



Prognostic Value of Pretreatment HER2 Status in Gastric Cancer Patients Treated with Postoperative Chemoradiotherapy

Ozan Cem GÜLER,¹ Mustafa KANDAZ,¹ Zümrüt BAHAT,¹ Emine CANYILMAZ,¹ Emine ÇAKIR,² Adnan YÖNEY,¹

¹Department of Radiation Oncology, Karadeniz Technical University, Trabzon-Turkey

²Department of Pathology, Karadeniz Technical University, Trabzon-Turkey

OBJECTIVE

Our purpose was to evaluate the prognostic or predictive importance of HER2 status in gastric cancer patients treated with postoperative chemoradiotherapy.

METHODS

We retrospectively analyzed the records of 49 gastric cancer patients treated with curative intent between April 2012 and January 2017; we also assessed the impact of HER2 status on prognosis and treatment outcomes.

RESULTS

During a median follow-up period of 14.6 months (range, 4.0–56.97 months), two patients (4%) had local recurrence and 21 patients (43%) developed distant metastasis. We found no statistically significant difference in metastasis frequency rates between HER2 negative (–) and positive (+) patients. The median overall survival (OS) and disease-free survival (DFS) for the whole group were 24.9 and 24.2 months, respectively. Although there was no significant difference in OS and DFS according to HER2 status, there was a negative trend in OS ($p=0.451$) and DFS ($p=0.633$) in HER2 (+) patients.

CONCLUSION

Although our study did not demonstrate any statistically significant importance of HER2 status in gastric cancer patients treated with postoperative chemoradiotherapy, the median OS of 13 months in HER2 (+) patients and 24.9 months for HER2 (–) patients warranted randomized trials with larger cohorts.

Keywords: Chemoradiotherapy; gastric cancer; HER2; radiotherapy.

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Introduction

Gastric cancer is the third most common cause of cancer-related mortality worldwide.[1] Although the main curative treatment strategy for this disease is surgery, adjuvant treatment is essential because of the risk of local recurrence.[2,3] Adjuvant treatment options may

vary with countries. Postoperative chemoradiotherapy is widely used in the US based on data from the Intergroup (INT)-0116 study, whereas only postoperative chemotherapy regimens (particularly in patients with D2 dissection) are common in Japan and Southern Europe.[4,5] In Europe, neoadjuvant chemotherapy is used more frequently.[6] Radiotherapy has potential

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Dr. Ozan Cem GÜLER
Karadeniz Teknik Üniversitesi,
Radyasyon Onkolojisi Bilim Dalı,
Trabzon-Turkey
E-mail: ocguler@gmail.com

to treat metastatic diseases, and it is used for palliative treatment. In Turkey, the most common treatment is postoperative chemoradiotherapy.

Targeted therapies are commonly used for other cancer types such as breast cancer.[7,8] Its application in the treatment of gastric cancer is still investigated. Approximately 7%–22% of gastric cancers overexpress human epidermal growth factor receptor 2 (HER2). Data from the INT-0116 trial suggested that the benefit from postoperative chemoradiotherapy may have been limited to the 90% of patients without HER2 amplification. They concluded that overexpression of HER2 may be associated with radiation resistance [4]. Trastuzumab has been approved for HER2 positive (+) advanced gastric cancer patients. Nevertheless, the role of this agent remains unclear because there were conflicting results in gastric cancer patients treated with postoperative chemoradiotherapy.[4,9]

In this study, we retrospectively analyzed gastric cancer patients treated with postoperative chemoradiotherapy. We divided patients into two groups according to their HER2 status to determine whether HER2 positivity has any prognostic or predictive importance in these patients both for local control and survival.

Materials and Methods

Patients and Treatment

We retrospectively analyzed records of more than 300 patients with biopsy-proven gastric cancer treated in our department since 2007. We excluded patients with unknown HER2 status or with metastatic disease at study initiation. The study population included 49 gastric cancer patients treated with curative intent between April 2012 and January 2017. We received the approval of the institutional review board for this retrospective analysis (Project No: 2017-50).

All patients underwent routine initial clinical staging before operation, including a detailed physical examination, endoscopic examination, complete blood count, blood chemistry test, and computerized tomography of the abdomen. We staged the patients according to the American Joint Committee on Cancer 7th Edition 2010.

The patients were treated according to the clinical protocol described in the INT-0116 trial. Chemotherapy regimen consisted of 5-fluorouracil (425 mg/m² per day) and leucovorin (20 mg/m² per day) or Capecitabine (825 mg/m², B.I.D, per day) administered for five days. After the first cycle of chemotherapy, patients were treated with a combination of 3-dimensional conformal or intensity-modulated external beam

radiotherapy. Clinical tumor volume included the tumor bed, regional lymph nodes, and safety margins for planning the tumor volume. A total dose of 45 Gy (1.8 Gy per fraction, per day) was delivered using 18 MV photons for five days. Nine patients (16%) were treated with radiation up to 50.4 Gy because of positive surgical margins. The second and third cycles of chemotherapy were administered along with radiotherapy. After radiotherapy, patients were treated with two cycles of adjuvant chemotherapy in the same regimen.

HER2 Analysis

Tissue specimens were evaluated using immunohistochemistry or FISH, where appropriate, for HER2 gene amplification status. In FISH assay, average HER2 gene copy numbers and average chromosome 17 centromeres were evaluated by counting the numbers of signals for at least 50 interphases. The ASCO/CAP scoring criteria was used: ratios <1.8 or HER2 signals <4 were reported as non-amplified; ratios of 1.8–2.2 or HER2 signals between 4 and 6 were reported as borderline amplification; and ratios >2.2 or HER2 signals >6 were reported as amplified.

Clinical Follow-up

The clinical follow-up of patients was performed every three months for two years and every six months after two years up to five years. Recurrence or metastasis was defined as biopsy-proven recurrence or documentation of disease progression on serial imaging studies. Failure patterns were described in two main groups as local recurrence or distant metastasis.

Statistical analysis

The time to event was calculated as the time interval from the date of surgery to the date of the first finding on clinical or imaging examination that suggested disease recurrence. Overall survival (OS) and disease-free survival (DFS) were calculated using the Kaplan–Meier method. The survival curves of subgroups were compared using two-sided log-rank tests. All p values were two-tailed, and p < 0.05 was considered statistically significant.

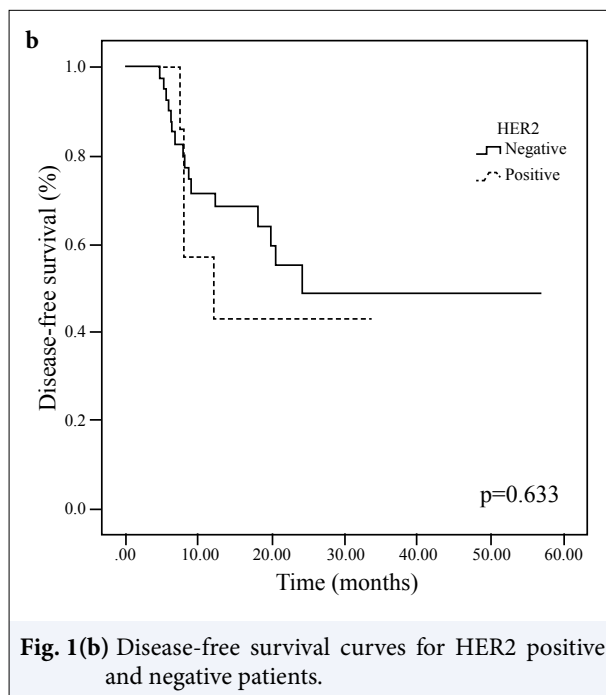
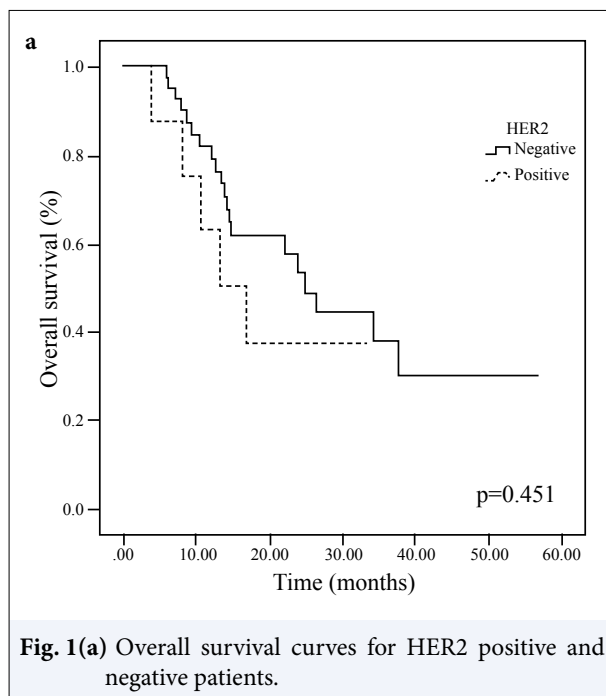
Results

Patient Characteristics

We summarized the patient characteristics in (Table 1). The median age of the patients was 57 (range, 29–78) years. More than half of the patients were males. The most common anatomical site of primary gastric can-

Table 1 Patient Characteristics	
	n (%)
Median Age	57
HER2	
Positive	8 (16)
Negative	41 (84)
Sex	
Female	17 (35)
Male	32 (65)
Anatomical Site	
Proximal - Middle	30 (61)
Distal	19 (39)
T Stage	
T1–T2	6 (12)
T3–T4	43 (88)
N Stage	
N0–N1	28 (57)
N2–N3	21 (43)
Histology	
Adenocarcinoma	44 (89)
Mucinous	5 (11)
RT Dose	
45 Gy	40 (82)
50.4 Gy	9 (18)
Surgical margins	
Negative	40 (82)
Positive	9 (16)
Chemotherapy	
FUFA	36 (74)
Capecitabine	12 (24)
None	1 (2)

cer was middle third, and majority of the patients had adenocarcinoma. Most patients had undergone total gastrectomy and D2 dissection with negative surgical margins and were treated with a total of 45 Gy concurrent chemoradiotherapy with FUFA. One patient (2%) refused chemotherapy and 12 (24%) patients were treated with concurrent Capecitabine. All patients received at least one cycle of adjuvant chemotherapy.



Local Recurrences and Distant Metastasis

During a median follow-up period of 14.6 (range, 4.0–56.97) months, two patients (4%) had local recurrence and 21 patients (43%) developed distant metastasis. Local recurrence was observed in two patients (4%) in the HER2 (–) group, but not in the HER2 (+) group.

We could not perform statistical analysis between the groups for local recurrence rates due to low event rates. Distant metastasis was observed in 17 patients (35%) with HER2 (–) and four patients (8%) with HER2 (+). There was no statistically significant difference in metastasis frequency rates.

Survival

The median OS and DFS for the whole group were 24.9 (12.9–36.9) months and 24.2 months, respectively. The median OS for HER2 (–) and (+) patients were 24.9 (range, 19.2–30.7) months and 13.0 (range, 5.0–21.0) months, respectively. Although HER2 (–) patients had a numerically better median OS, this difference did not have statistical significance ($p=0.451$). There was also no statistically significant difference in DFS between HER2 (+) and (–) patients ($p=0.633$; Fig. 1).

In univariate analysis, gender (male vs. female), T-stage (T1-2 vs. T3-4), and surgery (total vs. subtotal) did not show any significant difference for both OS and DFS. N-stage (N0-1 vs. N2-3) was predictive for DFS ($p=0.005$), and dissection status (D1 vs. D2) was statistically significantly favoring D2 for OS ($p=0.038$).

Discussion

Our study investigated the prognostic importance of HER2 status in gastric cancer patients treated with post-operative chemoradiotherapy. Although the main treatment for gastric cancer is tumor resection and lymphadenectomy, adjuvant treatment is a necessity because of the high relapse rates.[10,11] The pivotal INT-0116 trial demonstrated that the use of 5-FU-based adjuvant chemoradiotherapy increased DFS and OS along with the increased treatment-related toxicity.[12]

In the era of molecular oncology, targeted therapies have become more interesting. One of these therapies is trastuzumab, which is an anti-HER2 monoclonal antibody.[13] HER2 is a member of the epidermal growth factor receptor family of tyrosine kinases, which are involved in tumor proliferation, adhesion, differentiation, migration, and apoptosis.[14] Trastuzumab has been approved for HER2 (+) metastatic gastric cancer. In ToGA trial, a combination of chemotherapy and trastuzumab demonstrated a significant OS benefit in metastatic gastric cancer patients.[15] Its value as a prognostic factor of HER2 in gastric cancer is controversial and may vary based on whether the patient receives chemotherapy. For instance, Terashima et al.[16] investigated the HER2 status in gastric cancer and found that HER2 was not a prognostic marker in the

absence of chemotherapy. In addition, patients with HER2 (+) gastric cancer showed an improved outcome with chemotherapy. The association of HER2 status with prognosis in a total of 1562 gastric cancer patients undergoing R0 resection was also investigated by Shen et al.[17] They reported that there were no significant associations between HER2 status and DFS or OS in multivariate analysis.

In our study, the incidence of HER2 positivity was 16%. Although our cohort was relatively small and could not represent the whole population, the incidence was consistent with results of previous studies. Moreover, adenocarcinoma was the only histology in the HER2 (+) patients, and majority of the patients were male. We did not acquire any data about male predominance or adenocarcinoma histology association with HER2 (+) gastric cancer. Therefore, it is hard to say whether these findings are incidental or related to the disease.

A similar study, the INT-0116 clinical trial, retrospectively focused on the available tissue specimens for HER2 gene amplification and investigated the relation between HER2 expression and outcomes. They concluded that there was a significant interaction between HER2 amplification and treatment with respect to both DFS ($p=0.020$) and OS ($p=0.034$). Patients whose tumors had HER2 gene amplification had shorter DFS and OS (13 and 16 months, respectively) compared with the patients whose tumors lacked HER2 gene amplification (34 and 44 months; $p=0.026$ and 0.025 , respectively). The analysis of HER2 (+) patients indicated no significant difference between treatment regimens. Here the absence of benefit from adjuvant chemoradiotherapy should be interpreted with caution in view of the small patient sample [28 HER2 (+) patients]. The same study found no significant difference in OS or DFS based on HER2 amplification status among patients who only underwent surgery. Therefore, they concluded that HER2 may not be an insufficient prognostic marker of poor outcome in the absence of treatment.[18]

The MAGIC trial evaluated 415 specimens for HER2 status. The systemic treatment regimen consisted of anthracycline-based chemotherapy. HER2 status was not a prognostic factor in this study and did not have any predictive value for screening the treatment response to anthracycline-based chemotherapy.[19] Likewise, the ACTS-GC study did not demonstrate any influence of HER2 expression/amplification on the prognosis of gastric cancer patients.[16] In their in vitro study, Pietras et al.[20] demonstrated that inhibit-

ing HER2 with antibody caused significant changes in the radiosensitivity of tumor cells. Declining the radio-resistance by HER2 antibody may improve radiation-induced apoptosis.

A systematic analysis of data from Danish literature performed with 42 publications and over 12000 patients concluded that HER2 had a potential role as a negative prognostic factor in gastric cancer. In addition, they reported that HER2 overexpression and/or amplification may be a molecular abnormality linked to this disease development.[21]

In addition to the abovementioned studies, Li et al.[22] investigated the effectiveness of locoregionally administered trastuzumab armed with astatine-211 (211At-trastuzumab) against HER2 (+) peritoneal metastasis of gastric cancer in a xenograft mouse model. They concluded that locoregionally administered 211At-trastuzumab significantly prolonged the survival time of HER2 (+) peritoneal metastasis of gastric cancer mice compared with control treatments.

Our study has some limitations. First, as with any retrospective study, unpredictable biases may have influenced our results. Second, the limited cohort size makes it difficult to generalize the results to whole population. Nevertheless, we had a homogenous group of gastric cancer patients treated with the same protocol, and our study may help evaluate the prognostic significance of molecular therapies in the presence of conventional chemoradiotherapy protocols.

Conclusion

Although our study did not indicate any statistically significant importance of HER2 status in gastric cancer patients treated with postoperative chemoradiotherapy, the results suggested that there was a trend in favor of HER2 (-) patients. This study is not beyond hypothesis generation and needs to be confirmed before a routine assay of HER2 expression is used as a means of patient selection. Therefore, randomized studies with larger cohorts are warranted to acquire more reliable data on this important topic.

Disclosures

Ethics Committee Approval: This study was conducted in accordance with local ethical rules.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship contributions: Concept – O.C.G, A.Y; Design – O.C.G, A.Y; Supervision – A.Y; Materials – M.K, Z.B, E.C;

Data collection &/or processing – Z.B, E.C, E.Ç; Analysis and/or interpretation – E.C, Z.B; Literature search – M.K; Writing – O.C.G, A.Y; Critical review – O.C.G, M.K, Z.B, E.C, E.Ç, A.Y

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