Review Article

Comparisons of Gastric Cancer Treatments: East vs. West

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There has been a large amount of speculation concerning the differences in the outcomes in patients who have gastric cancer in the Eastern and Western worlds. The differences in biology, surgical and adjuvant treatment have been used to explain such differences. There are clear differences observed in the histology (diffuse vs. intestinal), tumor location (proximal vs. distal), environmental exposures, dietary factors and *Helicobacter pylori* status. A higher incidence of gastric cancer in the East has led to screening programs, and leading to an earlier stage at presentation. Surgical treatment differs in that the extended lymph node dissection is routinely practiced in the Asian countries. Additionally, different adjuvant therapeutic regimens are used in both regions. The purpose of this review is to describe the differences in both presentation and treatment between the East and the West.

Key Words: Gastric Cancer; Gastric adenocarcinoma; Western experience; Eastern experience; Gastric cancer survival

Introduction

Although the incidence of gastric cancer has been declining in most industrialized nations over the past two decades, it still remains the second leading cause of cancer related deaths worldwide.(1) The incidence is highest in Japan, Korea, China, Latin America and Eastern Europe. In Western countries like the United States, the incidence is lower, with 21,000 new cases diagnosed each year.(2) Survival outcomes differ considerably between Eastern and Western populations, with better overall survival reported in Eastern series.(3-7) Many authors have sought explanations for this based on either: 1) Stage Migration, 2) Differences in biology, or 3) Differences in treatment. The adoption of screening programs in Japan has led to screening programs which allow for earlier detection in the East.(8) Additionally, there is discrepancy in pathologic

review between Eastern and Western pathologists, with Eastern pathologists having a lower threshold for diagnosis of primary tumor than Western pathologists.(9) Differences in biology are clearly seen in the histology (diffuse vs. intestinal), tumor location (proximal vs. distal), environmental exposures, dietary factors and *Helicobacter pylori* status. Surgical treatment differs in that the extended lymph node dissection is routinely practiced in Asian countries, leading to greater lymph node retrieval. Whether this leads to stage migration or to a direct therapeutic effect has yet to be resolved. Laparoscopic gastrectomy has also been much more widely adopted in the East compared to the West. Furthermore, adjuvant therapy differs between the two regions.

The purpose of this review is to describe the differences in both presentation and treatment between the East and the West. We will highlight the differences in clinicopathological presentation, discuss the differences in both surgical and adjuvant treatment, and discuss the differences in survival outcomes.

Stage Differences

The incidence of gastric cancer is higher in Eastern countries compared to the West. This has led to the adoption of mass cancer

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screening programs in countries like Japan.(8) In Japan, annual screening with a double-contrast barium technique and endoscopy is recommended for persons over the age of 40 years. As such, many series have shown that gastric cancer tends to present with earlier staged lesions than their Western counterparts.(10,11) Based on reports from cancer registries, 53% of gastric cancers in Japan were localized when diagnosed, as opposed to 27% of those in the United States (US). This has been touted as a potential reason for the discrepancy in survival, although several series have demonstrated differences in survival when stratified by stage.(12,13) Additionally, there may be some variation in pathologic evaluation between the US and Japan.(9,14,15) Japanese pathologists rely heavily on nuclear cytologic and glandular architecture abnormalities, whereas Western pathologists require the presence of invasion to diagnose carcinoma. Therefore, it may be that patients in Japan may have less advanced tumors than US patients even within T-stage.

Biology

One major difference between Eastern and Western gastric cancer is the location of the tumor. Western countries have a much higher incidence of tumors located in the proximal third of the stomach.(10-12,16-18) In fact, the incidence of proximal gastric cancer has been increasing steadily in the US, even while the incidence of gastric cancer is on the decline.(19,20) Proximal tumors are known to be associated with worse outcomes and could explain the differences between the two regions.(21) However, even when compared by tumor location, there do appear to be survival differences favoring the East.(12)

Differences in histology are seen between the East and West. There is a higher prevalence of diffuse histology in Western patients.(12,13) The poor prognosis of diffuse and signet ring histology could explain worse outcomes in the West. Additionally, differences in the baseline characteristics of patients could explain worse outcomes in the US. Patients in the US develop gastric cancer later in life.(12,13,18) One study demonstrated a median difference of 10 years between Korean and US cohorts.(12) Western populations generally have a higher body mass index. Increased obesity has been shown in many series to be associated with increased perioperative complications in gastric cancer as well as many other tumors.(22,23) The prevalence of comorbidities such as diabetes and an increased use of tobacco in the US could also influence the discrepant outcomes between the East and West.

Differences in Surgical Treatment

1. Endoscopic mucosal resection (EMR)

The advent of early detection of gastric cancer by screening programs in the East has led to an increase in the prevalence of early gastric cancer (ECG) in those regions. EGC is defined as tumor invasion confined to mucosa or submucosa irrespective of the lymph node status. Database studies have demonstrated that the incidence of lymph node metastases in EGC confined to the mucosa is less than 4.9%, with a 5 year survival of 99%. The risk of lymph node metastases increases to 23.8% with submucosal invasion.(24) Multiple studies in the East have demonstrated the feasibility of EMR for EGC. Uedo et al.(25) reported on 124 Japanese patients with EGC less than 2 cm with no ulceration. All were completely resected and the disease specific survival (DSS) rates were 99% at 5 and 10 years. Kim et al.(26) reported on 514 patients with EGC who were treated at 13 institutions throughout Korea. The local recurrence rate was 6%, however there were no gastric cancer related deaths in these recurrences.

The use of EMR has been widely adopted in the East. It is estimated that approximately 50% of Stage IA gastric cancer is treated by EMR in Japan. Indications for EMR include well to moderately differentiated tumors that are confined to the mucosa. Superficially elevated tumors must be less than 2 cm and those that are flat or depressed should be less than 1 cm. There should be no ulceration or scar present and there should be no lymphatic or venous involvement.(27) Unlike Japan, EMR has not been as widely adopted in Western countries; however its use is starting to increase.

2. Lymph node dissection

The surgical approach to lymph node dissection has differed between the East and the West. D2 lymphadenectomy, which entails systematic dissection of the perigastric nodes along with the nodes along the celiac artery and its branches, is the standard of care in Japan and Eastern countries. In Western countries, D1 lymph node dissection (perigastric nodes only) is routinely performed. Lymph node dissection in the West has been driven by two large European randomized controlled trials which compared D1 to D2 lymphadenectomy (Table 1). Cuschieri et al.(28,29) reported the results of a multi-center randomized controlled trial from the United Kingdom (UK). In it, 400 patients were randomized to either D1 or D2 lymphadenectomy. The results showed a significantly higher morbidity (46% vs. 28%, P < 0.001) and mortality (13% vs. 6.5%, P=0.04) in the D2 arm. This was mainly driven by distal

Table 1. Summary of lymphadenectomy trails

Trial	Number of patients randomized	Study groups	Stratification	Morbidity (%)	Mortality (%)	Significance demonstrated	% change identified in trial
Western trials							
UK trial(28)	400	D1 (n=200)	Institution	28.0	6.5	None	35
		D2 (n=200)	Nodal status	46.0	13.0		33
			Tumor location				5-year survival
Dutch trial(30-32)	711	D1 (n=380)	Institution	25.0	4.0	Yes (survival at 15 years)	37
		D2 (n=331)		43.0	10.0		48
							15-year DSS
Eastern trials							
Wu et al.(35)	221	D1 (n=110)	None	7.3	0.0	Yes (survival)	53.6 D1 vs. 59.5 D3
		D2 (n=111)		17.1	0.0		5-year survival
JCOG 9501(33)	523	D2 (n=263)	T-stage	20.9	0.8	None	69.2
		D2+PAND	Borrman type	28.1	0.8		70.3
		(n=260)	Institution				5-year survival
JCOG 9502(36)	167	LTA (n=85)	Stage	49.0	4.0	None	37.9
		TH (n=82)	Borrman type	34.0	0.0		52.3
			Institution				5-year survival

UK = United Kingdom; DDS = disease specific survival; JCOG = Japan Clinical Oncology Group; PAND = para-aortic node dissection; LTA = left thoracoabdominal approach; TH = transhiatal approach.

pancreatectomy and splenectomy.(28) There was no difference seen in overall survival or disease-specific survival between D1 and D2 lymph node dissection.(29) This study was highly criticized due to contamination and non-compliance. The median number of lymph nodes retrieved was 17 in the D2 group and 13 for the D1. Additionally, many Eastern surgeons find the mortality rate unacceptably high. The second major European study was the Dutch Gastric Cancer trial, in which 711 patients were randomized to either D2 or D1 lymph node dissection. All surgeons were instructed by an expert from Japan and all D2 lymph node dissections were supervised by a specially trained surgeon. Despite this there was still non-compliance in 36% of D1 and 51% of D2 dissections.(30) As in the UK trial the D2 arm had higher morbidity (43% vs. 25%, P<0.001) and mortality (10% vs. 4%, P=0.004). The survival data has been reported at 3 separate time intervals.(30-32) In the first two publications, there was no difference in overall or disease-specific survival, with a reported 11 year overall survival of 35% in the D2 arm vs. 30% in the D1 arm (P=0.53). Management of gastric cancer in the West was greatly influenced by these outcomes. However, recently the 15 year results of the Dutch trial have been published. There remains no significant difference in overall survival. However, there is improved loco-regional control in the D2 arm and there is improved gastric cancer mortality in the D2 arm (37% vs.

48%, P=0.01).(32) Whether the 15 year results will influence treatment patterns in the US remains to be seen.

In the East, the standard of care is a D2 lymph node dissection. Many Japanese surgeons consider the results of the Dutch and UK trials to have an unacceptably high mortality rate and poor survival rates. Peri-operative mortality in the Japan Clinical Oncology Group (JCOG) 9501 trial was 0.8% and the 5 year survival was 70%,(33) whereas in the European trials mortality was 4~6% and 5-year survival 33~35%(7,34). Trials in the East have focused on more extensive lymph node dissections than D2. There has been one randomized trial out of Taiwan which compared D1 and D3 lymphadenectomy. In it, 221 patients were randomized at a single institution, in which 3 highly trained surgeons performed all the operations. In their hands, the morbidity rate was higher in the D3 group (17.1% vs. 7.3%, P=0.012) however there was no operative mortality reported in either group.(28) The D3 group had more lymph nodes removed (37.2 vs. 19.4), however there was no difference in number of nodes positive (3.9 vs. 3.4). The study demonstrated improved survival with D3 lymphadenectomy (59.5% vs. 53.6%, P=0.041).(35) This study suggests that in the hands of highly experienced surgeons, where the operative mortality is very low, D3 lymphadenectomy is superior to D1.

Two other Japanese trials have examined more extensive

lymphadenectomies. In JCOG 9501, 523 patients were randomized to D2 lymphadenectomy or D2+Para-aortic node dissection (PAND). The results demonstrated higher morbidity with D2+PAND (28.1% vs. 20.9%, P=0.07), however there was no difference in operative mortality (0.8% in both groups).(33) There was no difference in survival between the two groups, with 5 year survival rates of 70% and 69% (P=0.85). A second Japanese study, JCOG 9502, compared D2 lymphadenectomy with or without mediastinal nodal dissection. In this trial, 167 patients were randomized to either a left thoracoabdominal approach with mediastinal lymph node dissection or a trans-hiatal approach. There was no significant difference in post-operative morbidity or mortality. This study failed to demonstrate a survival advantage with the more extensive lymphadenectomy with a 5 year overall of 37.9% vs. 52.3% (P=0.92).(36)

Differences in Adjuvant Therapy

Approaches to multi-modality therapy differ between the East and West. Approaches in the West have been driven by two randomized controlled trials that showed a benefit to adjuvant therapy (Table 2). The US Intergroup study (INT) 0116, randomized 556 patients with Stage Ib-IVM0 cancer by the 1988 AJCC staging criteria.(6) Tumors were located at the gastroesophageal junction (GEJ) in 20% of patients. Patients were randomized to 45 Gy of radiation and 5-FU/Leucovorin or surgery alone. The study demonstrated improved local control and a clear survival benefit with a 3-year overall survival (OS) of 50% vs. 41% (P=0.005).

The Medical Research Council Adjuvant Gastric Cancer Infusional Chemotherapy (MAGIC) study from the UK reported a similar survival advantage with the use of peri-operative chemotherapy.(7) In this trial, patients were randomized to Epirubicin, Cisplatin, and 5-FU for 3 cycles pre-operatively and 3 cycles post-operatively. The patients consisted of adenocarcinoma of the stomach (74%), GEJ (15%), and lower esophagus (11%). The results of the trial demonstrated an improved overall and progression free survival in the peri-operative chemotherapy group, with 5-year survivals of 36% and 23% respectively.

These two trials have driven therapy in the West; however there are several criticisms that Eastern investigators have of these trials. The main criticism is the surgical quality of control in these trials. In the INT 0116 trial only 10% of patients had a D2 lymphadenectomy. In fact, 54% of the patients had a D0 lymphadenectomy. Similarly, in the MAGIC trial, only 41% of patients had a D2

Table 2. Summary of trials for adjuvant therapy

Trial	Number of patients randomized	Study groups	Inclusion criteria	Stratification	Lympha-denectomy	Significance demonstrated	% change identified in trial
Western trials							
INT 0116(6)	556	45 Gy+5-FU Surgery alone	Stomach/GEJ (80/20) Stage IB-IVM0 >1,500 cal/day	Stage	D0 (54%) D1 (36%) D2 (10%)	Yes (survival)	OS (50% vs. 41%) RFS (48% vs. 31%)
MAGIC(7)	503	ECF Surgery alone	Stomach/GEJ (74/26) Stage ≥II	Age Site Performance status Surgeon	N/A (40%) D1 (19%) D2 (41%)	Yes (survival)	OS (45% vs. 31%) PFS (38% vs. 25%)
Eastern trials							
ACTS-GC(3,4)	1,059	S1 Surgery alone	Stomach (100) Stage II-IIIB	Stage Site	≥D2 (100%)	Yes (survival)	OS (71.7% vs. 61.1%) RFS (65.4% vs. 53.1%) 5 year
CLASSIC	1,035	XELOX Surgery alone				Yes (DFS)	OS HR 0.74, 95% CI 0.53~1.03 DFS 74% vs. 60% 3-year

INT = US Intergroup study; MAGIC = Medical Reseach Council Adjuvant Gastric Cancer Infusion Chemotheraphy; ACTS-GC = Adjuvant Chemotherapy Trial of S1 in Gastric Cancer; ECF = epirubicin, cisplatin, 5-FU; GEJ = gastroesophageal junction; DFS = disease free survival; OS = overall survival; RFS = recurrence free survival; PFS = progression free survival; HR = hazard ratio; CI = confidence interval.

lymphadenectomy and in 40% of the patients the lymphadenectomy was unknown. Japanese surgeons would argue that perioperative chemotherapy or adjuvant chemoradiation compensates for inadequate surgery. Lending support to this, is the fact that the survival in the surgery alone arm is much lower in both Western trials than is seen in Japanese trials or series. Japanese surgeons would argue that the use of these modalities is unproven in patients with a D2 lymphadenectomy. Additionally, the MAGIC trial included lower esophageal lesions which confound its results.

In the East, there have been 3 trials which demonstrated a positive effect of adjuvant chemotherapy. In the National Surgical Adjuvant Study for Gastric Cancer (N-SAS-GC) trial 190 patients with T2N1-2M0 cancers were randomized to uracil-tegafur (UFT) for 16 months or observation.(37) The trial was designed to accrue 500 patients, but unfortunately was closed early due to slow accrual. The study showed a significant survival advantage with adjuvant UFT with 5 year overall survivals of 86% vs. 73% (P=0.017). This trial however has limited statistical power due to its small size.

A second trial from Japan examined the use of adjuvant S1 (tegafur, gimeracil, and oteracil) in Stage II and III gastric cancer. The Adjuvant Chemotherapy trial of S1 for Gastric Cancer (ACTS-GC) randomized 1,034 patients to 12 months of oral S1 or surgery alone.(3) The surgical quality control was excellent, with all centers performing 100 cases annually and all but 1 patient underwent a D2 or D3 lymphadenectomy.(4) The results of the trial demonstrated an improvement in 5 year overall survival of 71.7% vs. 61.1%. Interestingly, the survival benefit was more pronounced in Stage II patients.(3)

The CLASSIC trial, a multi-center trial out of South Korea, China and Taiwan, recently presented results at ASCO. In this trial, 1,035 patients with Stage II or III gastric cancer were randomized to XELOX (capecitabine and oxaliplatin) or surgery alone. There was improvement in the XELOX arm with a 3-year DFS of 74% vs. 60% (P<0.001). There was a trend to improved OS but it did not reach significance (hazard ratio 0.74, 95% confidence interval 0.53~1.03, P=0.0775).

It is difficult to compare the results of the Eastern and Western trials, mainly due to the differences in surgical techniques and survival rates. The survival in the surgery alone arms in all of the Eastern trials is greatly improved over the West. Whether this is a result of a more extensive lymphadenectomy or of differences in biology of disease is unknown.

Outcomes

There are clear discrepancies in the outcomes between the East and West which is apparent in the survival differences in the RCTs. Survival in the surgery alone arms have been 60~70% in Japanese trials as opposed to 30~40% in Western trials.(3,5-7,38) Eastern investigators argue that this is a result of more radical surgery while Western investigators argue that this is a result of earlier detection and differences in biology. There have been many studies that have tried to compare outcomes between Eastern and Western populations. All of these studies are retrospective and the majority of them compare registries. Two trials have evaluated the differences between Asian and Caucasian patients within US in order to assess whether there are inherent biologic differences. Schwartz and colleagues evaluated 75 patients treated at a single institution and compared by race.(16) Race was linked to tumor location, extent of operation and tobacco use but was not associated with differences in survival. This study was obviously limited by its size. Theuer et al performed a study on the California Cancer Registry and compared outcomes based on race in 2,416 patients.(10,11) They found that Asian patients were more likely to be younger, have lymph node negative, and have tumors located in the antrum. The survival was better in Asian Americans with an OS of 20.9% versus 10.2% (P<0.0001) and on multivariate analysis Asian race was a predictor of survival. Data for TMN stage was not available, so accurate comparisons by stage were not performed. A similar study was performed on registry data from 2,043 Canadian patients and demonstrated, however this study showed that ethnicity was not an independent predictor of survival.(39)

Several trials have compared Eastern and Western registries and have demonstrated that Eastern patients have more proximal tumors and lower stage.(18,40) However, even when these differences have been accounted for there still exist survival differences between the two regions.

Memorial Sloan-Kettering Cancer Center (MSKCC) has published two studies comparing outcomes between the East and the West.(12,13) The advantage of these studies is that it MSKCC is one of the few institutions in the US that routinely performs D2 lymph node dissections. The first study compared patients treated at MSKCC to Japanese patients from Kanagawa Cancer Center and Yokohama City University. Although there was a difference in survival between the two regions, when controlled for by tumor location and T stage there were similar survival results. The survival differences were only present in T1 or T2 tumors in the distal

gastric body or T3 tumors occurring in the middle and proximal third.(13) A second study from MSKCC compared US patients to Korean patients. Contrary to the previous study, Korean patients had an improved survival compared to US patients even when matched by T stage and location. The two cohorts were matched by an internationally validated nomogram for DSS of gastric cancer. When matched by nomogram, Korean patients exhibited a better DSS than US patients, suggesting an inherent biologic difference. (12) However, the authors excluded patients who received neoad-juvant therapy to prevent an advantage to the US patients. This left a higher proportion of patients in the Korean cohort that received adjuvant therapy (45% vs. 10%).

Conclusions

There exist clear differences in the both the surgical and adju-vant treatments as well as the long term outcomes in the treatment of gastric cancer between the East and the West. Eastern surgeons perform more radical lymph node dissections, while the practice in the West is driven by the negative results both the UK and Dutch trials. Whether the 15 year results of the Dutch trial will change practices remains to be seen. Western physicians either focus on peri-operative chemotherapy or adjuvant chemoradiotherapy, while those in the East use adjuvant S1.

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