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REVIEW ARTICLE

Differences in gastric cancer surgery outcome between East and West: differences in surgery or different diseases?

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Summary

The Dutch D1D2 Trial revealed a noncompliance rate of 51% in gastric cancer patients who should have undergone a D2 dissection, while it disclosed that the D2 lymph node dissection group of patients exhibited a higher 15-year overall survival (OS) rate, lower rates of local and regional recurrence, lower rates of liver metastases and lower cancer-related death rates compared to the D1 group, implying that the surgical technique per se may influence outcomes.
On the other hand, the predominant up-regulation of invasive and metastatic genes in the Western tumor libraries, the differences in the criteria used for gastric cancer diagnosis in the East and the steady finding that the Asian ethnicity is a favorable prognostic factor for patients with gastric cancer treated in the US, have been proposed as possible explanations for the differences observed in the gastric cancer outcome between the East and the West.
Moreover, literature addresses that gastric cancers in the East are mainly diagnosed at younger ages, they are of intestinal type, located distally, diagnosed at an early stage of disease, while gastric cancers in the West are mainly affecting elderly patients with comorbidities, they are of diffuse type, located proximally, and diagnosed at an advanced stage of disease.
Future discoveries in genetics and molecular biology may clarify the characteristics of each tumor, while future achievements in imaging modalities and biological or target therapies may establish "personalized" therapies. Until that time, all efforts for improving our surgical techniques and optimizing the perioperative care are mandatory.

Key words: *D2-lymphadenectomy, East, gastric cancer, prognosis, West*

General considerations

Gastric cancer represents the fifth most common malignancy in the world as nearly one million new cases are diagnosed annually. It is the third leading cause of death attributed to cancer globally, while more than 700,000 deaths linked to the disease *per se* are documented each year [1]. The age standardized incidence per 100,000 inhabitants is variable. In males, it ranges from 7.4 in North America to 12.8 in Western Europe and up to 62.1 in Japan. In females, it ranges from 3.4 in North America to 6.6 in Western Europe and up to 26.1 in Japan [2]. During the last 50 years, the incidence of gastric cancer is decreasing steadily in the West (reduction of 50% and 62% in US [3] and UK [4], respectively); however, the overall survival remains disappointing with observed 5-year survival rates of 18.9% and 30.6% in UK [5] and in US [4], respectively.

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Far East countries, implemented mass screening programs since the 60's are implemented due to the high prevalence of the disease. This facilitated prompt gastric cancer diagnosis with less than 30% of new cases diagnosed at stages III and IV. In Western countries, more than 60% of new gastric cancer cases are diagnosed at stages III and IV [6] only partially attributed to the fact that the disease is less commonly observed in the West. Also, the implementation of nationwide screening systems usually requires significant financial and human resources for effective prevention results. In that sense, cost effectiveness is influenced by clinical outcomes, cost, as well as incidence and screening rates [7]. Therefore, oncologic gastric surgery remains the cornerstone for survival and quality of life improvement in gastric cancer patients in Western countries.

Comparing the post-surgical results

The results of a US gastric cancer registry survey between 1982 and 1987 revealed that the survival rates of gastric cancer patients with stage I, II, III, and IV were 50, 29, 13, and 3%, respectively. In contrast, a Japanese registry survey between 1971 and 1985 showed that the respective survival rates of gastric cancer patients with stage I, II, III, and IV were 91, 72, 44, and 9%, respectively [8,9].

In 2000, a study comparing the survival rates of gastric cancer patients between USA and Japan institutes disclosed significantly worse post-surgical 5-year survival rate for US patients, regardless of disease stage. When survival was stratified by N category, it was significantly worse for US patients with N0, N1 and N2 disease [10].

In 2010, it was reported that the probability of death due to gastric cancer was significantly higher in US patients compared to Korean ones for stages I-III, while Korean patients had 30% improved disease specific-survival per stage even after adjusting for variables such as tumor location, T stage, lymph node status and stage *per se* [11].

In 2013, another report suggested that the persistence of better survival rates in Eastern compared to Western patients with gastric cancer, even after adjusting for age, sex, tumor depth, nodal status, type of gastrectomy and chemotherapy effect, might be at least partially attributed to other factors such as the surgical technique [12].

The 5-year survival rates at each gastric cancer stage amongst Korea, Japan, US (SEER data 1973–2005 diagnosed in 1991–2000) and China were as follows: 95.1, 94.2, 70.8, and 88.5% for stage Ia; 84.0, 80.8, 45.5, and 71.5% for stage IIa; 71.7, 69.6, 32.8, and 66.8% for stage IIb, respectively. In particular, for stage IIIa the 5-year survival rate in Korea was 58.4% versus 19.8% observed in the US (SEER data) [13].

Recently, it was stated that even after adjusting for all background characteristics, stage-specific overall survival and cancer-specific survival rates were significantly better in Japan than in UK [14].

Back in 2002, the results from the SWOG 9008/Intergroup 0116 randomized trial, showed that 54% of the enrolled patients underwent D0 lymphadenectomy, while D2 dissection was performed in only 10% [15]. Moreover, recent MD Anderson Cancer Center data showed that in 45% of US gastric cancer patients no D1+/D2 lymphadenectomy has ever been performed [16]. An 11-year follow-up study (The Dutch D1D2 Trial) revealed a noncompliance rate (i.e., non-treatment of node stations that should have been dissected) of 51% in patients who should have undergone a D2 dissection [17]. A rational question emerged: "Did such under-treatment influence survival in gastric cancer patients"? [15,17].

The aforementioned Dutch study confirmed that the D2 group of lymph node dissection compared to the D1 group of patients exhibited a higher 15-year overall survival rate (29 vs. 21%), lower rates of local and regional recurrence (12 vs. 22% and 13 vs. 19%, respectively), as well as lower rates of liver metastases (11 vs 17%) and cancer-related death rates (37 vs 48%), implying that the surgical technique *per se* may influence outcomes [17,18].

Researchers found that the 5-year survival at Memorial Sloan Kettering Cancer Center in US was 58% compared to 46% at the Beijing Cancer Hospital in China. The stage-specific probability of death was significantly higher in China, even after adjusting for important prognostic factors, and Chinese gastric cancer patients had a worse outcome than US gastric cancer patients [19]. Studies comparing the long-term survival rates of gastric cancer patients in China versus Korea revealed that Chinese patients still exhibited the worst outcome. This might be due to the fact that lower mean numbers of harvest lymph nodes in Chinese patients were documented even in cases of D2-lymphadenectomy [20,21]. Notwithstanding, a pertinent meta-analysis could address the aforementioned raised issues and possible discrepancies observed in comparison studies between Eastern and Western institutes.

Furthermore, the ARTIST and CRITICS Trials failed to demonstrate that postoperative chemoradiotherapy improves disease-free and/or overall survival in patients with D2 resected gastric cancer [22,23].

Table 1. Differences in gastric cancer patients between East and West

	East	*West*
Incidence per 100,000 inhabitants		
Males	7.4 (North Am) – 12.8 (West Eur)	62.1 (Jap)
Females	3.4 (North Am) – 6.6 (West Eur)	26.1 (Jap)
Ethnicity	Asian race was found as an independent predictor of better overall survival	Caucasian race provided a worse overall prognosis
Genetic differences		Up-regulation of invasive & metastatic genes are expressed
Localization of the primary tumor	Distal third of the stomach	Proximal third of the stomach
Diagnostic criteria	Nuclear and glandular architecture abnormalities presence, even in the absence of invasion.	Only when invasive growth of neoplastic epithelium into or beyond the lamina propria is observed
Histological type	Intestinal	Diffuse
Stage III & IV at the time of the diagnosis	<30%	>60%
Surgical technique	D2-lymphadenectomy as a routine	Even in PRT, a noncompliance rate of 51% in patients who should have undergone a D2 dissection, was found

Specific features in the East

For Eastern investigators, the previously mentioned favorable long-term outcome of the disease is attributable to the more radical surgery, whereas Western investigators may claim that these differences are attributable to the earlier detection and the differences in the biology of the tumor [24]. Differences in genetics, diagnostic criteria, histology, tumor location, ethnicity/race, environmental exposures, dietary factors and *H. pylori* status have been proposed as possible explanations for the wide variation both in the clinicopathological presentation as well as in the outcome of the gastric cancer between Eastern and Western countries [25] (Table 1).

The theory that specific genetic differences could result in a less aggressive form of gastric cancer in the East has been investigated. Although, neither KRAS mutations and DNA MMR deficiency [26] nor c-erb-B2 and p53 expressions [27] were found as related to the different gastric cancer incidence, and the predominant up-regulation of invasive and metastatic genes (COL1A1 and KLK10) in the Western tumor libraries might explain the observed differences in the gastric cancer outcome between the East and the West [28].

In Japan, gastric carcinoma diagnosis is based on nuclear cytologic and glandular architecture abnormalities criteria (even in the absence of invasion), while in Western countries the disease is diagnosed only when invasive growth of neoplastic epithelium into or beyond the lamina propria is observed. Thus, lesions characterized as precancerous in the West are frequently interpreted as carcinoma in Japan [24,29-31].

The subject of the ethnicity effect on the outcome of patients who were treated surgically in the US, minimizing the influence of differences in the use of D2 lymphadenectomy technique, has been extensively studied. Theuer et al. [32] disclosed that the Asian patients had significantly better overall survival and cancer-specific survival than the non-Asian ones. The better prognosis for Asian ethnicity remained even after adjusting for several commonly known prognostic variables at that time. A Canadian study [33] stated that Asian ethnicity was independently associated with superior survival after curative resection. The most recent results of the SEER Database [34] clearly stated that Asian ethnicity is a favorable prognostic factor for patients with gastric cancer treated in the US, even after adjusting for age, gender, tumor site, tumor grade, number of positive and number of total examined lymph nodes. A stage-by-stage analysis of the effect of race on the prognosis after curative gastrectomy revealed that Asian race was an independent predictor of overall survival providing a better prognosis, while, on the contrary, Caucasian race provided a worse overall prognosis [35]. The obvious survival differences after gastrectomy for gastric adenocarcinoma favoring Asian patients have been proposed as related to the different disease patterns (distal location) and the diminished patient risks (BMI, tobacco consumption, comorbidities) [36].

Analyzing the SEER Database between 1973 and 2000, Henson et al. [37] disclosed a progres-

sive decrease in the incidence of the intestinal type and an increase in the diffuse type of gastric carcinoma, especially the signet ring cell type, in whites of both genders. Other authors [10,11] stated that tumors with diffuse histology are more common in the West, while others [38] concluded that the diffuse histological type still remains predominant among Asians. Diffuse type gastric cancer represents a well-known independent dismal prognostic factor [39].

Several authors [10,11,13,32-34,36,40] agreed that tumors located in the proximal third of the stomach are more commonly observed in Western countries. The former represent an independently adverse prognostic factor usually due to a more advanced stage on diagnosis, larger tumor size and poorly differentiated histology [41]. Hence, we could argue that when comparing gastric tumors with similar features in terms of location and biology, the favorable outcome results published by Japanese and Korean centers need to be carefully reevaluated [42].

Minimum requirements for an adequate Western gastric cancer surgery

For an adequate gastric cancer operation plan in Western daily surgical practice, the following considerations are mandatory:

1. Negative resection margins are a prerequisite in all cases. A proximal margin of at least 3cm is recommended for T2 or higher stage tumors with "expansive growth pattern", while it is recommended a proximal margin of at least 5cm for tumors with "infiltrative growth pattern" [43]. Thus, total gastrectomy seems unnecessary for the majority of patients, under the premise of negative resection margins [44]. Frozen section examination is indicated in cases of poorly differentiated signet ring carcinomas. However, the argument for performing a total gastrectomy in patients with poorly differentiated tumors still exists [45].
2. Concomitant splenectomy is not recommended for tumors that do not invade the greater curvature or without direct invasion to the spleen as this manipulation increases intraoperative morbidity without improving survival [46]. Similarly, concomitant distal pancreatectomy is reserved solely for patients with T4 tumors [47].
3. D2 lymphadenectomy should be adopted as the "gold-standard" surgical procedure for advanced non-metastatic gastric cancers, since it offers the recommended 16 lymph nodes for pathology assessment. It has been proposed that the higher the number of pathologically assessed lymph nodes, the less the stage migration and the better the prognosis, since the stage-specific survival, the disease-free survival and the overall survival rates were longer [48].
4. Familiarization with the Maruyama computer program (MCP) and the "Maruyama index (MI) of unresected disease". The MCP is a Windows-based computer program which estimates the preoperative likelihood of disease in 16 defined nodal stations around the stomach based on 7 input variables. MI is defined as the sum of Maruyama program predictions for regional lymph node stations 1–12 left without dissection. The MI has already been tested in various European studies which all concluded that the former has high sensitivity, lower specificity and less than 10% false-negative rate [49-51]. Previous reports suggested that MI values below 5 were associated with a significantly higher survival rate and a reduced local relapse risk compared to patients who scored 5 or more [15,17,45,52]. Interestingly, a recent study showed that intraoperative sentinel lymph node examination is superior to preoperative evaluation by MCP, although further studies are clearly required to confirm the aforementioned results [51].
5. Centralization of gastric cancer surgical practice was implemented in European countries, setting the threshold of more than 40 resections to be performed annually. Thereafter, significant differences in the number of lymph node harvested [53] and/or postoperative mortality, as well as in the overall survival benefit were observed in countries which have centralized gastric cancer surgery practices [54,55].

Relevant literature shows that gastric cancers in the East are mainly diagnosed at younger ages, they are of intestinal type, located distally, and diagnosed at an early disease stage. On the other hand, gastric cancers in the West mainly affect elderly patients with comorbidities, they are of diffuse type, located proximally, and diagnosed at an advanced disease stage, even in patients younger than 40 years old [56]. However, the conclusion that in countries that are reporting better survival data unveils distinct surgical and biological features appears to be rather hasty and one-sided [57]. Future discoveries in genetics and molecular biology may clarify the characteristics of each tumor, while future achievements in imaging modalities and biological or target therapies may establish "per-

sonalized" therapies. Until that time, all efforts for improving our surgical techniques and optimizing the perioperative care are undoubtfully required.

Conflict of interests

The authors declare no conflict of interests.

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