents with proven efficacy, including cisplatin, capecitabine, docetaxel, irinotecan, and combination regimens containing transtuzumab in tumors expressing the human epidermal growth factor-2 (10, 11).

The median survival with the newer chemotherapeutic regimens in gastric cancer patients with peritoneal and/or extra-peritoneal metastases was increased to 9-14 months (8, 11-14). In the absence of other systemic metastases, it may be possible to achieve local control and even to improve survival with cytoreductive surgery and intraperitoneal hyperthermic chemotherapy (HIPEC), as shown in several studies (15, 16).

In many patients, peritoneal metastases are associated with no or only subtle symptoms at the initial stages of the disease. Therefore, the diagnosis can only be established during surgery in a certain proportion of patients (17). The prevalence and distribution of metastasis have been shown to correlate with the course of the disease (18). In this regard, peritoneal metastases are considered in three categories as follows: P1, local disease in the upper abdominal region; P2, distal to the transverse colon with multiple nodular involvement; and P3, diffuse peritoneal involvement (19). In approximately 5% to 20% of patients undergoing curative gastrectomy, peritoneal metastasis may be present (5, 7).

In this study, we retrospectively evaluated the presence of peritoneal metastasis and its association with prognosis in a group of patients with metastatic gastric carcinoma.

METHODS

A total of 87 patients who were cytologically or pathologically diagnosed with metastatic gastric adenocarcinoma between January 2005 and August 2014 and who had no missing data were included in this retrospective study.

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All patients were older than 18 years. Exclusion criteria were as follows: previous chemotherapy for metastatic gastric adenocarcinoma, an Eastern Cooperative Oncology Group (ECOG) performance status >3, the presence of a second malignancy, the presence of central nervous system metastasis at the time of diagnosis, insufficient renal functions (serum creatinine <1.5 mg/dl) for DCF (cisplatin 60 mg/m^2 Day 1, intravenous [i.v.] infusion; docetaxel 60 mg/m^2 Day 1, i.v. infusion; 5-fluorouracil 600 mg/m^2 Day 1-4, every 21 days), absence of adequate liver function (ALT <upper limit of normal x 2) and hematological profile (leukocyte count ≥3500 and absolute neutrophil count ≥1500), and pregnancy. Metastatic sites were identified with computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography-computed tomography (PET-CT) imaging. Peritoneal metastases were radiologically demonstrated based on the presence of the omental cake appearance, peritoneal tumor implants, and/or pathological SUV-max values in PET-CT.

Patient data including age (<65 y vs. ≥65 y), gender, the ECOG performance status (0-1 vs. 2-3), smoking status, pre-treatment hemoglobin (<10 vs. ≥10 g/dl), tumor differentiation, the presence of mucin component, and data regarding the metastatic sites were retrospectively screened. Patients were categorized into two age groups using a cut-off of 65 years based on the definition of the term "old age" by the World Health Organization, as well as the previous studies (20-22).

All patients received the same first-line palliative chemotherapeutic regimen (cisplatin 60 mg/m^2 Day 1, i.v. infusion; docetaxel 60 mg/m^2 Day 1, i.v. infusion; 5-fluorouracil 600 mg/m^2 Day 1-4, every 21 days, for a maximum of 6 courses). Patients received 2 to 6 courses of chemotherapy, depending on the response status and chemotherapy tolerance. The median number of chemotherapy cycles was 4 (range, 2-6). The response was assessed after the administration of 2 to 3 courses. Also, the treatment response was radiologically assessed in patients with clinical deterioration, regardless of the number of the chemotherapy cycles administered. The treatment was discontinued in case of radiologically confirmed disease progression or intolerance to therapy.

The treatment response was assessed with Response Evaluation Criteria in Solid Tumors version 1.1 using CT or MRI. The study protocol was approved by the Ethics Committee of Ankara Numune Research and Training Hospital.

Statistical Analysis

The median, frequency, and percentage for study data were determined. The overall survival was defined as the time from diagnosing metastasis to death, while progression-free survival was defined as the time from the start of first-line treatment (cisplatin 60 mg/m^2 Day 1, i.v. infusion; docetaxel 60 mg/m^2 Day 1, i.v. infusion; 5-fluorouracil 600 mg/m^2 Day 1-4, every 21 days for a maximum of 6 cycles) to disease progression. Survival data were analyzed using the Kaplan-Meier method, and the statistical significance was determined with a log-rank test. A p-value of less than 0.05 was considered statistically significant. In the univariate analysis, variables with a p-value <0.1 were further examined using a multivariate cox-regression analysis. Statistical analyses were done with the Statistical Package for Statistical Sciences version 18 for Windows (IBM Corp, Armong, NY, USA).

RESULTS

Patient Characteristics

The patient characteristics for the 87 participants are shown in Table 1. The median duration of follow up after diagnosis was 13.9 months (range, 1.58-71.62 months). The mean age was 56 years (31-72 y), and 70.1% were male. Twenty-one patients were aged ≥65 years. Prior to treatment, 65.5% of patients had an ECOG performance status of 0 or 1. At the time of diagnosis, 57.5% (n=50) were current smokers, and 34.5% (n=22) had a hemoglobin <10 g/dl prior to chemotherapy initiation. Most patients (89.7%) had moderately or poorly differentiated tumors, while 55.2% had a mucinous component, histopathologically. Eighteen patients (21%) had multiple sites of metastasis. In 27 patients (31%), the metastasis was confined to peritoneum, while 60 patients (69%) had no peritoneal metastasis. Among patients with peritoneal metastasis, 6 had more than one site of metastasis, while the corresponding figure among those with extra-peritoneal metastasis was 12 (Figure 1).

Survival Data

The median overall survival and progression-free survival were 13.9 and 7.5 months, respectively.

A univariate analysis was done to examine the association between patient characteristics and overall survival (Table 2). The overall survival was significantly better in patients with a good ECOG performance status (17.5 months vs. 8.2 months, p=0.04), no mucinous component (18.1 months vs. 11.9 months, p=0.043), or no peritoneal metastasis (14.2 months vs. 11.5 months, p=0.026), while the overall survival was not significantly associated with age (13.9 months vs. 13.8 months, p=0.935), gender (14.4 months vs. 13.8 months, p=0.775), smoking (11.5 months vs. 14.4 months, p=0.507), pre-treatment hemoglobin (14.4 months vs. 13.7 months, p=0.603), the presence of liver metastasis (14.29 months vs. 13.07 months, p=0.201), the presence of metastasis in more than one site (14.29 months vs. 11.13 months, p=0.175), the presence of isolated peritoneal metastasis (11.9 months vs. 13.9 months, p=0.108), and tumor differentiation (15.7 months vs. 13.83 months, p=0.946). Multivariate analysis, patients with peritoneal metastases had significantly worse overall survival (HR 1.681, 95% confidence interval [CI] 1.032-2.739; p=0.037); Figure 2a, Table 2).

Patients with an ECOG performance status of 0-1 had a significantly longer progression-free survival, both in the univariate analysis (8.1 months vs. 5.5 months, p=0.001) and in the multivariate analysis (HR 2.228; 95%CI, 1.395-3.553; p=0.001). On the other hand progression-free survival had no significant associations with age (7.5 months vs. 7.2 months, p=0.935), gender (7.6 months vs. 6.8 months, p=0.082), smoking (7.6 months vs. 7.2 months, p=0.989), hemoglobin level prior to treatment (7.4 months vs. 7.5 months, p=0.756), hepatic metastasis (7.98 months vs. 6.83 months, p=0.379), metastasis in more than one site (7.55 months vs. 6.96 months, p=0.175), isolated peritoneal metastasis (7.4 months vs. 7.5 months, p=0.991), tumor differentiation (7.5 months vs. 7.4 months, p=0.377), mucinous component (7.1 months vs. 7.7 months, p=0.922) and peritoneal metastasis (6.8 months vs. 7.6 months, p=0.792) (Figure 2b) (Table 3).

Table 1. Clinical and pathologic characteristics of study subjects

Characteristic	Patients, n=87 (%)
Age, years	
Median	56
Range	31-72
<65	66 (75.9)
≥65	21 (24.1)
Gender	
Male	61 (70.1)
Female	26 (29.9)
ECOG Performance Status	
0-1	57 (65.5)
2-3	30 (34.5)
Cigarette smoking	
Yes	50 (57.5)
No	37 (42.5)
Hgb prior to treatment	
<10	22 (65.5)
≥10	65 (34.5)
Differentiation	
Good	9 (10.3)
Moderate/Poor	78 (89.7)
Mucinous Component	
Yes	48 (55.2)
No	39 (44.8)
Site of metastasis	
Peritoneum	27 (31)
Single metastatic site	21 (24)
Multiple metastatic sites*	6 (7)
Extra-peritoneal	60 (69)
Single metastatic site†	48 (55)
Multiple metastatic sites*	12 (14)
Liver metastasis	
Yes	42 (48.3)
No	45 (51.7)

*Ovarian in 3, lung in 1, and other sites in 2 patients.†Hepatic in 34, lung in 3, other sites in 11 patients.

An assessment of the association between the clinical/pathologic variables and the presence of peritoneal metastasis showed that patients with peritoneal metastasis were less likely to have hepatic metastases as compared to those without such metastases (p<0.001). The association between the presence of mucinous component and peritoneal metastasis was close to statistical significance (p=0.056, Table 4).

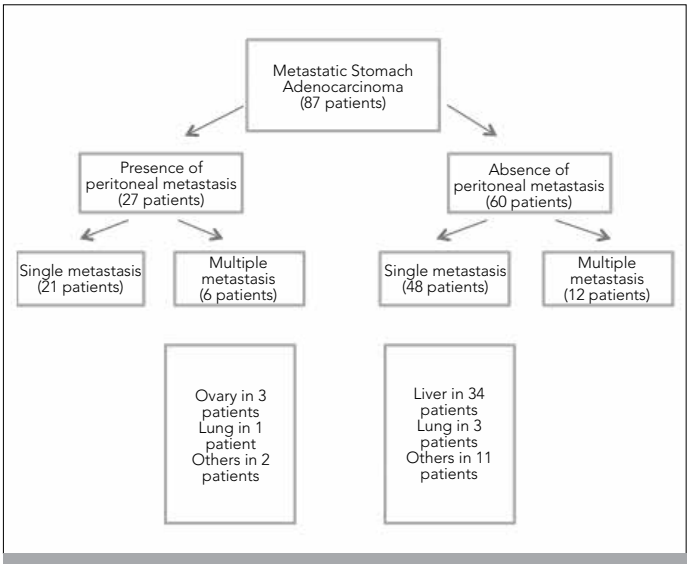

Figure 1. Flow chart of the classification of patients according to the presence of peritoneal metastasis

DISCUSSION

Peritoneal metastasis is a sign of poor prognosis in patients with carcinoma. In these patients, the median survival is approximately 4 months with supportive treatment, while it may be increased up to 8-14 months with intensive chemotherapy regimens (10, 23, 24). Peritoneal metastasis is associated with a poor prognosis, not only in patients with gastric cancer, but also in those with a number of other cancers, such as the colorectal or pancreatic cancer (24). In this study, the overall survival in our patient group with peritoneal metastasis was significantly shorter, which is consistent with previously reported data.

The main limitations of our study were its retrospective design and the absence of an assessment of treatments administered after progression. Also, our failure to provide data on the extent of the peritoneal metastasis represents another limitation. On the other hand, use of the same treatment protocol as a first-line treatment for metastatic gastric cancer allowed us to form a relatively homogenous study sample.

In contrast with disease spread via blood circulation or lymphatic system, peritoneal metastasis frequently results from the growth and direct invasion of the tumor cells. The intra-abdominal cell load correlates with peritoneal invasion (18). The first stage in the development of peritoneal metastasis is the separation of tumor cells from the primary tumor. A number of different mechanisms such as the inadequate lymphatic circulation and rapid tumor growth, tumor cells diffuse into the intra-abdominal cavity and invade the peritoneal surfaces (7). Mesothelial cells adhere to tumor cells via the intra-cellular adhesion molecules. Tumor cells also bind to integrins, leading to breakdown of mesothelial cells and consequent invasion into the tissues under the serosa. Also, free tumor cells may directly infiltrate the omentum in a process mediated by extracellular matrix components (25).

Table 2. Overall survival data in the univariate and multivariate analyses

		Univariate analysis		Multivariate analysis	
Patients	**Median n (%)**	**OS (months))**	**OS p**	**Hazard ratio (95% CI)**	**OS p**
All groups	87	13.9			
Age, years					
Median	56				
Range	31-72				
<65	66 (75.9)	13.99			
≥65	21 (24.1)	13.83	0.935		
Gender					
Male	61 (70.1)	14.42			
Female	26 (29.9)	13.89	0.775		
ECOG Performance Status					
0-1	57 (65.5)	17.54			
2-3	30 (34.5)	8.24	0.04	1.557 (0.988-2.451)	0.056
Cigarette smoking					
Yes	50 (57.5)	11.56			
No	37 (42.5)	14.42	0.507		
Hb prior to treatment					
<10 gr/dL	22 (34.5)	14.42			
≥10 gr/dL	65 (65.5)	13.79	0.603		
Differentiation					
Good	9 (10.3)	15.7			
Moderate/Poor	78 (89.7)	13.83	0.946		
Mucinous Component					
Yes	48 (55.2)	11.95			
No	39 (44.8)	18.16	0.043	1.721 (0.460-1.130)	0.153
Metastatic Disease					
Single metastatic site	69 (79.3)	14.29			
Multiple metastatic sites	18 (20.7)	11.13	0.175		
Site of metastasis					
Peritoneum	27 (31)	11.56			
Extra-peritoneal	60 (69)	14.29	0.026	1.681 (1.032-2.739)	0.037
Isolated Peritoneal Metastasis					
Yes	21 (24.1)	11.95			
No	66 (75.9)	13.99	0.108		
Hepatic Metastasis					
Yes	42 (48.3)	14.29			
No	45 (51.7)	13.07	0.201		

ECOG: Eastern Cooperative Oncology Group; Hgb: hemoglobin; OS: overall survival

Table 3. Progression-free survival data in the univariate and multivariate analyses

Patients	n (%)	Median PFS (months)	Univariate analysis	Multivariate analysis	
			PFS p	Hazard ratio (95% CI)	PFS p
All groups	87	7.5			
Age, years					
Median	56				
Range	31-72	7.55			
<65	66 (75.9)	7.22	0.935		
≥65	21 (24.1)				
Gender					
Male	61 (70.1)	7.65			
Female	26 (29.9)	6.83	0.082	1.410 (0.869-2.286)	0.164
ECOG Performance Status					
0-1	57 (65.5)	8.11			
2-3	30 (34.5)	5.58	0.001	2.228 (1.397-3.553)	0.001
Cigarette smoking					
Yes	50 (57.5)	7.65			
No	37 (42.5)	7.22	0.989		
Hb prior to treatment					
<10	22 (65.5)	7.45			
≥10	65 (34.5)	7.55	0.756		
Differentiation					
Good	9 (10.3)	7.55			
Moderate/Poor	78 (89.7)	7.45	0.377		
Mucinous Component					
Yes	48 (55.2)	7.16			
No	39 (44.8)	7.72	0.922		
Metastatic Disease					
Single metastatic site	69 (79.3)	7.55			
Multiple metastatic sites	18 (20.7)	6.96	0.946		
Site of metastasis					
Peritoneum	27 (31)	6.83			
Extra-peritoneal	60 (69)	7.65	0.792		
Isolated Peritoneal Metastasis					
Yes	21 (24.1)	7.42			
No	66 (75.9)	7.55	0.991		
Hepatic Metastasis					
Yes	42 (48.3)	7.98			
No	45 (51.7)	6.83	0.379		

ECOG: Eastern Cooperative Oncology Group; Hgb: hemoglobin; PFS: progression-free survival

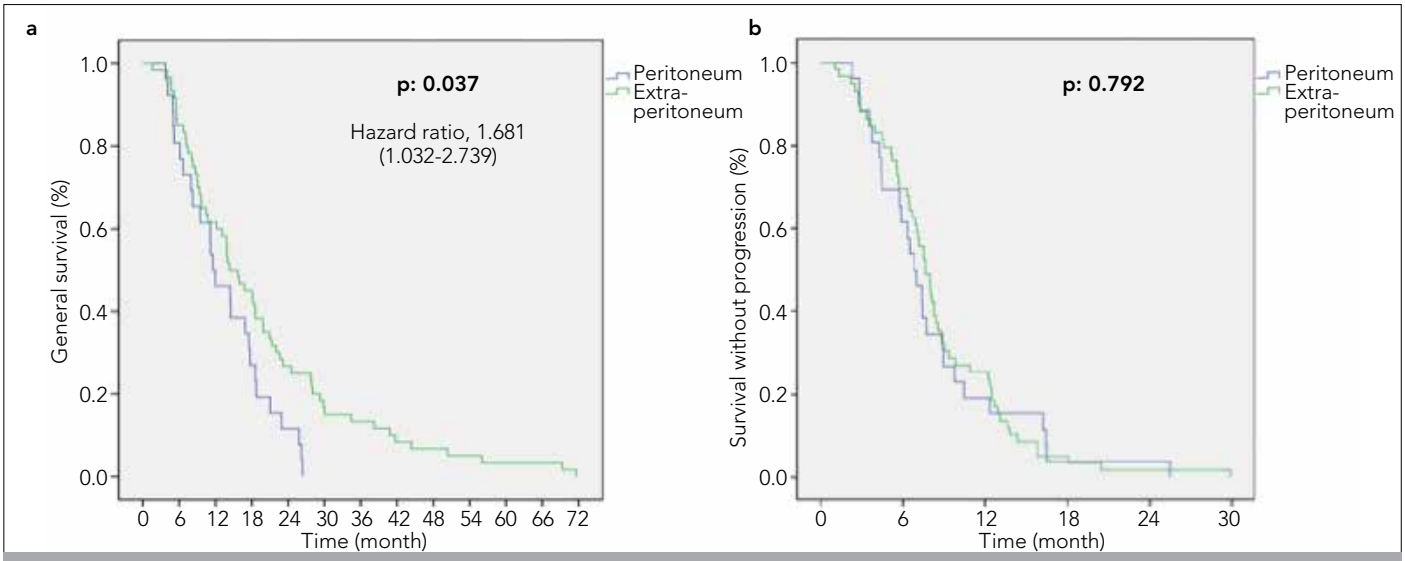

Figure 2. a, b. (a) The demonstration of general survivals of patients with and without peritoneal metastasis on the Kaplan-Meier curve, (b) The demonstration of survivals without progression in patients with and without peritoneal metastasis on the Kaplan-Meier curve,

Table 4. The association between patient characteristics and presence of peritoneal metastases

Characteristic	Peritoneal metastasis		p
	Yes (n=27)	No (n=60)	
Age, y (<65, ≥65)	21/6	45/15	0.779
Gender (m/f)	16/11	45/15	0.138
Differentiation (good/moderate/poor)	1/26	8/52	0.172
Mucin (present/absent)	19/8	29/31	0.056
Hepatic metastasis (present/absent)	0/27	42/18	<0.001
Multiple metastases (present/absent)	6/21	12/48	0.813
ECOG performance status (0-1/2-3)	17/10	40/20	0.737
Cigarette smoking (present/absent)	16/11	35/25	0.938
Hgb level prior to treatment (<10/≥10)	7/20	14/46	0.794

ECOG: Eastern Cooperative Oncology Group; m: male; f: female; Hgb: hemoglobin

As mentioned earlier, the overall median survival with systemic chemotherapy in metastatic gastric carcinoma patients is 8 to 14 months. In patients with peritoneal metastasis, the efficacy of chemotherapy is reduced, and the response rates may be decreased to 14% to 25% (9, 26, 27). This is due to the inability of the intravenously administered chemotherapeutic agents to adequately diffuse into the peritoneal tissue because of the peritoneal barrier (28).

Today, better survival rates may be achieved in selected cases using cytoreductive surgery and chemotherapy administered into the peritoneal cavity (29). The 5-year survival rates in patients with gastric cancer may rise up from 13% to 28% using these combined regimens. Also, surgical removal of the primary tumor may allow a median survival of up to 18 months in patients with isolated peritoneal metastasis (30-32).

In a study by Tan et al. (33) involving metastatic gastric cancer patients, the median overall survival with systemic chemotherapy was reported to be 10.9 months, while this figure was 7 months in the presence of peritoneal metastasis, and 8.9 months in the presence of isolated peritoneal metastasis. Again, Thomassen et al. (34) reported a median survival of 3.3 months and 4.6 months in patients with peritoneal metastasis and isolated peritoneal metastasis, respectively. In that same study, patients with peritoneal metastatic disease had a median overall survival of 7 months, and those with isolated peritoneal metastasis had a median overall survival of 8 months with chemotherapy.

In our study, peritoneal metastasis was associated with a shorter overall survival, while the progression-free survival was similar between patients with or without peritoneal metastasis. In the patient group with isolated peritoneal metastasis, overall and progression-free survival differences could not be found. This is probably due to the fact that variable treatments with different durations were administered to the patients after progression, with a potential effect on the overall survival. Furthermore, patients with isolated peritoneal metastasis comprised only 24.1% of the study population, which could confound statistical comparisons regarding overall and progression-free survival.

Patients with peritoneal metastasis had more frequent occurrence of mucinous component as compared to those without such metastases, although the difference was not significant (Table 4). This observation is in line with the previous reports suggesting an increased incidence of peritoneal metastases in mucinous adenocarcinomas (7, 23, 24).

In some previous studies, a better ECOG performance status (0-1) was not associated with better survival rates. In contrast, many other studies found a better overall and progression-free survival in metastatic gastric carcinoma patients with a better ECOG status (0-1) (35, 36). This may be explained on the basis of better treatment adherence and dose intensity as well as higher rates of patients receiving second-line chemotherapy (36, 37). In fact, overall and disease free survival were significantly longer among

patients with better ECOG status (0-1) in both the univariate and multivariate analyses. However, in the multivariate analysis, the significance remained only for the progression-free survival. From a clinical viewpoint, patients with a better performance status had a longer overall survival, although the difference was not statistically significant.

Peritoneal metastasis is a common finding associated with poor prognosis in patients with metastatic gastric carcinoma. In this study, the presence of peritoneal metastasis was an independent and significant predictor of poor overall survival among patients with gastric adenocarcinoma. Furthermore, patients with a better performance status prior to treatment had a significantly longer progression-free survival and a significantly better overall survival. In patients with peritoneal metastasis, several combination regimens (HIPEC, conventional intraperitoneal chemotherapy, primary tumor surgery, etc.) should also be considered in our armamentarium, as an addition to systemic chemotherapy alone. Further and larger prospective studies are warranted.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of University of Health Sciences Ankara Numune Training and Research Hospital.

Informed Consent: Due to the retrospective design of the study, informed consent was not taken.

Peer-review: Externally peer-reviewed.

Conflict of Interest: The author has no conflicts of interest to declare.

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REFERENCES

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA: a cancer journal for clinicians. 2011; 61: 69-90. [CrossRef]
2. Harewood GC. Treatment of gastric cancer. N England J Med 2006; 355: 1386. [CrossRef]
3. Taghavi S, Jayarajan SN, Davey A, Willis AI. Prognostic significance of signet ring gastric cancer. J Clin Oncol 2012; 30: 3493-8. [CrossRef]
4. Buzzoni R, Bajetta E, Di Bartolomeo M, Miceli R, Beretta E, Ferrario E, et al. Pathological features as predictors of recurrence after radical resection of gastric cancer. Br J Surg 2006; 93: 205-9. [CrossRef]
5. Bando E, Yonemura Y, Takeshita Y, Taniguchi K, Yasui T, Yoshimitsu Y, et al. Intraoperative lavage for cytological examination in 1,297 patients with gastric carcinoma. Am J Surg 1999; 178: 256-62. [CrossRef]
6. D'Angelica M, Gonen M, Brennan MF, Turnbull AD, Bains M, Karpeh MS. Patterns of initial recurrence in completely resected gastric adenocarcinoma. Ann Surg 2004; 240: 808-16. [CrossRef]
7. Ikeguchi M, Oka A, Tsujitani S, Maeta M, Kaibara N. Relationship between area of serosal invasion and intraperitoneal free cancer cells in patients with gastric cancer. Anticancer Res 1994; 14: 2131-4.
8. Huang J, Zhao Y, Xu Y, Zhu Y, Huang J, Liu Y, et al. Comparative effectiveness and safety between oxaliplatin-based and cisplatin-based therapy in advanced gastric cancer: A meta-analysis of randomized controlled trials. Oncotarget 2016; 7: 34824-31. [CrossRef]
9. Koizumi W, Narahara H, Hara T, Takagane A, Akiya T, Takagi M, et al. S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. Lancet Oncol 2008; 9: 215-21. [CrossRef]
10. Wagner AD, Unverzagt S, Grothe W, Kleber G, Grothey A, Haerting J, et al. Chemotherapy for advanced gastric cancer. Cochrane Database Syst Rev 2010; 17: CD004064. [CrossRef]
11. Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet 2010; 376: 687-97. [CrossRef]
12. Ajani JA, Moiseyenko VM, Tjulandin S, Majlis A, Constenla M, Boni C, et al. Clinical benefit with docetaxel plus fluorouracil and cisplatin compared with cisplatin and fluorouracil in a phase III trial of advanced gastric or gastroesophageal cancer adenocarcinoma: the V-325 Study Group. J Clin Oncol 2007; 25: 3205-9. [CrossRef]
13. Ross P, Nicolson M, Cunningham D, Valle J, Seymour M, Harper P, et al. Prospective randomized trial comparing mitomycin, cisplatin, and protracted venous-infusion fluorouracil (PVI 5-FU) With epirubicin, cisplatin, and PVI 5-FU in advanced esophagogastric cancer. J Clin Oncol 2002; 20: 1996-2004. [CrossRef]
14. Webb A, Cunningham D, Scarffe JH, Harper P, Norman A, Joffe JK, et al. Randomized trial comparing epirubicin, cisplatin, and fluorouracil versus fluorouracil, doxorubicin, and methotrexate in advanced esophagogastric cancer. J Clin Oncol 1997; 15: 261-7. [CrossRef]
15. Glehen O, Gilly FN, Arvieux C, Cotte E, Boutitie F, Mansvelt B, et al. Peritoneal carcinomatosis from gastric cancer: a multi-institutional study of 159 patients treated by cytoreductive surgery combined with perioperative intraperitoneal chemotherapy. Ann Surg Oncol 2010; 17: 2370-7. [CrossRef]
16. Yang XJ, Huang CQ, Suo T, Mei LJ, Yang GL, Cheng FL, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy improves survival of patients with peritoneal carcinomatosis from gastric cancer: final results of a phase III randomized clinical trial. Ann Surg Oncol 2011; 18: 1575-81. [CrossRef]
17. Glockzin G, Piso P. Current status and future directions in gastric cancer with peritoneal dissemination. Surg Oncol Clin N Am 2012; 21: 625-33. [CrossRef]
18. Yonemura Y, Bandou E, Kawamura T, Endou Y, Sasaki T. Quantitative prognostic indicators of peritoneal dissemination of gastric cancer. Eur J Surg Oncol 2006; 32: 602-6. [CrossRef]
19. Yonemura Y, Fujimura T, Fushida S, Fujita H, Bando E, Taniguchi K, et al. Peritonectomy as a treatment modality for patients with peritoneal dissemination from gastric cancer. Multimodality therapy for gastric cancer: Springer; 1999. p. 71-80.
20. Karve S, Lorenzo M, Liepa AM, Hess LM, Kaye JA, Calingaert B. Treatment Patterns, Costs, and Survival among Medicare-Enrolled Elderly Patients Diagnosed with Advanced Stage Gastric Cancer: Analysis of a Linked Population-Based Cancer Registry and Administrative Claims Database. J Gastric Cancer 2015; 15: 87-104. [CrossRef]
21. Muro K, Cho JY, Bodoky G, Goswami C, Chao Y, Dos Santos LV, et al. Age does not influence efficacy of ramucirumab in advanced gastric cancer: subgroup analyses of REGARD and RAINBOW. J Gastroenterology hepatol 2017 Sep 29. doi: 10.1111/jgh.14007. [Epub ahead of print] [CrossRef]
22. Pant S, Patel M, Kurkjian C, Hemphill B, Flores M, Thompson D, et al. A Phase II Study of the c-Met Inhibitor Tivantinib in Combination with FOLFOX for the Treatment of Patients with Previously Untreated Metastatic Adenocarcinoma of the Distal Esophagus, Gastroesophageal Junction, or Stomach. Cancer Invest 2017; 35: 463-72. [CrossRef]
23. Chu DZ, Lang NP, Thompson C, Osteen PK, Westbrook KC. Peritoneal carcinomatosis in nongynecologic malignancy. A prospective study of prognostic factors. Cancer 1989; 63: 364-7. [CrossRef]

24. Sadeghi B, Arvieux C, Glehen O, Beaujard AC, Rivoire M, Baulieux J, et al. Peritoneal carcinomatosis from non-gynecologic malignancies: results of the EVOCAPE 1 multicentric prospective study. Cancer 2000 ; 88: 358-63. [CrossRef]
25. Ceelen WP, Bracke ME. Peritoneal minimal residual disease in colorectal cancer: mechanisms, prevention, and treatment. Lancet Oncol 2009; 10: 72-9. [CrossRef]
26. Bilici A. Treatment options in patients with metastatic gastric cancer: current status and future perspectives. World J Gastroenterol 2014; 20: 3905-15. [CrossRef]
27. Van Cutsem E, Moiseyenko VM, Tjulandin S, Majlis A, Constenla M, Boni C, et al. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. J Clin Oncol 2006; 24: 4991-7. [CrossRef]
28. Jacquet P, Sugarbaker PH. Peritoneal-plasma barrier. Cancer Treat Res 1996; 82: 53-63. [CrossRef]
29. Gill RS, Al-Adra DP, Nagendran J, Campbell S, Shi X, Haase E, et al. Treatment of gastric cancer with peritoneal carcinomatosis by cytoreductive surgery and HIPEC: a systematic review of survival, mortality, and morbidity. J Surg Oncol 2011; 104: 692-8. [CrossRef]
30. Glehen O, Schreiber V, Cotte E, Sayag-Beaujard AC, Osinsky D, Freyer G, et al. Cytoreductive surgery and intraperitoneal chemohyperthermia for peritoneal carcinomatosis arising from gastric cancer. Arch Surg 2004; 139: 20-6. [CrossRef]
31. Rossi CR, Pilati P, Mocellin S, Foletto M, Ori C, Innocente F, et al. Hyperthermic intraperitoneal intraoperative chemotherapy for peritoneal carcinomatosis arising from gastric adenocarcinoma. Suppl Tumori 2003; 2: S54-7.
32. Yonemura Y, Fujimura T, Nishimura G, FallaR, Sawa T, Katayama K, et al. Effects of intraoperative chemohyperthermia in patients with gastric cancer with peritoneal dissemination. Surgery 1996; 119: 437-44. [CrossRef]
33. Tan HL, Chia CS, Tan GH, Choo SP, Tai DW, Chua CW, et al. Gastric peritoneal carcinomatosis - a retrospective review. World J Gastrointest Oncol 2017; 9: 121-8. [CrossRef]
34. Thomassen I, van Gestel YR, van Ramshorst B, Luyer MD, Bosscha K, Nienhuijs SW, et al. Peritoneal carcinomatosis of gastric origin: a population-based study on incidence, survival and risk factors. Int J Cancer 2014; 134: 622-8. [CrossRef]
35. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5: 649-55. [CrossRef]
36. Shitara K, Muro K, Matsuo K, Ura T, Takahari D, Yokota T, et al. Chemotherapy for patients with advanced gastric cancer with performance status 2. Gastrointest Cancer Res 2009; 3: 220-4.
37. Boku N, Yamamoto S, Fukuda H, Shirao K, Doi T, Sawaki A, et al. Fluorouracil versus combination of irinotecan plus cisplatin versus S-1 in metastatic gastric cancer: a randomised phase 3 study. Lancet Oncol 2009; 10: 1063-9. [CrossRef]