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Research Article

The Effect of MCV on Prognosis in Patients with Gastric Cancer and its Relationship with C-ERBB2 Positivity

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Abstract

Objectives: Many factors considered to influence prognosis in gastric cancers have been investigated. In this study, we aimed to present the demographic characteristics of gastric cancer patients followed in the medical oncology unit, to investigate the effects on prognosis of MCV values measured at diagnosis, after surgery, and after chemotherapy, and to evaluate the effect on prognosis among C-ERB B2–positive patients.

Methods: 248 patients who presented to and were followed by the İstanbul Eğitim ve Araştırma Hastanesi Medical Oncology Unit between 2010 and 2015 were examined retrospectively using the hospital automation system and the oncology unit file archive.

Results: A total of 248 patients diagnosed with gastric cancer (169 male, 79 female) were included. Among 50 stage 4 patients in whom C-ERB B2 was assessed, 8% (n=4) were 2+, 34% (n=17) were 3+, and 58% (n=29) were negative. Overall survival rates were 62.7% at 1 year, 44.6% at 2 years, 37.7% at 3 years, 30.7% at 4 years, and 28.8% at 5 years. On quantitative analysis of MCV values at diagnosis and after treatment, having MCV > 100 fL at any time point was not statistically significant in terms of prognosis. Likewise, a post-/pre-treatment MCV ratio >1.1 was not statistically significant. These parameters were also evaluated in the C-ERB B2–positive population and no significant difference was detected.

Conclusion: Although changes in MCV values did not show a significant effect on prognosis, it was considered that increasing the patient population might yield statistical significance.

Keywords: C-ERBB2, Gastric Cancer, MCV

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Cancer is the second most common cause of death in Türkiye after cardiovascular diseases.

Gastric cancer ranks fifth worldwide in cancer incidence and third among causes of cancer-related mortality. It is estimated that approximately 9,000 new gastric cancer cases occur annually in Türkiye. The incidence is about five times higher than in European countries and increases toward the eastern provinces, with the highest rates reported in Diyarbakır and Van. According to hospital registries and the Ministry of Health Cancer Control Department, gastric carcinoma is the fifth most common cancer in men and the sixth in women.[1] The average age at diagnosis in Türkiye is 64 years, with the youngest reported at 19 and the oldest at 85.[2]

The male-to-female ratio in gastric cancer is 2:1. The disease is rare before the age of 40, and its incidence increas-

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es with age, peaking in the sixth decade. Since the 1930s, the incidence of gastric cancer has declined in the United States and now ranks around the 15th most common cancer.[3] Although the precise reason is unclear, this decline has been attributed to planned public health services, advances in cancer screening, improved diet, reduced smoking, increased vitamin C intake, and active control of *Helicobacter pylori* infection.[4] Despite this, gastric cancer remains difficult to treat due to late diagnosis; even patients eligible for curative surgery with favorable prognostic indicators are often lost due to recurrence. Nevertheless, the use of postoperative chemoradiotherapy and preoperative chemotherapy has improved survival.[5,6]

The anatomic distribution of gastric cancer has shifted over the years toward the proximal stomach. Over the past two decades, especially in patients under 40 years of age, there has been a sharp increase in proximal gastric cancers, from approximately 10% to 30%. This may reflect differences in risk factors between proximal and distal gastric cancers. Despite the decline in the United States, the 5-year survival rate remains around 10–20%.

While the effects of some factors on prognosis in gastric cancer have been consistently observed, results vary among studies. Factors studied include gender, age, tumor location, tumor diameter, macroscopic type, histologic grade, stage, metastatic lymph node status, tumor markers (CEA, CA 19-9), preoperative albumin, perioperative hemogram parameters, type of operation, lymph node dissection (D1, D2), chemotherapy (yes/no), and radiotherapy in resected gastric cancer.

In this study, we retrospectively evaluated proposed prognostic factors—particularly elevations and changes in MCV—and investigated their effects on survival.

Methods

This retrospective study was approved by the Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (approval number: 2016/04-07, approval date: 25 April 2016). The study was conducted in accordance with the Declaration of Helsinki.

In our thesis, data for 248 patients who presented with a diagnosis of gastric cancer to the Department of Medical Oncology, Health Sciences, Istanbul Training and Research Hospital Outpatient Clinic between January 2010 and December 2013 were obtained retrospectively from the oncology unit file archive and the hospital automation system. Variables potentially associated with survival—age, gender, type of operation, disease stage (WHO 2010), histologic type, C-ERB B2 status, receipt of systemic adjuvant therapy, tumor markers such as CA 19-9 and CEA, MCV at diagnosis, and the ratio of post-treatment MCV to diagnostic MCV—were examined. CEA and CA 19-9 were measured using the DxI 800 Access (Beckman Coulter) analyzer, and hemogram parameters using the Mindray BC-6800 device. We also evaluated the effects on survival of these prognostic factors within the subgroup in whom C-ERB B2 was tested, comparing C-ERB B2–positive and –negative patients. At last follow-up, patients were categorized as disease-free, with disease, or deceased; deaths were verified through the national death notification system.

Overall survival (OS) was defined as the time from diagnosis to death, or to the date patient information was last updated for those alive. Disease-free survival (DFS) was defined as the time from diagnosis to local recurrence and/or development of metastasis.

For statistical analysis**,** SPSS 15.0 for Windows was used. Descriptive statistics were presented as number and percentage for categorical variables, and mean, standard deviation, minimum, and maximum for numerical variables. Comparisons between two independent groups were performed using the Student's t-test when normal distribution assumptions were met and the Mann–Whitney U test when they were not. Ratios of categorical variables between groups were tested with the chi-square test; when assumptions were not met, the Monte Carlo simulation method was applied. Survival analyses were performed using the Kaplan–Meier method. A statistical alpha significance level of $p<0.05$ was accepted.

Results

General Patient Characteristics

A total of 248 patients diagnosed with gastric cancer were included: 169 male and 79 female, with a mean age of 57.7±10.8 (range 28–80) years. According to TNM staging, 5.7% (n=14) were stage 1a, 3.6% (n=9) stage 1b, 8.5% (n=21) stage 2a, 9.7% (n=24) stage 2b, 10.1% (n=25) stage 3a, 9.7% (n=24) stage 3b, 15.8% (n=39) stage 3c, and 36.8% (n=91) stage 4. By histologic subtype, 71.9% (n=161) were adenocarcinoma, 3.1% (n=7) GIST, 4% (n=9) neuroendocrine tumor, and 21% (n=47) signet-ring cell carcinoma. Of 248 patients, 36.3% (n=90) were inoperable, 48.4% (n=120) underwent total gastrectomy, 14.5% (n=36) subtotal gastrectomy, and 0.4% distal esophagectomy with proximal gastrectomy.

Chemotherapy was administered to 75.8% (n=188). Regimens included MAYO (fluorouracil, folinic acid) in 78 patients (41.5%), DCF (docetaxel, cisplatin, fluorouracil) in 58 (30.9%), ECF (epirubicin, cisplatin, fluorouracil) in 35 (18.6%), cisplatin-capecitabine in 6 (3.2%), and other protocols (cisplatin-etoposide, DC) in 4 (3.3%). The duration of

chemotherapy varied between 1 and 6 months depending on tolerability and survival (Table 1).

Tumor Location

Tumor localization could be evaluated in 55% (n=135) of patients: antrum 51.9% (n=70), pylorus 5.9% (n=8), lesser curvature 7.4% (n=10), greater curvature 3% (n=4), corpus 5.2% (n=7), fundus 5.9% (n=8), cardia 16.3% (n=22), gastroesophageal junction 2.2% (n=3), diffuse/entire stomach 4.4% (n=6), posterior wall 0.7% (n=1).

Table 1. Demographic and clinical characteristics

Variable	Mean ± SD (Min–Max) / n (%)
Age	57.7±10.8 (28–80)
Sex	
Male	169 (68.1)
Female	79 (31.9)
Stage (new staging system)	
IA	14 (5.7)
IB	9 (3.6)
IIA	21 (8.5)
IIB	24 (9.7)
IIIA	25 (10.1)
IIIB	24 (9.7)
IIIC	39 (15.8)
IV	91 (36.8)
Operability / Surgical type	
Inoperable	90 (36.3)
Total gastrectomy	120 (48.4)
Subtotal gastrectomy	36 (14.5)
Distal esophagectomy + proximal gastrectomy	1 (0.4)
Histologic subtype	
Adenocarcinoma	161 (71.9)
GIST	7 (3.1)
Neuroendocrine tumor	9 (4.0)
Signet-ring cell adenocarcinoma	47 (21.0)
Chemotherapy administered	188 (75.8)
Chemotherapy regimen	
Cisplatin–Etoposide	4 (2.1)
Cisplatin–Capecitabine	6 (3.2)
DCF (Docetaxel–Cisplatin–5FU)	58 (30.9)
Supportive	5 (2.7)
ECF (Epirubicin–Cisplatin–5FU)	35 (18.6)
FUF(A) (5FU–Leucovorin)	78 (41.5)
Herceptin–Cisplatin	1 (0.5)
Imatinib	1 (0.5)

C-ERBB2 / FISH

C-ERBB2 IHC staining was performed in 50 patients: 34% (n=17) were 3+, 8% (n=4) were 2+, and 58% (n=29) were negative. FISH was performed in 43 of these patients: 37.2% (n=16) were positive and 62.8% (n=27) negative. FISH was not performed in 4 C-ERB B2–negative patients, 1 patient with C-ERB B2 2(+), and 2 patients with C-ERB B2 3(+). All patients with C-ERB B2 3(+) who underwent FISH were FISH-positive; among the four C-ERB B2 2(+) patients, one was FISH(+), two FISH(–), and one not tested by FISH.

Tumor Markers

CEA was measured in 174 patients. Mean CEA was 26.3±124.2 (0–1083); 23.6% (n=41) had CEA > 5 and 76.4% (n=133) ≤5. CA 19-9 was 890.1±7883.2 (0.6–102,255); 27.6% (n=48) had CA 19-9 > 37 and 72.4% (n=126) ≤37 (Table 2).

MCV Values

At diagnosis, the mean MCV was 82.1±10.0 fL (20.9–105.3); 97.9% (n=233) had MCV<99 and 2.1% (n=5) had MCV>99. After treatment, the mean MCV was 89.8±9.4 fL (55.1–113.8); 87.5% (n=189) had MCV<99 and 12.5% (n=27) had MCV >99. A 10% increase in MCV after treatment (post/diagnosis ratio >1.1) was evaluated as a separate parameter for its potential prognostic value: 60.2% (n=127) had such an increase, while 39.8% (n=84) did not (Table 3).

Patient Status and Survival Rates

Final status was available for all 248 patients: 39.5% (n=98) disease-free, 2.5% (n=6) with disease, and 58% (n=144) deceased.

Overall survival rates were 62.7% at 1 year, 44.6% at 2 years, 37.7% at 3 years, 30.7% at 4 years, and 28.8% at 5 years. Median estimated survival was 20.3 months (SE 3.0; 95% CI 14.5–26.2) (Table 4a, b).

Table 2. CEA and CA 19-9 levels

Variable	Mean ± SD (Min–Max)/n (%)
CEA (Mean ± SD, Min–Max)	26.3±124.2 (0–1083)
CEA n (%)	
>5	41 (23.6)
≤5	133 (76.4)
CA 19-9 (Mean ± SD, Min–Max)	890.1±7883.2 (0.6–102255)
CA 19-9 n (%)	
>37	48 (27.6)
≤37	126 (72.4)

Table 3. MCV values at diagnosis and after treatment

Variable	Mean ± SD (Min–Max) / n (%)
MCV at diagnosis (Mean ± SD, Min–Max)	82.1±10.0 (20.9–105.3)
MCV at Diagnosis n (%)	
≤99	233 (97.9)
>99	5 (2.1)
MCV After treatment (Mean ± SD, Min–Max)	89.8±9.4 (55.1–113.8)
MCV after treatment n (%)	
≤99	189 (87.5)
>99	27 (12.5)
Post/Diagnosis MCV ratio (Mean ± SD, Min–Max)	
Post/Diagnosis MCV ratio n (%)	
≤1.1	127 (60.2)
>1.1	84 (39.8)

Table 4a. Survival outcomes

Variable	Median	SE	95% CI
Estimated survival time (months)	20.3	3.0	14.5–26.2

Table 4b. Cumulative survival rates

Time	Survival (%)
6 months	79.2
1 year	62.7
2 years	44.6
3 years	37.7
5 years	30.7
6 years	28.8

Survival by Stage

Among patients alive at last follow-up, stage distribution was: 1a 13.5% (n=14), 1b 6.7% (n=7), 2a 11.5% (n=12), 2b 11.5% (n=12), 3a 12.5% (n=13), 3b 8.7% (n=9), 3c 19.2% (n=20), and 4 16.3% (n=17). Among the deceased: 1a 0%, 1b 1.4% (n=2), 2a 6.3% (n=9), 2b 8.4% (n=12), 3a 8.4% (n=12), 3b 10.5% (n=15), 3c 13.3% (n=19), and 4 51.7% (n=74). Stage distributions differed significantly between groups (p<0.001).

Other Survival Comparisons

Survival differed significantly by histologic subtype (adenocarcinoma, GIST, signet-ring cell carcinoma, neuroendocrine tumor) (p<0.001). Survival differed significantly by tumor stage (Fig. 1).

By operability, subtotal gastrectomy was associated with significantly different survival (p<0.001 across groups). Receipt of chemotherapy was also associated with survival (p=0.019).

By C-ERB B2 status, among 21 positive patients 42.8% (n=9) were alive and 57.2% (n=12) deceased; among 29 negative patients 44.8% (n=13) were alive and 55.2% (n=16) deceased—no significant difference (p=0.890).

For CEA, among 174 tested patients, 76 were alive; of these, 13.2% (n=10) had high CEA and 86.8% (n=66) low CEA. Among 98 deceased patients, 31.6% (n=31) had high CEA and 68.4% (n=67) low CEA; elevated CEA indicated higher mortality (p<0.004).

For CA 19-9, among 174 tested patients, 76 were alive; of these, 14.5% (n=11) had high CA 19-9 and 85.5% (n=65) low. Among 98 deceased patients, 37.8% (n=37) had high CA 19-9 and 62.2% (n=61) low; elevated CA 19-9 indicated higher mortality (p<0.001) (Table 5a,b).

No significant associations with mortality were found for diagnostic MCV, post-treatment MCV, or a post/diagnosis MCV ratio >1.1 (Table 6).

In the subgroup with C-ERB B2 testing, overall survival did not differ by C-ERB B2 status (p=0.859) (Fig. 2).

Among patients with C-ERB B2 testing, no significant differences in survival were observed according to post/diagnosis MCV increase (10%) within C-ERB B2–positive or –negative groups.

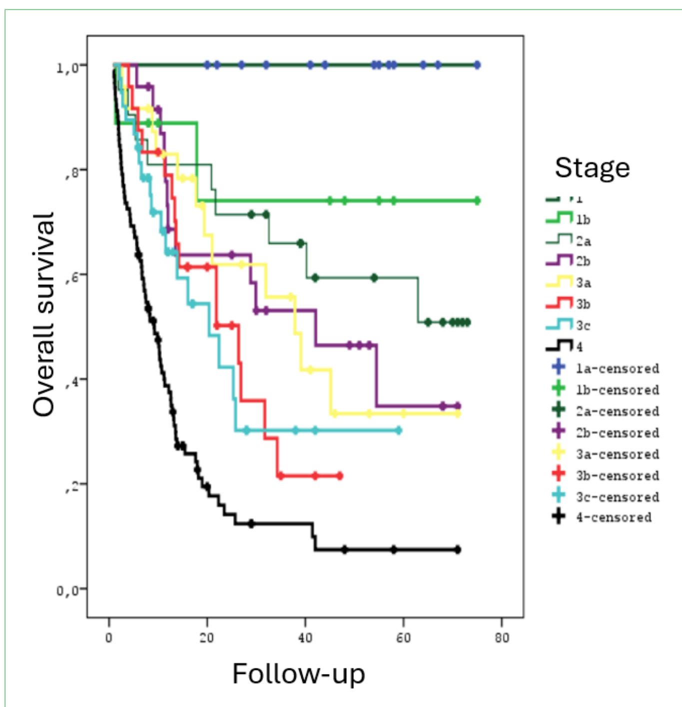

Figure 1. Overall survival by stage.

Table 5a. Survival analysis by CEA and CA 19-9 levels

Variable	Alive (Mean ± SD or n (%))	Exitus (Mean ± SD or n (%))	p
CEA (Mean ± SD)	3.6±8.1	43.9±163.5	0.006
>5	10 (13.2)	31 (31.6)	0.004
≤5	66 (86.8)	67 (68.4)	

Table 5b. CA 19-9 levels and survival

Variable	Alive (Mean ± SD or n (%))	Exitus (Mean ± SD or n (%))	p
CA 19-9 (Mean ± SD)	45.7±133.7	1544.8±10480.0	0.001
>37	11 (14.5)	37 (37.8)	0.001
≤37	65 (85.5)	61 (62.2)	

Table 6. Survival analysis by MCV levels at diagnosis, after treatment, and post/diagnosis ratio

Variable	Alive (Mean ± SD or n (%))	Exitus (Mean ± SD or n (%))	p
MCV at Diagnosis (Mean ± SD)	82.6±8.7	81.7±10.9	0.770
≤99	100 (98.0)	133 (97.8)	1.000
>99	2 (2.0)	3 (2.2)	
MCV After Chemotherapy (Mean ± SD)	90.8±8.5	89.2±10.0	0.208
≤99	76 (86.4)	113 (88.3)	0.675
>99	12 (13.6)	15 (11.7)	
Post/Diagnosis MCV ratio (Mean ± SD)	1.11±0.12	1.12±0.26	0.359
≤1.1	49 (56.3)	78 (62.9)	0.336
>1.1	38 (43.7)	46 (37.1)	

Discussion

Although the incidence of gastric cancer continues to decline today, it remains the third leading cause of cancer-related death worldwide. The disease is often detected at advanced stages due to late symptoms and diagnosis, minimizing the chance for curative surgery. In countries with high incidence such as Japan, screening programs have increased early-stage detection and improved curative treatment success.

Gastric cancer occurs more frequently in men than in women worldwide—fifth most common in men and sixth in women—and ranks third among cancer-related deaths. In our cohort, 31.9% were women and 68.1% men, consistent with the literature. The average age for gastric cancer in Türkiye is 56; its frequency increases after age 60. Our patients' mean age was 57.7±10.8.[7,8]

By tumor site, 51.9% were antral, 5.9% pyloric, 7.4% lesser curvature, 3% greater curvature, 5.2% corpus, 5.9% fundus, 16.3% cardia, 2.2% gastroesophageal junction, 4.4% diffuse, and 0.7% posterior wall. Histologically, 71.9% were adenocarcinoma, 3.1% GIST, 4% neuroendocrine tumor, and 21% signet-ring cell carcinoma. TNM distribution was: stage 1a 5.7%, 1b 3.6%, 2a 8.5%, 2b 9.7%, 3a 10.1%, 3b 9.7%, 3c 15.8%, and 4 36.8%. Compared with the literature (Table 4), proportions up to stage 3B were almost identical; our stage 3C was slightly higher and stage 4 slightly lower.

Despite short survival, many prognostic factors relate to outcomes after treatment in gastric cancer. The most important are stage and lymph node metastasis; others include gender, age, tumor location and size, histologic grade, perineural invasion, vascular invasion, intestinal metaplasia, preoperative tumor markers (CEA, CA 19-9), preoperative albumin, received treatments, and hemogram parameters. Knowing prognosis after treatment is important not only for postoperative survival assessment but also for determining whether closer follow-up and earlier treatment at recurrence are warranted.

Links between immune system–cancer progression and hematologic parameters—leukocyte and platelet counts, MPV, and MCV—have been studied, demonstrating prognostic importance.[9-11] The neutrophil-to-lymphocyte ratio (NLR) has been shown as a marker of systemic inflammatory response; similarly, the preoperative platelet-to-lymphocyte ratio is an important prognostic factor in pancreatic

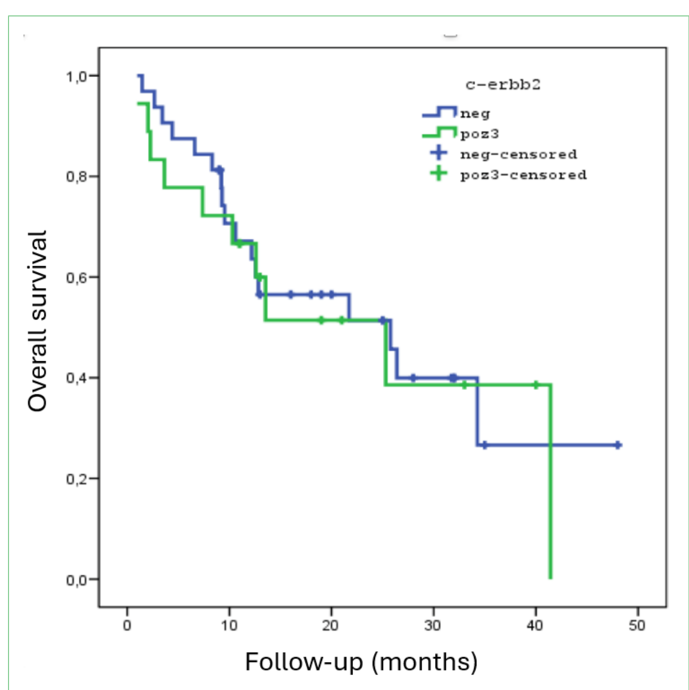

Figure 2. Overall survival by C-ERBB2 status.

cancer.[12] NLR and thrombocytosis have also been reported as prognostic factors in cancer patients.[13,14]

High MCV levels occur in alcohol users and in folate or vitamin B12 deficiency. Elevated MCV is more common among alcohol consumers with inactive aldehyde dehydrogenase-2 deficiency; alcohol use predisposes to esophageal squamous cell carcinoma. In May 2013, Yu-Zhen Zhang et al. hypothesized a link between esophageal squamous cell carcinoma and high MCV, evaluated preoperative MCV in 298 patients via ROC analysis (cut-off 95.6 fL), and concluded that higher preoperative MCV correlated with worse overall survival. Another reason to suspect an association between MCV and prognosis is that macrocytosis may indicate malnutrition, a negative prognostic factor. In gastric cancer, dysphagia may reduce oral intake and lower electrolyte, glucose, and amino acid concentrations, reducing the crystalloid osmotic pressure—the major regulator of erythrocyte volume—and thus causing erythrocyte enlargement.[15]

Jung et al.[16] evaluated MCV in "Changes in the mean corpuscular volume after capecitabine treatment are associated with clinical response and survival in patients with advanced gastric cancer. Capecitabine is known to increase MCV. Eighty-nine patients receiving first-line capecitabine+cisplatin (±epirubicin) had MCV measured on day 1 and week 3; an increase >10 fL was defined as macrocytosis. Day-1 macrocytosis was present in ~90% and week-3 macrocytosis in 42%. The study assessed the relationship between macrocytosis and response; patients received chemotherapy every 3 weeks absent toxicity or progression, and were evaluated by abdominopelvic CT or baseline imaging after two cycles. Analyses considered age, sex, ECOG, treatment arm (±epirubicin), peritoneal dissemination, baseline hemoglobin, number of cycles, and cumulative capecitabine dose. Macrocytosis was associated with greater treatment efficacy and favorable overall and progression-free survival.

Based on these data, we investigated whether elevated MCV at diagnosis is a negative prognostic factor and whether post-chemotherapy MCV elevation might be a positive prognostic factor. We also evaluated general demographics such as age, sex, stage, tumor site, CA 19-9, CEA, and C-ERBB2 positivity.

Our survival rates were 62.7% at 1 year, 44.6% at 2 years, 37.7% at 3 years, 30.7% at 4 years, and 28.8% at 5 years. By stage, survival was significantly higher in stages 1a ($p<0.001$) and 1b, and—as expected—declined with increasing stage thereafter. Another survival marker was elevated CA 19-9: among 174 tested patients, 14.5% of survivors had high CA 19-9 versus 37.8% of deceased patients ($p<0.001$). No significant associations with mortality were observed for diagnostic MCV, post-treatment MCV, or a post/diagnosis MCV ratio >1.1.

At diagnosis, only five patients had MCV above our laboratory cut-off of 99 fL; the remaining 243 were below 99 fL, suggesting that a ROC-based cut-off might be explored in a future analysis. Among 248 patients with diagnostic MCV, post-treatment MCV was available for 211; 84 (39.8%) had a ≥10% increase (post/diagnosis >1.1) and 127 (60.2%) did not. A 10% increase in MCV was not associated with mortality (Table 6).

We also examined the frequency of C-ERB B2 positivity and its relationship with MCV. In Western countries, because many gastric cancer patients are diagnosed at unresectable stages, systemic chemotherapy is the mainstay to improve survival and quality of life. Objective response with combination regimens can reach 30–60%. Platinum agents, fluoropyrimidines, anthracyclines, taxanes, and irinotecan are used for this purpose. Although many regimens have been tested in randomized trials, a standard protocol has not been agreed upon. Given the poor survival despite chemotherapy, new treatments are being sought. Understanding molecular alterations has enabled targeted therapies aimed at improving survival. HER-2, a transmembrane tyrosine kinase receptor of the EGFR family encoded on chromosome 17q21, activates signaling that influences proliferation, apoptosis, adhesion, migration, and differentiation. Acting as an oncogene, high-level amplification leads to protein overexpression, conferring a survival advantage to malignant cells. HER-2 is positive in 10–34% of invasive breast cancers and is associated with poor prognosis and inferior response to chemotherapy and endocrine therapy. HER-2 overexpression has also been observed in colon, bladder, ovary, endometrium, lung, cervix, head-neck, esophagus, and gastric cancers. Trastuzumab, a monoclonal antibody binding the extracellular domain of HER-2, improves survival in HER-2–positive breast cancer.

TNM classification is the most important prognostic factor in gastric cancer; however, because prognosis varies among patients with the same stage, additional parameters are needed to delineate biological subgroups. HER-2 overexpression in gastric cancer was first described immunohistochemically in 1986; in 1990, series reported HER-2 positivity rates of 9–38%. More recent studies, using IHC (HercepTest) and FISH amplification, reported similar frequencies. In our study, C-ERB B2 IHC was performed in 50 patients: 34% 3+, 8% 2+, and 58% negative; FISH was performed in 43, with 37.2% positive. These data indicate a higher frequency of HER-2 expression in our population.

The prognostic significance of HER-2 in gastric and gastroesophageal junction cancers is controversial. Early studies

found no association with prognosis.[17,18] Some authors proposed HER-2 expression as a direct adverse prognostic factor; a retrospective study of 108 patients associated HER-2 with poor 10-year survival.[19] Nakajima et al.[20] reported HER-2 expression as the worst prognostic variable after nodal status. In ToGA, HER-2–positive patients were randomized to chemotherapy (capecitabine+cisplatin or fluorouracil+cisplatin) vs chemotherapy+trastuzumab: OS was 13.8 months with trastuzumab vs 11.1 months with chemotherapy alone.[21] The Lancet discussion noted the 11.1-month OS in the chemo-only arm was longer than expected; although other studies linked HER-2 with aggressive disease, ToGA suggested HER-2 expression might not indicate poor prognosis—warranting further investigation. Jørgensen and colleagues performed a 2012 systematic analysis of studies from 1986 to August 2011 assessing HER-2 expression and survival (overall, disease-free, or stage) in cohorts with ≥100 patients and IHC/FISH data.[22] Among 12,749 patients, most articles (71%) indicated that HER-2 positivity correlated with survival; while not as definitive as in breast cancer, HER-2 overexpression appeared to be a negative prognostic factor.

Conclusion

In our study, among 50 patients tested for C-ERB B2, 18 were positive and 32 negative. C-ERB B2 positivity had neither a favorable nor unfavorable effect on overall survival (Table 5). We also examined whether post-treatment MCV increase influenced prognosis within the C-ERB B2–positive subgroup; no significant differences in survival rate or time were detected between C-ERB B2–positive and –negative groups according to MCV increase (Table 6).

Limitations of our study include its retrospective design; variability in surgical and chemotherapy standards because some patients presented from other centers; incomplete follow-up related to economic constraints; and lack of systematic assessment of BMI, nutritional status, and hypovitaminoses (B1, B6, B12). Expanding the patient population and conducting prospective follow-up may yield more robust conclusions.

Disclosures

Ethics Committee Approval: This retrospective study was approved by the Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (approval number: 2016/04-07, approval date: 25 April 2016).

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