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MICROSATELLITE INSTABILITY-HIGH GASTRIC CANCER PATIENTS MAY BENEFIT FROM ADJUVANT RADIOTHERAPY

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Summary

Gastric cancer remains one of the deadliest types of cancer despite the improvements in therapy regimens. The knowledge about specific molecular and histopathologic features of gastric tumors leads toward targeted therapy protocols. Patients with microsatellite instability-high cancer exhibit special characteristics regarding the response to therapy. These patients benefit from specific immunotherapy regimens and respond poorly to conventional therapy. Our study aimed to evaluate the effect of chemotherapy and chemoradiotherapy on the survival of patients with microsatellite instability gastric cancer in our institution. The results of our study show an increase in survival in the microsatellite instability-high group of patients who received radiotherapy (p=0.04). Since all the recent studies recommend radiotherapy only in patients with incompletely resected disease or those with less than D2 lymphadenectomy, our study offers a novelty suggestion in consideration of therapeutic options. If the benefit of radiotherapy can be confirmed in a larger sample of patients, radiotherapy could be a part of tailored therapy for microsatellite instability-high (MSI-H) gastric cancer.

KEYWORDS: *MSI; gastric cancer; survival; radiotherapy*

INTRODUCTION

Over one million new cases of gastric carcinoma were diagnosed worldwide in 2020, making it the fifth most common cancer type and the fourth leading cause of cancer-related death, contributing to 7.7% of all cancer deaths(1). The annual incidence of gastric cancer in Croatia is 520 in males and 357 in females, with mortality of 412 and 285 cases, respectively(2). The improvement in the therapy of gastric cancer represents an ongoing challenge. The current standard of curative surgical treatment is radical gastrectomy(3), with D2 lymphadenectomy recommended for the treatment of advanced gastric cancer (T3-4 stage)(4). Combining perioperative chemotherapy with surgery showed a significant improvement compared with surgery alone, representing the standard of care(5). The previously established regimen of chemotherapy, ECF/ECX (epirubicin and cisplatin plus either fluorouracil or capecitabine), is now replaced with the perioperative FLOT therapy (fluorouracil, leucovorin, oxaliplatin, and docetaxel), resulting in 15 months superior overall survival(6). Increasing knowledge of specific molecular and histopathologic features of gastric tumors led to the division into four subgroups of gastric can-

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cer: EBV (Epstein-Barr Virus) infection-positive tumors, microsatellite unstable tumors, genomically stable tumors, and tumors with chromosomal instability(7). Microsatellites are short tandem repeats of nucleotides prone to DNA replication errors which are corrected through the mismatch repair (MMR) system consisting of MutL homolog 1 (MLH1), MutL homolog 3 (MLH3), MutS homolog 2 (MSH2), MutS homolog 3 (MSH3), MutS homolog 6 (MSH6), post-meiotic segregation increased 1 (PMS1), and post meiotic segregation increased 2 (PMS2) as the primary repair enzymes. A deficient DNA mismatch repair system will result in the microsatellite instability phenotype(8). Microsatellite unstable gastric cancers have better overall survival than microsatellite stable when patients are treated with surgery alone, but poorer outcomes and a higher risk of death after chemotherapy administration(9,10). Pietrantonio et al. conducted the individual-patient-data meta-analysis of the prognostic/ predictive role of microsatellite instability in patients with resectable gastric cancer from four randomized control trials: the MAGIC, CLASSIC, ARTIST, and ITACA-S trials, which supported the results of previous studies. In the microsatellite instability-high gastric cancer group, the 5-year disease-free survival after surgery and chemotherapy compared with surgery only was 70% versus 77% (HR, 1.27; 95% CI, 0.53 to 3.04), and the 5-year overall survival was 75% versus 83% (HR, 1.50; 95% CI, 0.55 to 4.12)(11). Considering the widespread expression of immune-checkpoint ligands in microsatellite instability-high gastric cancers, there are promising results with an immunotherapeutic approach (anti-PD1 or anti-CTLA4 antibodies)(12,13). Considering the specific features and clinical behavior of microsatellite unstable gastric cancer, future perspectives of treatment go towards individualized therapy.

The goal of this study was to evaluate the effect of chemotherapy and chemoradiotherapy on the survival of patients with microsatellite instability gastric cancer in our institution.

MATERIALS AND METHODS

The study is conducted with the approval of the Ethics Committee of Sestre milosrdnice University Hospital Center.

We retrospectively analyzed the data of 71 patients who underwent surgical resection of gastric cancer in our institution between January 2010 and March 2020. The data were collected from the medical records archive. Patients with missing data and loss of follow-up were excluded from the study. The patient's patohistological material was retrieved from the pathology archive to perform the immunohistochemical analysis of the mismatch repair proteins, thus determining microsatellite instability. Rabbit antibodies were used for the detection of the following mismatch repair system proteins: MutL homolog 1(MLH1, clone ES05, Dako, USA), MutS homolog 2(MSH2, clone FE11, Dako USA), MutS homolog 6(MSH2, clone EP49, Dako USA), PMS1 homolog 2 (PMS2, clone EP51, Dako USA).

Statistic analysis was performed using the software package Statistica. The level of statistical significance was set at 0.05. We used the Kaplan-Meier survival analysis for microsatellite instability status and the therapy received.

RESULTS

During the observed period, 71 patients underwent surgery due to a diagnosis of gastric cancer. Thirty-nine were female, and thirty-two were male, with a mean age of 61.2 years. Patients were stratified into three groups according to microsatellite instability status (table 1). Eight patients were in the microsatellite instability-high group, 13 in the microsatellite instability-low group, and 50 in the microsatellite instability-negative group. We did not find any statistically significant difference in survival between different microsatellite instability

Table 1.
Patient distribution according to age, sex, received radiotherapy and tumor size

Characteristic	MSI high	MSI low	MSI neg	P value
Number	8	13	50	
Age	64.25 ± 7.42	61.38 ± 10.63	60.5 ± 10.79	0.94
Sex				
Female	4 (50%)	8 (61.5%)	27 (54%)	0.593
Male	4 (50%)	5 (39.5%)	23 (46%)	
Radiotherapy				
Yes	4 (50%)	6 (46.2%)	18 (36%)	0.867
No	4 (50%)	7 (53.8%)	32 (64%)	
Tumor size	78.13 ± 20.17	54.33 ± 18.11	47.44 ± 27.95	**0.01**

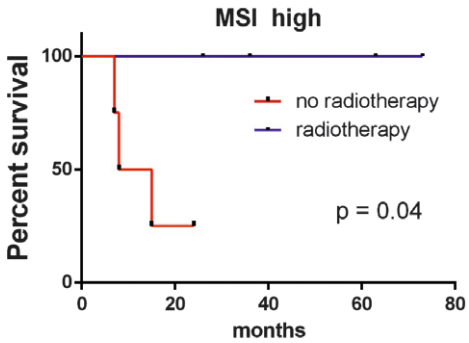

Figure 1. Survival of MSI high patients

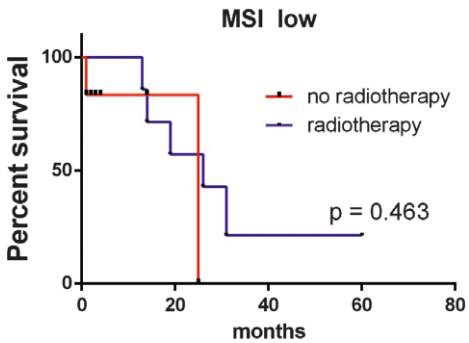

Figure 2. Survival of MSI low patients

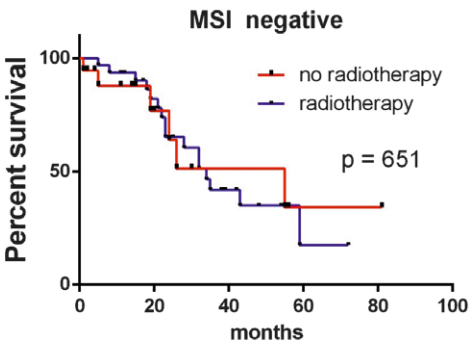

Figure 3. Survival of MSI negative patients

groups of patients who underwent chemotherapy protocols. However, we got a statistically significant increase in survival in the microsatellite instability-high group of patients who received radiotherapy (p=0.04) (figure 1). In the microsatellite instability-low and negative group, radiotherapy did not impact survival. (figures 2 and 3).

DISCUSSION

The results of our study suggest that microsatellite instability-high gastric cancer is correlated with a good response to radiotherapy. Conducted randomized clinical trials investigating adjuvant therapy of localized gastric cancer(14,15) showed that the chemoradiotherapy group had worse 5-year overall survival than the chemotherapy group, and adding radiotherapy to chemotherapy did not significantly improve the disease-free survival. Current ESMO guidelines recommend consideration of adjuvant radiotherapy in patients who have not received preoperative chemotherapy and have not undergone an appropriate D2 lymphadenectomy(3). Although conducted on a small sample size, our study indicates that microsatellite instability-high gastric cancer demonstrates specific clinical behavior. Further studies on larger cohorts are required to confirm the potential of radiotherapy in microsatellite instability-high patients.

Even the most recent data indicate that adjuvant radiotherapy could be recommended as a therapy option only in patients with less than D2 lymphadenectomy or those with incompletely resected locally advanced tumors(16). The same study indicates that chemoradiotherapy does not improve survival in patients treated with platinum-based protocols.

According to meta-analyses of randomized controlled trials, adjuvant chemotherapy is not recommended in microsatellite instability-high gastric cancer since there is no evidence of added benefit for this subgroup of patients(11). Our study also did not observe any benefit of adjuvant chemotherapy in microsatellite instability-high patients. Regardless of the type of adjuvant therapy, treatment adherence remains a critical issue(5,17), thus emphasizing the role of preoperative therapy regimens.

A relatively small cohort in our study is associated with the fact that only one-fifth of patients diagnosed with gastric cancer in Croatia qualified for surgical treatment, and most require prehabilitation. Only half are candidates for curative surgery after surgical exploration(18).

Programmed cell death protein 1 (PD-1) antibodies targeting immune checkpoint inhibitors are efficient therapy for microsatellite instability-high, advanced, and metastatic gastric cancer. Studies(19,20) confirmed improved survival with pembrolizumab therapy vs. chemotherapy. However, the response rate to this therapy is 50%, and several markers of intrinsic resistance are identi-

fied(21). These findings indicate heterogeneity among microsatellite instability-high gastric cancer and a necessity for a more detailed stratification of patients and tailored therapy.

To the best of our knowledge, our study is the first to indicate the benefit of radiotherapy in microsatellite instability-high patients. All of the studies cited above, including ours, had patients who received radiotherapy as a part of the chemoradiotherapy protocol. A more extensive study on the effect of radiotherapy on microsatellite instability-high patients should be conducted to clarify our study's suggestions.

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Sažetak

ZRAČENJE MOŽE KORISTITI PACIJENTIMA S KARCINOMOM ŽELUCA S VISOKO IZRAŽENOM MIKROSATELITNOM NESTABILNOSTI

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Karcinom želuca jedan je od najsmrtonosnijih karcinoma usprkos napretku u njegovom liječenju. Spoznaje o specifičnim molekularnim i histopatološkim značajkama tumora želuca vode nas prema ciljanim terapijskim protokolima. Pacijenti s karcinomom želuca s visoko izraženom mikrosatelitnom nestabilnosti pokazuju posebne značajke u odgovoru na terapiju. Ovi pacijenti dobro reagiraju na specifične imunoterapijske režime, ali imaju loš odgovor na konvencionalnu terapiju. Cilj našeg istraživanja je bila procjena učinka kemoterapije i kemoradioterapije na preživljenje pacijenta s karcinomom želuca s izraženom mikrosatelitnom nestabilnošću u našoj ustanovi. Rezultati naše studije pokazuju produljenje preživljenja u skupini pacijenata s visoko izraženom mikrosatelitnom nestabilnošću koji su primili radioterapiju (p=0.04). S obzirom da sva recentna istraživanja preporučuju zračenje samo pacijentima s nepotpuno reseciranim tumorom ili onima kod kojih je učinjeno manje od D2 limfadenektomije, naše istraživanje donosi moguću novost u razmatranju terapijskih opcija. U slučaju potvrde pozitivnog učinka zračenja u studijama s većim brojem pacijenata, radioterapija bi mogla postati dio ciljane terapije za karcinome želuca s visoko izraženom mikrosatelitnom nestabilnšću.

KLJUČNE RIJEČI: *mikrosatelitna nestabilnost; karcinom želuca; preživljenje; zračenje*