Review Article

Gastric cancer surgery: historical background and perspective in Western countries versus Japan

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Abstract: Gastrectomy plus D2 lymphadenectomy plays a decisive role in the management of resectable gastric cancer in Japan. Before recent advances in chemotherapy, Japanese surgeons considered that extensive surgery involving extended lymphadenectomy with combined resection of neighboring organ(s) was required to eliminate any possible lymphatic cancer spread and improve patient survival. This approach differs radically from that in Western countries, which aim to improve survival outcomes by multidisciplinary approaches including perioperative chemotherapy and/or radiotherapy with limited lymph node dissection. However, a randomized controlled trial conducted in Japan found that more extensive lymphadenectomy including the para-aortic lymph nodes provided no survival benefit over D2 lymphadenectomy. Splenic hilum dissection with splenectomy also failed to show superiority over the procedure without splenectomy in patients with proximal gastric cancer, except in cases with tumor invasion of the greater curvature. Furthermore, bursectomy recently demonstrated similar outcomes to omentectomy alone. Although "D2 lymphadenectomy" as carried out in Japan contributes to low local recurrence rates and good survival outcomes, the results of randomized controlled trials have led to a decreased extent of surgical resection, with no apparent adverse effects on survival outcome. Notably, gastrectomy with D2 dissection has tended to become acceptable for advanced gastric cancer in Western countries, based on the latest results of the Dutch D1D2 trial. Differences in surgical practices between the West and Japan have thus lessened and procedures are becoming more standardized. Japanese D2 lymphadenectomy for advanced gastric cancer is evolving toward more minimally invasive approaches, while consistently striving to achieve the optimal surgical extent, thereby promoting consensus with Western counterparts.

Keywords: Gastric cancer; surgery; lymphadenectomy; Western countries; Japan

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Introduction

Despite a substantial decline in its global incidence, gastric cancer remains the fifth most frequently diagnosed cancer and the third leading cause-related deaths worldwide (1), with an estimated 1,033,701 newly diagnosed cases and 782,685 related deaths in 2018 (2). The incidence rates of gastric cancer in both sexes are highest in Eastern Asia, especially Mongolia, the Republic of Korea, and Japan (2). The first gastrectomy was performed successfully by Billroth in 1881, and radical gastrectomy remains the first choice for achieving a cure in patients with resect able gastric cancer (3-5). Radical gastrectomy involves eradication of the primary lesion with a satisfactory resection margin (R0), together with radical dissection of regional lymph nodes.

However, surgeons have also explored more extensive surgeries aiming to eliminate any possible lymphatic spread by applying extended lymphadenectomy, such as super-extended (D3) lymphadenectomy (6-12) or standardized extended (D2) lymphadenectomy plus para-aortic nodal dissection (PAND) (13-17), together with combined resection, such as prophylactic splenectomy (18-24) or bursectomy (25-30). Radical gastrectomy with D2 dissection has been the standard procedure for locally advanced gastric cancer (AGC) in Japan since 1961 (5,31-36). Gastrectomy with D2 dissection has also recently tended to become acceptable for AGC in Western countries, in light of the latest 15-year follow-up results of the Dutch D1D2 trial, which showed significant survival benefits of D2 over standardized limited (D1) lymphadenectomy (36).

Rapid advances in surgical oncology worldwide have significantly improved the safety of gastrectomy. The 30-day post-gastrectomy mortality rates for patients with gastric cancer in Western countries over the last two decades have ranged from 1.9% to 5.1% (10,37-39), with postoperative in-hospital mortality rates of 5.8% to 9.8% (36,40-42). In contract, the overall operative mortality rates in Japan from 2011 to 2012 were 2.3% after total gastrectomy (43) and 1.07% after distal gastrectomy (44), and the equivalent 30-day mortality rates were 0.9% (43) and 0.45% (44), respectively, which appeared to indicate better outcomes than in Western countries (36-38,40-42,45). However, there remains scope for further global improvements in the safety of gastric cancer surgery. According to the theory of epistemology, involving practice, understanding, re-practice, and re-understanding, the preferred extent of gastric resection and lymph node dissection has experienced a pendulum-like phenomenon, from narrowed to extended, and then narrowed again, gradually rationalized from the original bias. Here, we review and compare the historical backgrounds and perspectives of gastric cancer surgeries in Western countries and Japan.

Epidemiology

Gastric cancer was estimated to account for over a million newly diagnosed cases and nearly 783,000 deaths (equating to 1 in 12 deaths) worldwide in 2018 (2), largely due to population aging and growth (46). One in 27 men and 1 in 68 women will develop gastric cancer before the age of 79 years, with the highest and lowest odds for men in middle (1 in 15) and low-middle sociodemographic index (SDI) countries (1 in 48), respectively, and the highest and lowest odds for women in low (1 in 58) and low-middle (1 in 83) SDI countries, respectively (46). The mortality rates of gastric cancer in men [calculated as age-standardized mortality rate per 100,000 (ASR)] ranged from 4.2 in Switzerland to 24.6 in the Russian Federation among Europe countries, 2.6 in the USA, 25.3 in the Republic of Korea, and 21.0 in Japan during the period 2005–2009 (47). The ASRs for women ranged from 1.9 in France to 10.1 in the Russian Federation, 1.3 in the USA, 9.2 in the Republic of Korea, and 8.0 in Japan, over the same period (47).

Non-cardia gastric cancer (NCGC) is more frequent than cardia gastric cancer (CGC) in most countries, with an estimated 691,000 cases of NCGC and 260,000 cases of CGC worldwide in 2012 (48). Approximately 90% of new NCGC cases were considered to be associated with *Helicobacter pylori* (*H. pylori*) infection (49). However, the incidence of NCGC has been declining worldwide over the last half century, as a result of the decreased prevalence of *H. pylori* and improved food-storage conditions (2). In contract, the incidence of CGC has been steadily increasing, particularly in high income countries, following the distribution characteristics of esophagus cancer in developed countries (50,51), where the incidence rates of Barrett's esophagus are higher than in Eastern countries. The proportion of men with CGC among all gastric cancer cases ranged from 11.6% in Belarus to 72.0% in Finland, and was higher in Northern and Central Europe compared with Southern and Eastern Europe (47). Notably, the incidence of CGC remained unchanged in the USA, according to a recent report (52).

Although the incidence of gastric cancer was expected to follow a decreasing trend owing to a lower incidence of *H. pylori* infection among the younger generation in Japan (53), its incidence has remained the highest of all types of cancers in both males and females (male-to-female ratio >2:1) (54). Considering this high incidence, a cost-effective screening program was initiated to increase the rate of early detection of gastric cancer in Japan. Approximately 48.8% cases were diagnosed with early gastric cancer and 80% of tumors were located in the middle or lower third of the stomach (54-56), with improvements attributed to the screening program (57-62). Notably, the 5-year overall survival rates in Japan were reported to be about 70.0% (54,56), and the good survival outcomes were considered to be least partly attributable to the large proportion of patients diagnosed at an early stage (63).

Table 1 Standards of D1 and D2 lymphadenectomy in Western countries and Japan

Guidelines, year	Country/Region	D1 lymphadenectomy		D2 lymphadenectomy	
		Gastrectomy type	Lymph node stations	Gastrectomy type	Lymph node stations
ESMO, 2016 (4)	Europe	ND	No. 1, 2, 3, 4, 5, 6	ND	No. 1, 2, 3, 4, 5, 6, 7, 8, 9, 11
NCCN, 2017 (3)	USA	ND	No. 1, 2, 3, 4, 5, 6	ND	No. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11
JGCA, 2017 (5)	Japan	Total gastrectomy	No. 1, 2, 3, 4, 5, 6, 7	Total gastrectomy	No. 1, 2, 3, 4, 5, 6, 7, 8a, 9, 10, 11p, 11d, 12a
JGCA, 2011 (32)		Distal gastrectomy	No. 1, 3, 4sb, 4d, 5, 6, 7	Distal gastrectomy	No. 1, 3, 4sb, 4d, 5, 6, 7, 8a, 9, 11p, 12a

ESMO, European Society for Medical Oncology; NCCN, National Comprehensive Cancer Network; JGCA, Japanese Gastric Cancer Association; ND, no details; No. 1, right paracardial lymph node; No. 2, left paracardial lymph node; No. 3, perigastric lymph node along lesser curvature; No. 4sb, perigastric lymph node along greater curvature (left group, lymph node along left gastroepiploic artery and short gastric arteries); No. 4d, perigastric lymph node along greater curvature (right group, lymph node along right gastroepiploic artery); No. 4, perigastric lymph node along greater curvature; No. 5, suprapyloric lymph node; No. 6, infrapyloric lymph node; No. 7, lymph node along left gastric artery; No. 8, lymph node along common hepatic artery; No. 8a, lymph node along common hepatic artery (anterosuperior group); No. 9, lymph node around celiac artery; No. 10, lymph node at splenic hilum; No. 11p, lymph node along proximal splenic artery; No. 11d, lymph node along distal splenic artery; No. 11, lymph node along splenic artery; No. 12a, lymph node in hepatoduodenal ligament (along hepatic artery).

D1 and D2 lymphadenectomy

The extent of lymph node dissection with radical gastrectomy has been extensively debated worldwide. According to the recent clinical practice guidelines of European Society for Medical Oncology (ESMO) for gastric cancer, D1 involves perigastric lymph nodes (LNs) of No. 1, 2, 3, 4, 5, 6 and D2 dissection involves LNs of No.1, 2, 3, 4, 5, 6, 7, 8, 9, 11 (4). In addition, based on the latest National Comprehensive Cancer Network (NCCN) guidelines, D1 involves LNs of No. 1, 2, 3, 4, 5, 6 and D2 dissection involves LNs of No. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 (3). Notably, the Japanese Gastric Cancer Association has clearly identified the extent of systematic lymph node dissection with gastrectomy type. In total gastrectomy, D1 involves LNs of No.1, 2, 3, 4, 5, 6, 7 and D2 dissection involves LNs of No. 1, 2, 3, 4, 5, 6, 7, 8a, 9, 10, 11p, 11d, 12a (5,32). Whereas, in distal gastrectomy, D1 involves LNs of No. 1, 3, 4sb, 4d, 5, 6, 7 and D2 dissection involves LNs of No. 1, 3, 4sb, 4d, 5, 6, 7, 8a, 9, 11p, 12a (5,32) (*Table 1*).

Both the ESMO and NCCN guidelines did not clarify clear relations between gastrectomy types and extents of systematic lymph node dissection; furthermore, both classified No. 7 lymph node in D2 dissection (3,4). Japanese surgeons, on the other hand, have already changed No. 7 lymph node into D1 dissection for any type of gastrectomy, since the 3rd version of the Japanese gastric cancer treatment guidelines in 2011 (5,31,32). The nodal grouping based on the tumor location was abandoned because that it was too complicated to be accurately understood worldwide; notably, the lymph node stations to be dissected in D1 and D2 dissection have been defined according to gastrectomy type regardless of tumor location in Japan since then (31,32).

Surgery in Western countries

The preferred extent of gastric resection has experienced a pendulum-like phenomenon, switching from narrowed to extended, and then narrowed again, gradually becoming rationalized. The first successful case of distal gastrectomy in the West was performed by Billroth in 1881, though the first patient to undergo distal gastrectomy with Billroth I type reconstruction only survived for 115 days. Schlatter *et al.* performed the first total gastrectomy in 1897, while Mikulicz was reported to be the first to successfully perform cardiectomy (64). Notably, they stressed the importance of studying the pathways of gastric cancer spread, and established the foundation of surgical therapy for gastric cancer as follows: direct infiltration of the submucosa and muscularis (operable), dissemination via the lymphatics (operable), transperitoneal spread with lesions involving the full thickness of the stomach wall (inoperable), and dissemination through the blood stream to distant organs (inoperable) (64). This period represented the dawn of gastric cancer surgery, attributed to Mikulicz's theory of lymphatic drainage of the stomach with removal of all

palpable nodes, along with Billroth's contribution to gastric cancer surgery.

Groves *et al.* reported the first case of omentobursectomy in 1910 (65). They addressed the importance of complete removal of the great omentum by cutting through the peritoneum, which passes from the back of the omentum to the front of the transverse colon, followed by stripping the peritoneum off the upper surface of the transverse mesocolon to the front of the pancreas. Furthermore, they emphasized the need for a more systematic attempt to remove the whole of the associated lymphatic area (65). Although the 3-year survival rate was only 7.6%, possibly due to incomplete lymphadenectomy, his theory nevertheless contributed to later lymphadenectomy practices.

During the period from 1940 to1960, many experts in the West reported extensive surgeries with combined resection of neighboring organs with the aim of improving patient survival (66-68); however, the postoperative morbidity and mortality rates were very high. Cattell *et al.* reported combined resection of the stomach and transverse colon in 1946 (69). In 1947, Pack *et al.* reported total gastrectomy for gastric cancer, with an operative mortality of 20–30% (70), followed later by a series of clinical studies of radical or palliative surgeries for gastric cancer (71-74). Brunschwig *et al.* performed the first gastrectomy with pancreatoduodenectomy (PD) for distal gastric cancer invading the head of pancreas in 1948 (66), and Appleby *et al.* introduced a combined procedure in 1953, including resection of the whole stomach, distal pancreas, spleen, and regional lymph nodes (75). Lawrence *et al.* reported 5-year survival rates before and after the application of extensive surgery of 21.6% from 1931–1950, and 23.3% from 1951–1954 (68); however, no randomized controlled trial (RCTs) were available until 1985 to provide sufficient evidence for any strong recommendations.

Whether or not total gastrectomy could improve the survival of patents with distal gastric cancer thus remained to be validated in the West, and several studies comparing survival rates after total and subtotal gastrectomy for distal gastric cancer were conducted after 1970. McNeer *et al.* reported a better 5-year survival rate following total gastrectomy (43.7%) compared with subtotal gastrectomy (29.8%) (76). A similar result was reported by Lortat-Jacob *et al.*, with total gastrectomy showing a higher 5-year overall survival rate but a higher postoperative mortality than subtotal gastrectomy (77). In contrast, however, Gennari *et al.* in 1986 reported a higher 5-year survival rate after subtotal compared with total gastrectomy in patients with lymph node involvement (78). However, those were all retrospective studies with high risks of bias. Notable, the first global RCT comparing total versus subtotal gastrectomy for gastric antrum cancer was conducted in French in 1989 (79), and demonstrated no survival benefits of total over subtotal gastrectomy. A subsequent RCT by the Italian Gastrointestinal Tumor Study Group in 1999 also found no advantage of total gastrectomy over subtotal gastrectomy (80) (*Table 2*). It is therefore necessary to bear in mind the saying of Confucius, that "excess is just as bad as deficiency".

The issue of whether patients may benefit from D2 dissection remained controversial in Western countries (13,34-36). The United Kingdom Medical Research Council Gastric Cancer Surgical Trial (MRC, ST01) confirmed no survival advantages of D2 over D1 dissection (40,81) (*Table 2*). Similarly, the Dutch D1D2 trial in the Netherlands demonstrated D2 dissection was associated with a higher risk of postoperative morbidity (43% *vs.* 25%; P<0.001) and mortality (10% *vs.* 4%; P=0.004) compared with D1 dissection, with no differences in overall survival rate after the 11-year follow-up period (35% *vs.* 30%; P=0.53) (33). Another RCT conducted by the Italian Gastric Cancer Study Group suggested that D2 dissection may only be a better choice only in patients with nodal metastases (45). However, more recent results of the Dutch D1D2 trial after a 15-year follow-up period showed significant survival benefits of D2 over D1 dissection in terms of cancer-related death rate (48% *vs.* 37%), local recurrence (12% *vs.* 22%) and regional recurrence (13% *vs.* 19%) (36).

In light of those findings and the good survival outcomes after D2 dissection in Japan, gastrectomy with D2 dissection is becoming increasingly acceptable in Western countries. The latest National Comprehensive Cancer Network guidelines for gastric cancer stated that D2 dissection should be considered as a recommended but not a required procedure, nothing that the technical aspects of D2 dissection require a significant degree of training and expertise (3). In addition, the latest European Society for Medical Oncology guidelines for gastric cancer suggested that medically fit patients should undergo D2 dissection in specialized, high-volume centers in Western countries (4,82-84) (*Table 2*). However, further studies are still needed to determine if D2 dissection should become the standard procedure for gastric cancer patients in Western countries.

Table 2 Survival and safety outcomes after gastric cancer surgery in Western countries

References	Country	Study type	Population	pT3-T4	pN (+)	Gastrectomy type	Lymphadenectomy	Adjuvant therapy	Survival rate	Morbidity and mortality
Gouzi, *et al.* 1989 (79)	France 1980–1985	Multicenter, prospective, RCT	169	58%	55.1%	TG: 45%; STG: 55%	ND	None	5-YSR: 48%	Postoperative morbidity: 3.7% (TG: 32%, STG: 34%); postoperative mortality: 2.4% (TG: 1.3%, STG: 3.2%)
Cuschieri, *et al.* 1999 (81)	Italy 1982–1993	Multicenter, RCT	618	48.7%	54.5%	TG: 49.0%; STG: 51.0%	D2: 100%	AC: 1.6%	5-YSR: 64.0% (TG: 62.4%, STG: 65.3%)	Overall mortality: 1.8% (TG: 2.3%, STG: 1.3%)
Cuschieri, *et al.* 1996 (40) Bozzetti, *et al.* 1999 (80)	UK 1986–1994	MRC ST01, prospective, RCT	400	43%	ND	TG: 54.5%; DG: 44.8%	D1: 50%; D2: 50%	None	5-YSR: (D1: 35%, D2: 33%)	Serious morbidity: (D1: 12.5%, D2: 23.5%); postoperative mortality: 9.8% (D1: 6.5%, D2: 13%)
Hartgrink, *et al.* 2004 (33) Songun, *et al.* 2010 (36) Bonenkamp, *et al.* 1999 (41)	Netherlands 1989–1993	Dutch D1D2 (DGCT), RCT	711	26.4%	54.9%	TG: 33.9%; PAG: 66.1%	D1: 53.4%; D2: 46.6%	None	11-Y OS rate: (D1: 30%, D2: 35%); 15-Y OS rate: (D1: 21%, D2: 29%)	Morbidity: (D1: 25%, D2: 43%); postoperative mortality: (D1: 4%, D2: 10%)
Edward, *et al.* 2004 (10)	UK 1996–2002	UK NHS Trust, Prospective	118	69.5%	53.4%	TG: 36.4%; STG: 63.6%	D1: 30.5%; D2: 69.5%	None	5-YSR: (D1: 32%, D2: 59%)	Morbidity: (D1: 25%, D2: 23.2%); 30-day mortality: (D1: 8.3%, D2: 7.3%)
Deqiuli, *et al.* 2014 (45)	Italy 1998–2006	IGCSG-R01, multicenter, RCT	267	28.8%	53.2%	TG: 24.7%; DG: 75.3%	D1: 49.8%; D2: 50.2%	No chemotherapy before or after surgery, until recurrence	5-Y OS rate: (D1: 66.5%, D2: 64.2%)	Morbidity: (D1: 12.0%, D2: 17.9%); operative mortality: (D1: 3.0%, D2: 2.2%)
Selby, *et al.* 2015 (38)	U.S. 2003–2012	Retrospective	238	59%	51%	TG: 92%; MITG: 8%	ND	NAC: 43%; AC: 34%	ND	Major morbidity: 28%; 30-day mortality: 2.5%; 90-day mortality: 2.9%

Table 2 (*continued*)

Table 2 (*continued*)

References	Country	Study type	Population	pT3-T4	pN (+)	Gastrectomy type	Lymphadenectomy	Adjuvant therapy	Survival rate	Morbidity and mortality
Papenfuss, *et al.* 2014 (37)	U.S. 2005–2010	ACS NSQIP, multicenter, prospective	2,580	ND	ND	TG: 38.7%; PAG: 61.3%	ND	NAC: 4.8%; NAR: 2.0%	ND	Serious morbidity: 23.6% (TG: 29.3%, PG: 19.9%); 30-day mortality: 4.1%; (TG: 5.4%, PG: 3.4%)

TG, total gastrectomy; PAG, partial gastrectomy; STG, subtotal gastrectomy; PG, proximal gastrectomy; DG, distal gastrectomy; SG, subtotal gastrectomy; NAR, neoadjuvant radiotherapy; NAC, neoadjuvant chemotherapy; AC, adjuvant chemotherapy; MITG, minimally invasive total gastrectomy; 5-YSR, 5-year survival rate; OS: overall survival; RFS: relapse-free survival; PAND, para-aortic nodal dissection; NCD, National Clinical Database; ACS NSQIP, the American College of Surgeons National Surgical Quality Improvement Program; DGCT, Dutch Gastric Cancer Trial; ACTS-GC, Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer; JCOG, Japan Clinical Oncology Group; pT, pathological T stage; pN, pathological N stage; N (+), lymph node metastasis; RCT, randomized controlled trial; ND, no details.

Surgery in Japan

The first successful case of distal gastrectomy in Japan was performed in 1897 by Kondo, a professor from the First Department of Surgery of Tokyo University Hospital (85), while the first case of total gastrectomy in Japan was reported by Miyake *et al.* in 1918. Based on the fact that nodal metastasis was the most frequent type of cancer spread, surgeons in Japan gradually focused on lymphadenectomy from around 1940, with the aim of eliminating any possible nodal metastasis and thus improving survival. Kuru *et al.* first stressed the use of systematic radical lymphadenectomy in 1935 (86), and Kajitani *et al.* in 1944 emphasized the importance of wide lymphadenectomy to eliminate any possible nodal metastasis (87).

Extended surgeries involving extended lymphadenectomy or combined resection of neighboring organs were subsequently performed to improve patient survival. Extended radical surgery with PD was first reported in Japan by Kajitani *et al.* in 1952, for the treatment of distal gastric cancer involving the head of pancreas (88). Jinnai *et al.* advocated the theory of systematic radical lymphadenectomy and stressed the use of extended lymphadenectomy in 1961 (89). Ohashi *et al.* reported 5-year survivors of gastric cancer treated with PAND in 1976 (90) and Kajitani *et al.* introduced left upper abdominal quadrant evisceration for proximal advanced cancer in 1981 (91). In 1989, Ohta *et al.* stressed the value of total gastrectomy combined with pancreaticosplenectomy for middle gastric cancer (92). However, the lack of evidence from RCTs meant that the role of extended surgery in improving patient survival remained controversial until the past two decades.

D2 dissection plus PAND has not demonstrated any survival benefits over D2 dissection alone. The Japan Clinical Oncology Group (JCOG) conducted a multicenter, RCT (JCOG9501) and showed that D2 dissection plus PAND could be performed safely in patients with low operative risk by specialized surgeons, but no significant improvement in survival was observed (13). Notably, the final results of JCOG 9501 in 2008 confirmed that D2 dissection plus PAND (No.16a2, b1) did not improve 5-year overall survival [hazard ratio (HR), 1.03, 95% confidence interval (CI), 0.77–1.37; P=0.85] or recurrence-free survival (HR, 1.08, 95% CI, 0.83–1.42; P=0.56) in patients with curable gastric cancer, compared with D2 dissection alone (16).

Pancreatic resection frequently resulted in pancreatic-juice leakage, subphrenic abscess, and postoperative diabetes, leading Maruyama *et al.* to develop pancreas-preserving surgery in 1979. They also demonstrated gastric cancer tumors only invaded the pancreas directly, rather than by metastasis to the pancreas. Pancreas-preserving surgery proved superior to pancreas resection in terms of operative mortality, hospital mortality, surgical morbidity, and 5-year survival rate (93). Accordingly, lymphatic channels from the stomach did not flow into the pancreas parenchyma, and surgeons could remove the spleen, splenic artery, fatty connective tissues, and lymph nodes completely without dissecting the pancreas parenchyma or splenic vein (93). The results of an RCT conducted by Furukawa *et al.* in 2000 also supported the superiority of pancreas-preserving surgery (total gastrectomy with dissection of lymph nodes along the splenic artery) over pancreas resection in terms of surgical risk and postoperative glucose tolerance (94).

Splenic hilum nodal dissection with splenectomy showed no benefits over the procedure without splenectomy in patients with proximal gastric cancer (24). A recent, multi-institutional, RCT (JCOG0110) conducted in 505 patients from 36 institutions in Japan (24) confirmed that the addition of splenectomy was associated with higher morbidity and blood loss, but similar operation time. The 5-year survival rates were 75.1% in the splenectomy group and 76.4% in the spleen preservation groups (P=0.025). Splenectomy thus increase operative morbidity without improving survival, and should therefore be avoided in patients undergoing total gastrectomy for proximal gastric cancer, unless it invades the greater curvature.

The role of bursectomy in preventing peritoneal metastasis has long been controversial. One RCT found no survival benefit but a high risk of morbidity for bursectomy in patients with cT3-4a gastric cancer (95). In addition, a recent, phase 3 RCT (JCOG1001) that enrolled 1,204 patients from 57 hospitals in Japan confirmed that bursectomy had no survival advantages over non-bursectomy, indicating that D2 dissection with omentectomy alone should be the recommended surgery for resectable cT3-4a gastric cancer in Japan (96). Furthermore, the Japanese Gastric Cancer Association (JGCA) recommended gastrectomy with D2 dissection as the standard surgical procedure for potentially curable gastric cancer (clinical stage ≥ cT2 and/or cN+) in Japan (5).

Japanese surgeons had long believed that gastric cancer patients should receive extensive surgery, including extended lymphadenectomy or with combined resection of neighboring organs, to eliminate any possible nodal spread and thus improve patient survival. In 1991, 67.6% of Japanese patients with gastric cancer underwent D2 dissection, 9.9% underwent D3 or D4 dissection, 30.7% received total gastrectomy, and 30.3% received combined resection of neighboring organs (1,515 splenectomy, 726 pancreatomy) (56). This situation remained unchanged until the introduction of the new anticancer agent, S-1, for advanced gastrointestinal cancer in Japan in 1999, which proved effective against advanced or recurrent gastrointestinal cancer, with generally mild toxicities and no toxic deaths (97,98) (*Table 3*). Since then, rapid advances in chemotherapy (95,99-111), including targeted therapy (112-114), have led Japanese experts gradually to adopt the Western strategy of improving survival by multidisciplinary approaches, including neoadjuvant or adjuvant chemotherapy. The differences in surgical practice for gastric cancer between the West and Japan have thus gradually lessened, and are becoming increasingly standardized.

Future perspectives

Surgical therapy for gastric cancer originated in Western countries and developed rapidly in Japan. Japanese experience suggests that screening programs should be implemented to improve the early detection of gastric cancer, particularly in high incidence areas. Surgical safety and maximizing the probability of a cure should remain the highest priorities; however, chemotherapy, along with genetic diagnosis and targeted therapy, are gaining importance worldwide. Further studies are needed to consider how best to balance the combinations among neoadjuvant or adjuvant chemotherapy and surgery in patients with gastric cancer. Attempts should also be made to reduce the incidence of gastric cancer, in addition to taking account of quality of life and economic costs. Recent developments and modifications of minimally invasive techniques have also attracted increasing interest (115-118), especially in Japan (119-122). Overall, international cooperation between Western and Eastern countries should be encouraged to establish global standards for the diagnosis and therapy of gastric cancer.

Table 3 Survival and safety outcomes after gastric cancer surgery in Japan

Reference	Country	Study type	Population	pT3-T4	pN (+)	Gastrectomy type	Lymphadenectomy	Adjuvant therapy	Survival rate	Morbidity and mortality
Maruyama, *et al.* 2006 (56)	Japan 1991	JGCA registry, retrospective	7,935	26.6%	40.7%	TG: 30.7%; DG: 66.0%; PG: 3.1%; unknown: 0.2%	D1: 19.1%; D2: 67.6%; D3: 8.4%; Others: 4.9%	ND	5-YSR: 68.2% (stage I: 89.9%, stage II: 69.1%, stage III: 43.5%, stage IV: 9.9%)	Direct mortality: 1.0%
Sasako, *et al.* 2008 (16)	Japan 1995–2001	JCOG9501, multicenter, RCT	523	46.5%	66.5%	TG: 74.6%; DG: 4.0%; others: 21.4%	D2: 50.3%; D2 + PAND: 9.7%	No adjuvant therapy before recurrence	5-Y OS rate: (D2: 69.2%, D2+PAND: 70.3%); 5-Y RFS rate: (D2: 62.6%, D2+PAND: 61.7%)	Surgery-related morbidity: (D2: 20.9%, D2+PAND: 28.1%); major surgery-related morbidity: (D2: 2.3%, D2+PAND: 1.9%); 30-day mortality: (D2: 0.8%, D2+PAND: 0.8%)
Sasako, *et al.* 2011 (95)	Japan 2001–2004	ACTS-GC, RCT	1,059	45.4%	89.2%	ND	D2: 100%	S-1 after surgery: 50%	5-Y OS rate: (surgery alone: 61.1%, S-1 after surgery: 1.7%)	ND
Nashimoto, *et al.* 2013 (54)	Japan 2002	JGCA registry, retrospective	13,002	23.5%	40.2%	TG: 30.5%; DG: 59.6%; Others: 9.9%	D1[a]: 41.6%; D2: 49.2%; others: 9.2%	ND	5-YSR: (stage IA/IB: 92.2%/85.3%, Stage II: 72.1%, stage IIIA/IIIB: 52.8%/31.0%, stage IV: 14.9%)	Direct mortality: 0.48%
Sano, *et al.* 2017 (24)	Japan 2002–2009	Multicenter, RCT	505	26.7%	57.8%	TG + splenectomy: 50.3%; TG +spleen preservation: 49.7%	D2: 100%	No adjuvant therapy in the original protocol; later adjuvant S-1 therapy for stage II/III cases for a year	5-Y OS rate: (splenectomy: 75.1%, spleen preservation: 76.4%); 5-Y RFS rate: (splenectomy: 68.4%, spleen preservation: 70.5%)	Postoperative morbidity: 23.6% (splenectomy: 30.3%, spleen preservation: 16.7%); hospital mortality: 0.6% (splenectomy: 0.4%, spleen preservation: 0.8%)
Watanabe, *et al.* 2014 (43)	Japan 2011	NCD, retrospective	20,011	ND	ND	TG: 100%	ND	ND	ND	Morbidity: 26.2%; 30-day mortality: 0.9%; in hospital mortality: 2.2%; Overall operative mortality: 2.3%

Table 3 (*continued*)

Table 3 (*continued*)

Reference	Country	Study type	Population	pT3-T4	pN (+)	Gastrectomy type	Lymphadenectomy	Adjuvant therapy	Survival rate	Morbidity and mortality
Kunisaki, *et al.* 2017 (44)	Japan 2011–2012	NCD, retrospective	65,906	ND	ND	DG: 100%	ND	ND	ND	30-day mortality: 0.5%; Operative mortality: 1.0%
Kurokawa, *et al.* 2018 (96)	Japan 2010–2015	JCOG1001, RCT	1,204	78.7%	49.1%	TG: 34.6%; DG: 65.4%; bursectomy: 50%; omentectomy: 50%	D2: 100%	AC: 60.6%; bursectomy: 60%; omentectomy: 61%	5-Y OS rate: bursectomy: 76.9%, omentectomy: 76.7%	Serious morbidity: 11.7% (bursectomy: 13%, omentectomy: 11%); hospital mortality: 0.5% (bursectomy: 0.17%, omentectomy: 0.83%)

TG, total gastrectomy; PAG, partial gastrectomy; STG, subtotal gastrectomy; PG, proximal gastrectomy; DG, distal gastrectomy; SG, subtotal gastrectomy; NAR, neoadjuvant radiotherapy; NAC, neoadjuvant chemotherapy; AC, adjuvant chemotherapy; MITG, minimally invasive total gastrectomy; a, including D1, D1+α and D1+β; 5-YSR, 5-year survival rate; OS: overall survival; RFS: relapse-free survival; PAND, para-aortic nodal dissection; NCD, National Clinical Database; ACS NSQIP, the American College of Surgeons National Surgical Quality Improvement Program; DGCT, Dutch Gastric Cancer Trial; ACTS-GC, Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer; JCOG, Japan Clinical Oncology Group; pT, pathological T stage; pN, pathological N stage; N (+), lymph node metastasis; RCT, randomized controlled trial; ND, no details.

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Footnote

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