Gastric cancer : staging, treatment, and surgical quality assurance

Dikken, J.L.

PART III

Surgical quality assurance

CHAPTER 10

Quality of care indicators for the surgical treatment of gastric cancer: a systematic review

Johan L. Dikken[a,b*], Jurriën Stiekema[c*], Cornelis J.H. van de Velde[a], Marcel Verheij[b], Annemieke Cats[d], Michel W.J.M. Wouters[a,c], Johanna W. van Sandick[c]

Annals of Surgical Oncology 2012

Department of Surgery[a], Leiden University Medical Center, Leiden, the Netherlands
Departments of Radiotherapy[b], Surgery[c], and Gastroenterology[d],
The Netherlands Cancer Institute - Antoni Leeuwenhoek Hospital, Amsterdam, the Netherlands
*These authors contributed equally to the preparation of this manuscript

ABSTRACT

BACKGROUND

Quality assurance is increasingly acknowledged as a crucial factor in the (surgical) treatment of gastric cancer. The aim of the current study was to define a minimum set of evidence-based quality of care indicators for the surgical treatment of locally advanced gastric cancer.

METHODS

A systematic review of the literature published between January 1990 and May 2011 was performed, using search terms on gastric cancer, treatment, and quality of care. Studies were selected based on predefined selection criteria. Potential quality of care indicators were assessed based on their level of evidence, and were grouped into structure, process, and outcome indicators.

RESULTS

A total of 173 articles were included in the current study. For structural measures, evidence was found for the inverse relationship between hospital volume and postoperative mortality as well as overall survival. Regarding process measures, the most common indicators concerned surgical technique, perioperative care and multimodality treatment. The only outcome indicator with supporting evidence was a microscopically radical resection.

CONCLUSIONS

Although specific literature on quality of care indicators for the surgical treatment of gastric cancer is limited, several quality of care indicators could be identified. These indicators can be used in clinical audits and other quality assurance programs.

INTRODUCTION

Quality assurance is increasingly acknowledged as a crucial factor in the (surgical) treatment of gastric cancer, mainly because outcomes between different providers and different countries vary considerably.[1-3] In Europe, mortality rates after gastric cancer resections range from below 2% in specialized centers,[4] to above 10% in certain nationwide registries,[2] while in Japan mortality rates below 1% are achieved in specialized centers.[5] Also, long term survival rates in Asian centers are superior to those in Western centers, and even within Europe long-term survival shows substantial differences.[3,6,7] In an attempt to reduce these variations in outcomes and to pursue delivery of high quality oncologic care, the European Organisation for Research and Treatment of Cancer (EORTC) has advocated quality assurance programs for radiotherapy and medical oncology.[8,9] More recently, surgical audits for gastric cancer treatment were initiated in the United Kingdom, Denmark, and the Netherlands.[10-12]

Evidence-based treatment guidelines provide a framework for clinical decision making, but seldom incorporate all available quality indicators. Donabedian has proposed a model to evaluate patient care in terms of structure, process, and outcome measures.[13] With this model, quality of care indicators can be assessed in a structural and uniform way. This has been performed for esophageal cancer and breast cancer.[14,15] As yet, no systematic assessment of quality of care indicators for gastric cancer treatment has been performed.

The aims of the present study were to identify evidence-based standards for the surgical treatment of locally advanced gastric cancer, based on a systematic review of the literature, and to construct a minimum set of quality of care indicators for registration and benchmarking in gastric cancer surgery.

METHODS

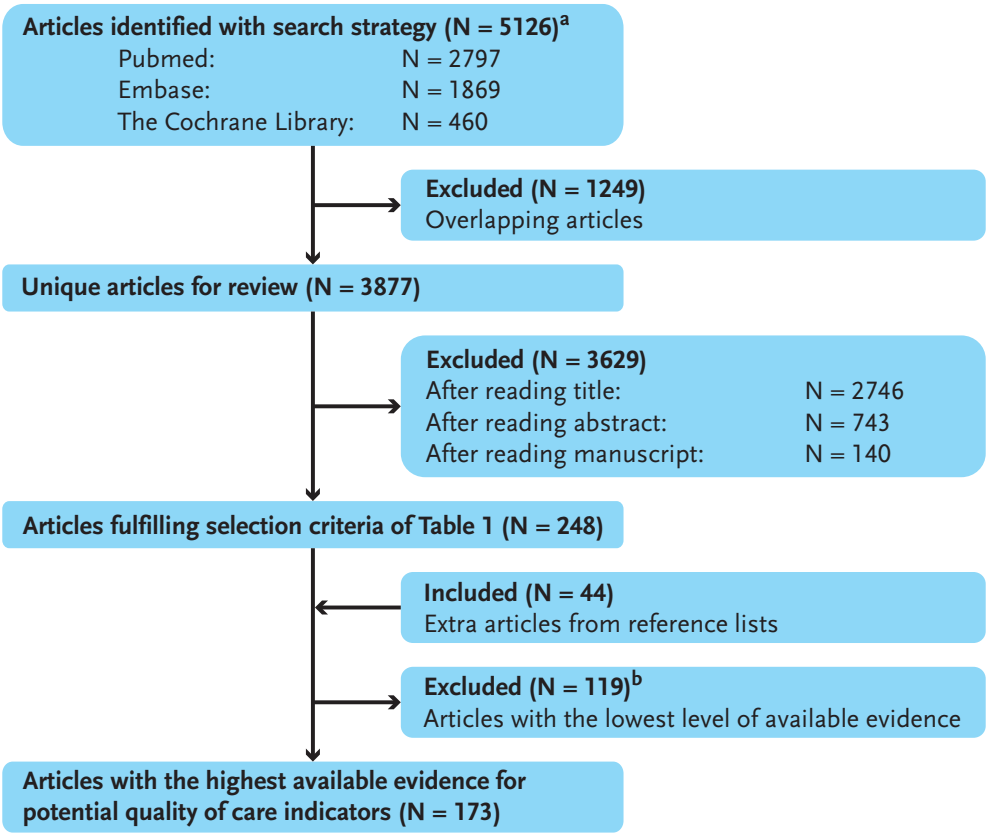
SEARCH STRATEGY

Literature that was published between January 1990 and May 2011 was assessed through Pubmed, Embase, and the Cochrane library, using a search strategy that was constructed by a specialized librarian (Appendix). Search terms on gastric neoplasms were combined with treatment-related search terms (surgery, chemotherapy, and radiotherapy). Because there is no universal Medical Subject Headings (MeSH) term available to identify studies on quality of care, a variety of search terms related to this subject was used to select studies appropriate for this review.

SELECTION OF STUDIES

Study selection criteria were created using a Delphi technique[16] with four authors (JLD, JS, JWvS and MWJMW) and are shown in Table 1. Only comparative studies on locally advanced (at least T2), non-metastatic gastric cancer were selected. Treatment should

Figure 1. Selection process



[a] The used search strategy is outlined in the Appendix
[b] Levels of evidence are described in the Methods section (Selection of studies)

consist of a gastric resection, with or without chemotherapy and/or radiotherapy before and/or after the operation. Two investigators (JLD and JS) independently reviewed each title, abstract, and manuscript (Figure 1). Disagreements on selecting a study were solved by discussion, or by consulting a third reviewer (JWvS). Reference lists of the selected articles were then searched for additional studies.

Different levels of evidence were distinguished. A meta-analysis of at least 2 randomized controlled trials (RCTs) was considered the highest level of evidence. The next level of evidence consisted of one or more RCTs, and the lowest level of evidence comprised non-randomized studies (prospective or retrospective). When at least five meta-analyses were available for a certain indicator, RCTs on the same subject were not included in the current review. When at least one RCT with at least 100 patients was available for a certain indicator, non-randomized studies on the same subject were not included.

Table 1. Inclusion and exclusion criteria

	Included	Excluded
Publication	January 1990 - May 2011 English language	before 1990, after May 2011 non-English language
Study design	In order of availability: meta-analysis RCT[1] non-randomized comparative study[2]	non-comparative study (including systematic reviews, non-systematic reviews, case reports, phase I/II studies)
Study population	≥50 gastric cancer patients at least T2 tumor	gastric cancer patients with: T1 tumor metastatic disease recurrent disease
Treatment	open or laparoscopic gastric cancer surgery with or without (neo)adjuvant chemo- and/ or radiotherapy	palliative treatment salvage surgery emergency surgery esophageal-cardia resection endoscopic (sub)mucosal resection intraperitoneal chemotherapy intraoperative radiotherapy targeted therapy

RCT: Randomized Controlled Trial
[1] when at least five meta-analyses were available for a certain indicator, RCTs on the same subject were not included in the current review
[2] when at least one RCT with at least 100 included patients was available for a certain indicator, non-randomized studies on the same subject were not included in the current review

QUALITY OF CARE INDICATORS

Potential quality of care indicators were grouped into the three categories as defined by Donabedian: structure, process, and outcome.[13] *Structure* indicators relate to the setting in which care takes place. *Process* indicators refer to the actual medical treatment that is applied to the patient. *Outcome* indicators reflect the outcome of healthcare.

To be entered into a minimum set of evidence-based quality of care indicators for gastric cancer surgery, indicators needed support of at least one meta-analysis, two RCTs, or one RCT either with at least 100 patients or with an adequate power analysis supporting less than 100 included patients, or at least three non-randomized studies with multivariate analysis. In case of conflicting evidence for a certain indicator, RCTs were considered decisive over non-randomized studies. For conflicting studies with equal levels of evidence, the number of non-supporting studies was subtracted from the number of supporting studies.

RESULTS

A total of 3.877 unique articles published between January 1990 and May 2011 was identified with the literature search. These articles were reviewed, and 248 articles fulfilled the selection criteria shown in Table 1. In the reference lists of the selected articles, 44 studies matched with the selection criteria for this study. Articles were then grouped by subject and categorized based on their level of evidence. In the final selection step, articles with the highest level of evidence for a certain indicator were separated from

those with lower levels of evidence on that subject. In total, 173 articles were included in the current review (Figure 1).

STRUCTURE INDICATORS (TABLE 2)

Many studies have been performed analyzing possible volume-outcome relations in gastric cancer surgery (Table 2). In the majority of these studies, the effect of hospital volume on postoperative mortality was investigated, with variable results.[12,17-33] Of note, in most large studies, a benefit for high annual hospital volume was found, while in smaller studies no difference between high volume and low volume hospitals was detected (Figure 2). In none of these studies, high hospital volume was associated with poor outcomes. In the studies that did find a relation between volume and outcomes, there was no uniform threshold for what should be considered high volume surgery, although it was most frequently set at 20 per year.

In a limited number of studies surgeon volume and surgeon experience were investigated, with a benefit for increasing surgeon volume,[17,20,23,34,35] but no benefit for increasing surgeon experience.[20,36] In two studies, outcomes between university/teaching and non-university/non-teaching hospitals were compared, but no difference in survival was documented.[26,37]

PROCESS INDICATORS – SURGERY (TABLE 3)

EXTENT OF LYMPH NODE DISSECTION

Numerous studies have been performed in which a limited lymph node dissection (D1) was compared with an extended lymph node dissection (D2), but only four of these studies were RCTs.[4,38-40] None of these RCTs revealed a difference in overall survival, except for a small, early study.[39]

The increased postoperative mortality in the D2 group is likely the result of the high number of splenectomies and distal pancreatectomies, combined with a lack of experience with D2 lymph node dissections in Europe. As gastric-cancer specific survival in the Dutch D1D2 study was higher after a D2 dissection, it has been suggested that a D2 dissection without splenectomy, performed in an experienced center will lead to improved survival as compared to a D1 dissection.[40] In a Taiwanese RCT performed in specialized centers, a D3 dissection led improved overall survival over a D1 dissection.[41] Combining an extended lymph node dissection with removal of the paraaortic nodes did not result in a survival benefit.[5,42,43]

LAPAROSCOPIC RESECTION

Laparoscopic resections for gastric cancer are mainly performed in Asia, where the incidence of early gastric cancer is high. In the majority of studies on laparoscopic surgery, only patients with early gastric cancer were included. There is one RCT comparing laparoscopic distal gastrectomy (LDG) with open distal gastrectomy in

Table 2. Structure Measures

Structure measure	End point	Indicator	MA (+/-/=)	RCT (+/-/=)	NRS (+/-/=)	Ref.
Hospital volume (high versus low)	overall survival	high volume	NA	NA	5/0/2	17,28,31,33,138-140
	postoperative mortality	high volume			11/0/8	12,17-33
	postoperative morbidity	high volume			2/0/2	25,29,141,142
	length of hospital stay	high volume			0/0/1	29
	number of lymph nodes	high volume			2/0/0	12,143
Surgeon volume (high versus low)	postoperative mortality	high volume	NA	NA	3/0/1	17,20,23,34
	postoperative morbidity	high volume			1/0/0	34
	overall survival	high volume			0/0/2	17,35
Surgeon experience (experienced versus non-experienced)	postoperative mortality	experienced	NA	NA	0/0/2	20,36
	postoperative morbidity	experienced			0/0/1	36
	peroperative blood loss	experienced			0/0/1	36
University/teaching hospital	overall survival	university/teaching hospital	NA	NA	0/0/2	26,37
NCI-NCCN Center[a]	postoperative mortality	NCI-NCCN Center	NA	NA	1/0/0	143
	number of lymph nodes	NCI-NCCN Center			1/0/0	143

[a]only in United States

Legend to Tables 2-7

+	number of studies indicating a positive effect of the indicator on the endpoint listed
-	number of studies indicating a negative effect of the indicator on the endpoint listed
=	number of studies with no significant difference between the indicator and its opposite with regard to the endpoint listed
Excl.	excluded
LDG	laparoscopic distal gastrectomy
LG	laparoscopic gastrectomy
LMWH	low molecular weight heparin
LN	lymph nodes
LND	lymph node dissection
MA	meta analysis
NA	not available
NCI-NCCN Center	National Cancer Institute - National Comprehensive Cancer Network Center
NRS	non randomized study
ODG	open distal gastrectomy
OG	open gastrectomy
PAND	paraaortic lymph node dissection
R0	microscopically radical resection
R1	microscopically irradical resection
RCT	randomized controlled trial
Ref.	references
RY	roux-en-y reconstruction
SG	subtotal gastrectomy
TG	total gastrectomy
TG-PS	total gastrectomy + pancreaticosplenectomy
TG-S	total gastrectomy + splenectomy

patients with advanced gastric cancer.[44] LDG was associated with less blood loss, earlier resumption of food intake and shorter hospital stay (*postoperative recovery* in Table 3), but postoperative mortality and morbidity, and overall survival were comparable between the two groups. Likewise, in most non-randomized comparative series, laparoscopic gastric cancer surgery was comparable to open surgery with respect to both short- and long-term results.[45-53] In several non-randomized studies, one should be aware of a significant difference in disease stage between the laparoscopic and open surgery group.

Table 3. Process Measures - surgery

Process measure	End point	Indicator	MA (+/-/=)	RCT (+/-/=)	NRS (+/-/=)	Ref.
Extent of lymph node dissection						
D1 versus D2 LND	overall survival	D2 LND	0/0/2	0/1/2	Excl.	38-40,144,145
	disease-specific survival		NA	1/0/0		40
	recurrence rate		1/0/0	0/0/1		40,144
	postoperative mortality		0/2/0	0/2/1		4,40,144-146
	postoperative morbidity		0/0/1	0/2/1		39,40,144,146
	transfusion requirement		NA	0/1/0		39
D1 versus D3 LND	overall survival	D3 LND	NA	1/0/0	Excl.	41
	postoperative morbidity			0/1/0		147
	operating time			0/1/0		147
	quality of life			0/0/1		148
D2 versus D2+PAND	overall survival	D2+PAND	0/0/1	0/0/2	Excl.	5,42,43
	postoperative mortality		0/0/1	0/0/2		42,149,150
	postoperative morbidity		0/0/1	0/1/1		42,149,150
	body weight		NA	0/0/1		151
	functional outcomes			0/0/1		151
	operating time			0/1/0		152
	blood loss			0/1/0		152
Removal of celiac nodes	long term complaints	celiac node removal	NA	NA	0/1/0	153
D1/2 versus D3/4	lymphorrea	D1/2	NA	NA	1/0/0	154
Laparoscopic resection						
LDG versus ODG	overall survival	LDG	NA	0/0/1	0/0/2	44,47,52
	postoperative mortality			0/0/1	0/0/5	44,47-49,52,53
	postoperative morbidity			0/0/1	0/0/5	44,47-49,52,53
	postoperative recovery			1/0/0	5/0/0	44,47-49,52,53
	number of lymph nodes			0/0/1	0/0/2	44,48,52
LG versus OG	overall survival	LG	NA	NA	0/0/2	46,50
	postoperative mortality				0/0/3	46,50,51
	postoperative morbidity				0/1/3	45,46,50,51
	postoperative recovery				2/0/0	46,51
	number of lymph nodes				1/0/1	46,50
	resection margins				0/0/2	46,50
	intraperitoneal cancer cells				0/0/1	155
Type of resection						
Total versus subtotal gastrectomy	overall survival	SG	NA	0/0/1	1/0/6	54,156-162
	postoperative mortality			0/0/1	0/0/6	55,156,159-163
	postoperative morbidity			0/0/1	0/0/6	55,156,159-163
	postgastrecomty symptoms			1/0/0	NA	164
	weight			NA	2/0/0	159,163
	quality of life			1/0/0	2/0/0	163-165
TG versus TG-S	overall survival	TG	0/0/1	0/0/2	NA	56,166,167
	postoperative mortality		0/0/1	0/0/2		56,166,167
	postoperative morbidity		0/0/1	0/1/1		56,166,167
	number of harvested LNs		0/0/1	0/0/1		166,167

Table 3 (continued)

Process measure	End point	Indicator	MA (+/-/=)	RCT (+/-/=)	NRS (+/-/=)	Ref.
TG-S versus TG-PS	overall survival	TG	NA	0/0/1	0/1/2	57,58,168,169
	postoperative mortality			0/0/1	0/1/2	57,58,168,169
	postoperative morbidity			0/0/1	0/3/0	57,58,168,169
	number of harvested LNs			0/0/1	1/0/0	57,168
	glucose intolerance			0/1/0	0/2/0	57,58,168
TG versus TG-PS	overall survival	TG	NA	NA	0/1/2	59-61
	postoperative mortality				0/0/3	59-61
	postoperative morbidity				0/3/0	59-61
Bursectomy	postoperative mortality	bursectomy	NA	0/0/1	NA	62
	postoperative morbidity			0/0/1		62
Multiorgan resection (yes versus no)	overall survival	multiorgan resection	NA	NA	0/1/2	170-172
	postoperative mortality				0/0/2	171,172
	postoperative morbidity				0/0/2	171,172
Type of reconstruction						
Pouch reconstruction after total gastrectomy (yes versus no)	postoperative mortality	pouch	0/0/2	0/0/3	Excl.	63,64,66,173,174
	postoperative morbidity		0/0/2	0/0/3		63,64,66,173,174
	post gastrectomy symptoms		1/0/1	0/0/2		63,64,173,174
	quality of life		2/0/0	2/0/1		63-66,174
	weight		1/0/1	1/0/3		63-66,173,174
Billroth I versus Billroth II reconstruction	overall survival	Billroth II	NA	0/0/1	NA	67
	postoperative mortality			0/0/1	NA	67
	postoperative morbidity			1/0/0	0/0/1	67,70
	hospital stay			NA	0/0/1	70
Billroth I/II versus RY reconstruction	postoperative morbidity	RY	NA	0/0/1	0/0/1	68,69
	hospital stay			0/0/1	1/0/0	68,69
	bile reflux			0/0/1	NA	68
Hand sewn versus stapled anastomosis	postoperative mortality	stapled	NA	0/0/1	0/0/2	71-73
	postoperative morbidity			0/0/1	0/0/2	71-73
	delayed gastric emptying			NA	0/1/0	71
	operation time			0/0/1	1/0/0	71,72
Other surgery-related factors						
Use of Ligasure (yes versus no)	postoperative mortality	Ligasure	NA	0/0/1	NA	175
	postoperative morbidity			0/0/1		175
	operating time/blood loss			1/0/0		175
	number of harvested LN			0/0/1		175
Seprafilm versus no seprafilm	postoperative mortality	Seprafilm	NA	0/0/1	NA	176
	postoperative morbidity			0/0/1		176
	small bowel obstruction			0/0/1		176
Duration of surgery	surgical site infection	shorter operation time	NA	NA	1/0/0	177
Ligation versus cauterization of lymphatic vessels	postoperative lymphorroea	ligation	NA	NA	1/0/0	154
Transverse versus midline incision	postoperative morbidity	transverse	NA	0/0/1	NA	178
	intestinal obstruction			0/0/1		178
	postoperative pain			0/0/1		178
Prophylactic drain versus no drain	postoperative morbidity	no drain	NA	0/0/2	NA	179,180
	postoperative mortality			0/0/1		180
	analgesic use			1/0/0		179
	hospital stay			1/0/1		179,180
Intra-operative blood loss	peritoneal recurrence	< 475 ml blood loss	NA	NA	1/0/0	181

TYPE OF RESECTION

In the largest RCT on subtotal versus total gastrectomy for distal gastric tumors, no difference was observed in overall survival or postoperative mortality or morbidity.[54,55] Routine (pancreatico)splenectomy has been advocated to obtain a more thorough lymph node dissection. However, a survival benefit has never been shown. In contrast, routine splenectomy increased the number of postoperative septic complications in a Chile RCT.[56] The addition of a pancreatectomy also increased postoperative morbidity in a number of studies.[57-61] A bursectomy did not result in increased postoperative morbidity and mortality, but a survival analysis is yet to be performed in the single RCT on this subject.[62]

TYPE OF RECONSTRUCTION

A benefit of creating a reservoir or pouch after total gastrectomy was found in two meta-analyses and two RCTs.[63-66] Studies on reconstructive techniques after subtotal gastric resection have shown varying results, and no large RCTs are available on this subject.[67-70] In two studies comparing a stapled with a hand-sewn anastomosis, no difference was found in postoperative mortality or morbidity, while in one retrospective study, stapler use was associated with an increase in delayed gastric emptying.[71-73]

Several other subjects related to surgical technique are shown in Table 3.

PROCESS INDICATORS – PERIOPERATIVE CARE (TABLE 4)

The administration of perioperative parenteral nutrition reduced postoperative morbidity in malnourished patients in one retrospective study.[74] In another study, there was no significant difference between the groups with and without enteral and/or parenteral nutritional support.[75] In three RCTs, immunonutrition was associated with less infectious complications and a shorter hospital stay.[76-78] Due to its high costs, shorter hospital stay did not lead to less overall costs.[77]

In earlier days, nasogastric decompression has been used routinely to prevent anastomotic leakage, enhance bowel function and shorten hospital stay. However, in none of the studies, a benefit in postoperative morbidity or mortality of routine nasogastric or nasojejunal decompression was documented. In contrast, in three RCTs, hospital stay increased with the use of nasogastric decompression.[79-81]

In both RCTs on fast-track gastric cancer surgery, fast-track care improved postoperative recovery (return to normal gastro-intestinal function, analgesic use, mobilization, and hospital stay) as compared to conventional care.[82,83] Both RCTs were performed in China. One of the two studies also showed a significant decrease in medical costs with fast-track care.[83]

Randomized studies on the prognostic impact of perioperative blood transfusions in gastric cancer surgery are not available, and non-randomized studies show conflicting results. In nine retrospective series, an association was found between no blood

Table 4. Process Measures - perioperative care

Process measure	End point	Indicator	MA (+/-/=)	RCT (+/-/=)	NRS (+/-/=)	Ref.
Perioperative nutritional support versus normal diet	postoperative mortality	nutritional support	NA	NA	0/0/2	74,75
	postoperative morbidity				1/0/1	74,75
Immunonutrition	postoperative mortality	immunonutrition	NA	0/0/3	NA	76-78
	postoperative morbidity			3/0/0	NA	76-78
Nasogastric decompression	postoperative mortality	nasogastric decompression	0/0/1	0/0/6	Excl.	79-81,182-185
	postoperative morbidity		0/0/1	0/0/6		79-81,182-185
	time to flatus/intake		0/1/0	0/3/3		79-81,182-185
	hospital stay		0/0/1	0/3/3		79-81,182-185
Early versus traditional oral feeding	postoperative mortality	early feeding	NA	NA	0/0/1	186
	postoperative morbidity				0/0/1	186
	postoperative recovery				1/0/0	186
Fast track care versus conventional care	postoperative mortality	fast track	NA	0/0/2	NA	82,83
	postoperative morbidity			0/0/2		82,83
	postoperative recovery			2/0/0		82,83
Perioperative transfusion versus no transfusion	overall survival	no transfusion	NA	NA	4/0/5	84-92
	postoperative mortality				0/0/2	92,187
	postoperative morbidity				0/0/2	92,187
LMWH prophylaxis vs no prophylaxis	postoperative morbidity	LMWH prophylaxis	NA	NA	0/1/0	188
	postoperative recovery				0/0/1	188
Selective bowel decontamination	anastomotic leakage	selective bowel decontamination	NA	1/0/0	NA	93
Single versus multiple dose antibiotics	surgical site infection	multiple dose antibiotics	NA	1/0/0	NA	94

transfusion and a better survival rate in univariate analysis.[84-92] In four of these studies, this adverse effect remained significant in multivariate analysis considering other prognostic factors.[85,88,90,91]

In one RCT on selective bowel decontamination, a decreased anastomotic leakage rate was found.[93] In another study, the use of multiple dose antibiotics was associated with less surgical site infections than the use of single dose antibiotics.[94]

PROCESS INDICATORS – MULTIMODALITY THERAPY (TABLE 5)

NEOADJUVANT THERAPY

In several studies, the role of preoperative chemotherapy was assessed, but in none of these individual studies a benefit compared to surgery alone was found.[95-97] However, in a recent meta-analysis on preoperative chemotherapy, a benefit in survival was documented.[98] In the British MAGIC study, perioperative chemotherapy improved overall survival.[99] In a study comparing preoperative with postoperative chemotherapy, a higher treatment compliance was observed in the preoperative chemotherapy group.[100] Preoperative radiotherapy has only been tested positive in a study with gastric cardia cancer patients.[101]

Table 5. Process Measures - multimodality treatment

Process measure	End point	Indicator	MA (+/-/=)	RCT (+/-/=)	NRS (+/-/=)	Ref.
Neo-adjuvant treatment						
Preoperative chemotherapy	overall survival	preoperative chemotherapy	1/0/0	0/0/3		95-98
	R0 resection rate		1/0/0	1/0/1	Excl.	95,96,98
	morbidity		NA	1/0/0		96
Preoperative versus postoperative chemotherapy	treatment compliance	preoperative chemotherapy	NA	1/0/0	Excl.	100
	morbidity			0/0/1		100
Perioperative chemotherapy	overall survival	perioperative chemotherapy	NA	1/0/0	Excl.	99
	R0 resection rate			0/0/1		99
Preoperative radiotherapy	overall survival	preoperative radiotherapy	NA	0/0/1	Excl.	189
	mortality			0/0/1		189
	morbidity			0/0/1		189
Adjuvant treatment						
Adjuvant chemotherapy	overall survival	adjuvant chemotherapy	9/0/1	Excl.	Excl.	102-111
Single-agent versus combination chemotherapy	overall survival	combination chemotherapy	1/0/0	Excl.	Excl.	111
Postoperative chemoradiotherapy	overall survival	postoperative chemoradiotherapy	NA	1/0/0	Excl.	112
Postoperative radiotherapy	overall survival	postoperative radiotherapy	NA	0/0/1	Excl.	190
Postoperative chemotherapy versus postoperative chemoradiotherapy	overall survival	postoperative chemoradiotherapy	NA	0/0/2	Excl.	191,192
Postoperative D-galactose	overall survival	postoperative D-galactose	NA	1/0/0	NA	193
	hepatic metastases			1/0/0		193

ADJUVANT THERAPY

Many studies have been performed on adjuvant chemotherapy after a gastric cancer resection, and most of these studies have been incorporated in several meta-analyses.[102-111] In all but one of the meta-analyses, a small, but significant benefit for the use of adjuvant chemotherapy was shown. Multi-drug regimens have been associated with better survival when compared to single-drug regimens.[111] In the Intergroup 0116 study, overall survival was higher in the postoperative chemoradiotherapy group when compared to the surgery alone group.[112]

OUTCOME INDICATORS (TABLE 6)

In many studies, the prognostic benefit of a microscopically radical (R0) resection over microscopically irradical (R1) resection has been shown.[35,113-128] Patients who have clear resection margins have a higher survival, and fewer local recurrences. In three studies, an association between an increasing number of removed lymph nodes and higher survival was reported.[129-131]

Table 6. Outcome Measures

Outcome measure	End point	Indicator	MA (+/-/=)	RCT (+/-/=)	NRS (+/-/=)	Ref.
R0 versus R1 resection	overall survival	R0 resection	NA	NA	15/0/1	[35,113-128]
	local recurrence				1/0/0	[113]
Clear versus involved esophageal margin	overall survival	clear margin	NA	NA	0/0/1	[114]
	local recurrence				1/0/0	[114]
	postoperative morbidity				0/0/1	[114]
	postoperative mortality				0/0/1	[114]
Number of lymph nodes evaluated (<15 versus >15)	overall survival	>15 nodes	NA	NA	2/0/0	[129,130]
Number of lymph nodes evaluated (<26 versus >26)	overall survival	>26 nodes	NA	NA	1/0/0	[131]
	postoperative mortality				0/0/1	[131]
	postoperative morbidity				0/0/1	[131]

MINIMUM SET OF QUALITY OF CARE INDICATORS

After applying the predefined selection rules as outlined in the Methods section (subheading Quality of care indicators), thirteen evidence-based quality of care indicators were identified (Table 7). Hospital volume was the only indicator on the structure of healthcare. As high annual hospital volume was defined as at least 20 resections per year in the majority of positive studies, this number has been added to the indicator. The majority of indicators in the set reflect the process of care. A microscopically radical resection was the only outcome indicator.

DISCUSSION

In this systematic review of the literature, evidence-based quality of care indicators for the surgical treatment of gastric cancer were identified. Possible indicators were evaluated in terms of structure, process and outcome measures as proposed by Donabedian.[13]

STRUCTURE INDICATORS

High volume gastrectomy was associated with lower postoperative mortality in most large studies (>5,000 patients included), but not in the smaller studies (Figure 2). This indicates that sufficient patient numbers are needed in order to show a significant volume-outcome relation. Limited evidence was found for surgeon volume as a quality indicator. This underlines the importance of the multidisciplinary and perioperative team in the (surgical) treatment of gastric cancer. Both findings are in concordance with a recent meta-analysis on hospital and surgeon volume in the surgical treatment of esophageal cancer.[132] Nevertheless, results of volume – outcome analyses need to be interpreted with caution. Heterogeneity in patient population and treatment can introduce bias in such studies and ideally, outcome data are adjusted for case-mix factors. Nationwide registries in which patient and treatment characteristics are prospectively collected will give further insight in structure of care indicators in the future.

Table 7. Minimum set of evidence-based quality of care indicators for gastric cancer surgery

Type	Quality of care indicator	Improved end points	Level of evidence
Structure	high hospital volume (>20/year)	overall survival postoperative mortality	NRS
Process	D2/3 lymph node dissection[a]	disease specific survival overall survival	RCT
	no routine (pancreatico)splenectomy	postoperative morbidity	NRS
	pouch reconstruction	quality of life	MA
	fast-track care	postoperative recovery	RCT
	no perioperative blood transfusion	overall survival	NRS
	selective bowel decontamination	anastomotic leakage rate	RCT
	multiple dose antibiotics	surgical wound infection rate	RCT
	preoperative chemotherapy	overall survival	MA
	perioperative chemotherapy	overall survival	RCT
	adjuvant (combination) chemotherapy	overall survival	MA
	postoperative chemoradiotherapy	overall survival	RCT
Outcome	R0 resection	overall survival	NRS

[a]in centers with low postoperative mortality

PROCESS INDICATORS

In the published literature on quality of gastric cancer surgery, a broad variety of process indicators has been analyzed.

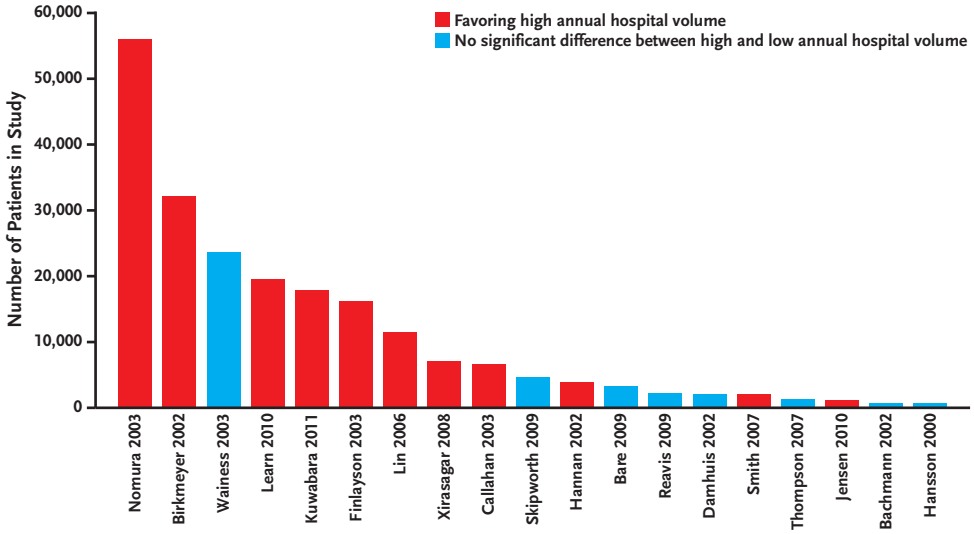
SURGICAL TECHNIQUE

The extent of lymph node dissection has been the subject of many studies. In initial reports, a D2 lymph node dissection was associated with increased postoperative mortality without a survival benefit as compared to D1 surgery.[38,133] Long term results from the Dutch D1D2 study, however, revealed an improved gastric cancer specific survival after a D2 dissection.[40] From this, it can be concluded that, when postoperative mortality can be avoided, a D2 lymphadenectomy should be recommended. In experienced centers, postoperative mortality after a D2 lymph node dissection is low.[4] Additional (pancreatico) splenectomy has been associated with increased postoperative morbidity without any survival benefit.[59-61]

PERIOPERATIVE CARE

While fast-track surgery has proven its benefit in colorectal cancer surgery, the number of studies in gastric cancer is limited. In two recent RCTs, fast-track care was shown to be feasible (in China) and was associated with a shorter hospital stay, less medical costs, and improved quality of life at discharge when compared to conventional care.[82,83] The widespread introduction of fast-track surgery programs or clinical care pathways in the management of gastric cancer patients deserves further attention as it potentially contributes to a higher level of care.

Figure 2. Studies on the relation between annual hospital volume and postoperative mortality, ordered by the number of included gastric cancer patients[12,14-30]



A negative impact of perioperative blood transfusion on overall survival was seen in univariate analysis in nine studies. In only four studies, blood transfusion remained an adverse prognostic factor in multivariate analysis, and it should be avoided without jeopardizing best supportive care.[85,88,90,91] Similar results have been observed in colorectal cancer surgery.[134] Selective bowel decontamination emerged as a quality of care indicator as it decreased the risk of anastomotic leakage and its clinical sequelae in a large RCT.[93] In a more recent RCT, preoperative intravenous administration of multiple dose antibiotics was associated with less surgical wound infections than the use of single dose antibiotics.[94]

MULTIMODALITY TREATMENT

In a recent meta-analysis, preoperative chemotherapy was associated with improved survival.[98] In this meta-analysis, patients from trials on perioperative chemotherapy were also included. Adjuvant chemotherapy has been administered for many years, and its survival benefit has been confirmed in several meta-analyses.[102-111] In the Western world however, an optimal regimen for postoperative chemotherapy has not been yet established. In Japan, postoperative chemotherapy is standard of care. Following the results of the Intergroup 0116 study, postoperative chemoradiotherapy is currently standard of care in the United States.[112,135] In Europe, perioperative chemotherapy has been advocated, according to the results of the MAGIC study.[99] The international multicenter CRITICS study will give an answer to the question whether postoperative chemoradiotherapy improves survival as compared to postoperative chemotherapy in patients who undergo gastric cancer resection after preoperative chemotherapy.[136]

OUTCOME INDICATORS

Radicality of the resection and the number of resected lymph nodes are frequently used as outcome parameters when measuring quality of oncologic surgery. In gastric cancer surgery, a large number of studies support a microscopically radical resection to be considered as a quality of care indicator.[35,113-128] The number of studies on the number of evaluated lymph nodes in relation to outcomes was too small to identify this factor as an evidence-based quality of care indicator.[129-131]

CONCLUSIONS

From the current review, it becomes clear that improving the quality of care in the treatment of gastric cancer is a multidisciplinary team effort in which surgical technique is only one of the contributing factors. High quality perioperative care asks for well trained nurses, experienced anesthesiologists, and ICU staff.[137] Furthermore, outcome of gastric cancer surgery is obviously dependent on the experience of other specialists in the multidisciplinary team (i.e., medical oncologists, gastroenterologists, radiation oncologists).

The set of indicators that was derived from the current study can be used for registration and benchmarking in gastric cancer surgery. Most indicators in clinical audits, as established in the United Kingdom, Denmark, Sweden, and the Netherlands are derived from expert panel discussions. With the current review, the datasets in these audits may be supplemented with evidence-based quality of care indicators. Furthermore, the proposed minimum set of indicators can be used for uniform reporting in future studies on quality of gastric cancer surgery.

A limitation of the current study is the absence of a MeSH search term for studies related to 'quality of care'. Therefore, the search strategy included a variety of search terms for different aspects of care. This might have influenced the set of studies in the final selection. Furthermore, due to the large number of studies that emerged from the search strategy, stringent criteria for inclusion were used. Approximately 60% of included manuscripts in the current literature review are from Western countries, whereas approximately 40% of the included manuscripts are from Asia. A large amount of literature from Asia was excluded from the current review because part of these studies are written in non-English languages, while another large part focused on early gastric cancer, which was not the subject of the current review. Therefore, quality of care indicators derived from the current study are likely to be more applicable to Western countries than to Asian countries. Finally, although the identified quality of care indicators reflect best practice for gastric cancer surgery, none of the studies actually validated a best practice indicator as a tool to measure differences in quality of care between different providers.

Appendix. Pubmed, Embase, and Cochrane search terms

Pubmed
Limits activated: English, Publication Date from 1990
("stomach neoplasms"[mesh] OR (stomach[All Fields] OR gastric[all fields]) AND (neoplasms[all Fields] OR neoplasm[all fields] OR tumor[all fields] OR tumors[all fields] OR tumor[all fields] OR tumors[all fields] OR cancer[all fields] OR cancers[all fields] OR carcinoma[all fields] OR carcinomas[all fields])))
AND
("gastrectomy"[mesh] OR "gastrectomy"[all fields] OR "gastrectomies"[all fields] OR "gastric resection"[all fields] OR "Stomach Neoplasms/surgery"[mesh] OR "Lymph Node Excision"[mesh] OR "Surgical Procedures, Operative"[mesh:noexp] OR "Neoadjuvant Therapy"[mesh] OR "Chemotherapy, Adjuvant"[mesh] OR "Radiotherapy, Adjuvant"[mesh] OR adjuvant[tiab] OR neoadjuvant[tiab])
AND
("quality indicators, health care"[mesh] OR ("quality"[all fields] AND ("indicators"[all fields] OR indicator[all fields])) OR "health care quality indicators"[all fields] OR "Quality Assurance, Health Care"[mesh] OR "health care quality assessment"[all fields] OR "benchmarking"[mesh] OR "benchmarking"[all fields] OR "Outcome and Process Assessment (Health Care)"[mesh:noexp] OR "outcome assessment"[all fields] OR "Process Assessment"[all fields] OR "Delivery of Health Care"[mesh] OR "Risk Adjustment"[mesh] OR "risk adjustment"[all fields] OR "Clinical Audit"[mesh] OR "audit"[all fields] OR "Quality of Health Care"[mesh:noexp] OR "Quality Control"[mesh] OR "Guideline Adherence"[mesh] OR "Clinical Competence"[mesh] OR "Hospital Mortality"[mesh] OR "Mortality"[mesh:noexp] OR "Mortality"[ti] OR "Morbidity"[mesh:noexp] OR "Postoperative Complications"[mesh] OR "Complications" [ti] OR "Treatment Outcome"[mesh])
NOT
((animals[mesh] NOT humans[mesh]))

Embase
Limits activated: English, Publication Date from 1990
(exp *"stomach tumor"/ OR ((stomach.ti. OR gastric.ti.) AND (neoplasms.mp. OR neoplasm.mp. OR tumor.mp. OR tumors.mp. OR tumor.mp. OR tumors.mp. OR cancer.mp. OR cancers.mp. OR carcinoma.mp. OR carcinomas.mp.)))
AND
(exp *gastrectomy/ OR "gastrectomy".mp. OR "gastrectomies".mp. OR "gastric resection".mp. OR exp *stomach tumor/su OR "Lymph Node Excision".mp. OR exp *lymphadenectomy/ OR *surgery/ OR surgical.mp. OR adjuvant.ti,ab. OR exp *ADJUVANT CHEMOTHERAPY/ OR neoadjuvant.ti,ab. OR exp *adjuvant therapy/)
AND
(exp *health care quality/ OR (quality.ti,ab. AND indicators*.ti,ab.) OR "quality assurance".ti,ab. OR exp *quality control/ OR "health care quality assessment".ti,ab. OR benchmark*.ti,ab. OR exp *outcome assessment/ OR "outcome assessment".ti,ab. OR "Process Assessment".ti,ab. OR "delivery of health care".ti,ab. OR exp *health care delivery/ OR exp *risk assessment/ OR "risk adjustment".ti,ab. OR exp *medical audit/ OR "audit".ti,ab. OR "health care quality access evaluation".ti,ab. OR exp *health care access/ OR exp *"evaluation and follow up"/ OR exp *clinical assessment/ OR exp *clinical evaluation/ OR exp *evaluation/ OR exp *evaluation research/ OR exp *outcome assessment/ OR "quality control".ti,ab. OR exp *quality control/ OR "guideline adherence".ti,ab. OR "guidelines as topic".ti,ab. OR "clinical coti,abetence".ti,ab. OR exp *clinical competence/ OR "hospital mortality".ti,ab. OR *mortality/ OR morbidity.ti,ab. OR *morbidity/ OR complication*.ti,ab. OR exp *postoperative complication/ OR treatment outcome.ti,ab. OR exp *treatment outcome/)
AND
(exp human/)

Cochrane Library
Limits activated: English, Publication Date from 1990
"stomach neoplasms"
AND
(gastrectomy OR "lymph node excision" OR adjuvant OR neoadjuvant)

REFERENCES

1 Verlato G, Roviello F, Marchet A, et al. *Indexes of surgical quality in gastric cancer surgery: experience of an Italian network*. Ann Surg Oncol 2009;16:594-602.

2 Lepage C, Sant M, Verdecchia A, Forman D, Esteve J, Faivre J. *Operative mortality after gastric cancer resection and long-term survival differences across Europe*. Br J Surg 2010;97:235-239.

3 Sant M, Allemani C, Santaquilani M, Knijn A, Marchesi F, Capocaccia R. *EUROCARE-4. Survival of cancer patients diagnosed in 1995-1999. Results and commentary*. Eur J Cancer 2009;45:931-991.

4 Degiuli M, Sasako M, Ponti A. *Morbidity and mortality in the Italian Gastric Cancer Study Group randomized clinical trial of D1 versus D2 resection for gastric cancer*. Br J Surg 2010;97:643-649.

5 Sasako M, Sano T, Yamamoto S, et al. *D2 lymphadenectomy alone or with para-aortic nodal dissection for gastric cancer*. N Engl J Med 2008;359:453-462.

6 Strong VE, Song KY, Park CH, et al. *Comparison of gastric cancer survival following R0 resection in the United States and Korea using an internationally validated nomogram*. Ann Surg 2010;251:640-646.

7 Isobe Y, Nashimoto A, Akazawa K, et al. *Gastric cancer treatment in Japan: 2008 annual report of the JGCA nationwide registry*. Gastric Cancer 2011;14:301-316.

8 Kouloulias VE, Poortmans PM, Bernier J, et al. *The Quality Assurance programme of the Radiotherapy Group of the European Organization for Research and Treatment of Cancer (EORTC): a critical appraisal of 20 years of continuous efforts*. Eur J Cancer 2003;39:430-437.

9 Therasse P, De Mulder PH. *Quality assurance in medical oncology within the EORTC. European Organisation for Research and Treatment of Cancer*. Eur J Cancer 2002;38 Suppl 4:S152-154.

10 The Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland. (Accessed at http://www.augis.org/.)

11 Dutch Upper GI Cancer Audit. (Accessed at http://www.clinicalaudit.nl/duca/.)

12 Jensen LS, Nielsen H, Mortensen PB, Pilegaard HK, Johnsen SP. *Enforcing centralization for gastric cancer in Denmark*. Eur J Surg Oncol 2010;36 Suppl 1:S50-S54.

13 Donabedian A. *Evaluating the Quality of Medical Care*. The Milbank Memorial Fund Quarterly 1966;44:166-203.

14 Courrech Staal EFW, Wouters MWJM, Boot H, Tollenaar RAEM, van Sandick JW. *Quality-of-care indicators for oesophageal cancer surgery: A review*. Eur J Surg Oncol 2010;36:1035-1043.

15 Stordeur S, Vrijens F, Devriese S, Beirens K, Van Eycken E, Vlayen J. *Developing and measuring a set of process and outcome indicators for breast cancer*. Breast 2011.

16 de Villiers MR, de Villiers PJ, Kent AP. *The Delphi technique in health sciences education research*. Med Teach 2005;27:639-643.

17 Bachmann MO, Alderson D, Edwards D, et al. *Cohort study in South and West England of the influence of specialization on the management and outcome of patients with oesophageal and gastric cancers*. Br J Surg 2002;89:914-922.

18 Bare M, Cabrol J, Real J, et al. *In-hospital mortality after stomach cancer surgery in Spain and relationship with hospital volume of interventions*. BMC Public Health 2009;9:312.

19 Birkmeyer JD, Siewers AE, Finlayson EV, et al. *Hospital volume and surgical mortality in the United States*. N Engl J Med 2002;346:1128-1137.

20 Callahan MA, Christos PJ, Gold HT, Mushlin AI, Daly JM. *Influence of surgical subspecialty training on in-hospital mortality for gastrectomy and colectomy patients*. Ann Surg 2003;238:629-636; discussion 636-629.

21 Damhuis RA, Meurs CJ, Dijkhuis CM, Stassen LP, Wiggers T. *Hospital volume and post-operative mortality after resection for gastric cancer*. Eur J Surg Oncol 2002;28:401-405.

22 Finlayson EV, Goodney PP, Birkmeyer JD. *Hospital volume and operative mortality in cancer surgery: a national study*. Arch Surg 2003;138:721-725; discussion 726.

23 Hannan EL, Radzyner M, Rubin D, Dougherty J, Brennan MF. *The influence of hospital and surgeon volume on in-hospital mortality for colectomy, gastrectomy, and lung lobectomy in patients with cancer*. Surgery 2002;131:6-15.

24 Hansson LE, Ekstrom AM, Bergstrom R, Nyren O. *Surgery for stomach cancer in a defined Swedish population: current practices and operative results. Swedish Gastric Cancer Study Group*. Eur J Surg 2000;166:787-795.

25 Kuwabara K, Matsuda S, Fushimi K, Ishikawa KB, Horiguchi H, Fujimori K. *Hospital volume and quality of laparoscopic gastrectomy in Japan*. Dig Surg 2009;26:422-429.

26 Learn PA, Bach PB. *A decade of mortality reductions in major oncologic surgery: the impact of centralization and quality improvement*. Med Care 2010;48:1041-1049.

27 Lin HC, Xirasagar S, Lee HC, Chai CY. *Hospital volume and inpatient mortality after cancer-related gastrointestinal resections: the experience of an Asian country*. Ann Surg Oncol 2006;13:1182-1188.

28 Nomura E, Tsukuma H, Ajiki W, Oshima A. *Population-based study of relationship between hospital surgical volume and 5-year survival of stomach cancer patients in Osaka, Japan*. Cancer Sci 2003;94:998-1002.

29 Reavis KM, Hinojosa MW, Smith BR, Wooldridge JB, Krishnan S, Nguyen NT. *Hospital volume is not a predictor of outcomes after gastrectomy for neoplasm*. Am Surg 2009;75:932-936.

30 Smith DL, Elting LS, Learn PA, Raut CP, Mansfield PF. *Factors influencing the volume-outcome relationship in gastrectomies: a population-based study*. Ann Surg Oncol 2007;14:1846-1852.

31 Thompson AM, Rapson T, Gilbert FJ, Park KG. *Hospital volume does not influence long-term survival of patients undergoing surgery for oesophageal or gastric cancer*. Br J Surg 2007;94:578-584.

32 Wainess RM, Dimick JB, Upchurch GR, Jr., Cowan JA, Mulholland MW. *Epidemiology of surgically treated gastric cancer in the United States, 1988-2000*. J Gastrointest Surg 2003;7:879-883.

33 Xirasagar S, Lien YC, Lin HC, Lee HC, Liu TC, Tsai J. *Procedure volume of gastric cancer resections versus 5-year survival*. Eur J Surg Oncol 2008;34:23-29.

34 Fujita T, Yamazaki Y. *Influence of surgeon's volume on early outcome after total gastrectomy*. Eur J Surg 2002;168:535-538.

35 de Gara CJ, Hanson J, Hamilton S. *A population-based study of tumor-node relationship, resection margins, and surgeon volume on gastric cancer survival*. Am J Surg 2003;186:23-27.

36 Moriwaki Y, Kobayashi S, Kunisaki C, et al. *Is D2 lymphadenectomy in gastrectomy safe with regard to the skill of the operator?* Dig Surg 2001;18:111-117.

37 Siemerink EJ, Schaapveld M, Plukker JT, Mulder NH, Hospers GA. *Effect of hospital characteristics on outcome of patients with gastric cancer: a population based study in North-East Netherlands*. Eur J Surg Oncol 2010;36:449-455.

38 Cuschieri A, Weeden S, Fielding J, et al. *Patient survival after D1 and D2 resections for gastric cancer: long-term results of the MRC randomized surgical trial. Surgical Co-operative Group*. British Journal of Cancer 1999:1522-1530.

39 Robertson CS, Chung SC, Woods SD, et al. *A prospective randomized trial comparing R1 subtotal gastrectomy with R3 total gastrectomy for antral cancer*. Ann Surg 1994;220:176-182.

40 Songun I, Putter H, Kranenbarg EMK, Sasako M, van de Velde CJH. *Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial*. The Lancet Oncology 2010;11 (5):439-449.

41 Wu CW, Hsiung CA, Lo SS, et al. *Nodal dissection for patients with gastric cancer: a randomised controlled trial*. Lancet Oncol 2006;7:309-315.

42 Chen XZ, Hu JK, Zhou ZG, et al. *Meta-analysis of effectiveness and safety of D2 plus para-aortic lymphadenectomy for resectable gastric cancer*. J Am Coll Surg 2010;210:100-105.

43 Yonemura Y, Wu CC, Fukushima N, et al. *Randomized clinical trial of D2 and extended paraaortic lymphadenectomy in patients with gastric cancer*. International journal of clinical oncology / Japan Society of Clinical Oncology 2008:132-137.

44 Huscher CG, Mingoli A, Sgarzini G, et al. *Laparoscopic versus open subtotal gastrectomy for distal gastric cancer: five-year results of a randomized prospective trial*. Ann Surg 2005;241:232-237.

45 Chang HM, Lee SW, Nomura E, Tanigawa N. *Laparoscopic versus open gastrectomy for gastric cancer patients with COPD*. J Surg Oncol 2009;100:456-458.

46 Chouillard E, Gumbs AA, Meyer F, et al. *Laparoscopic versus open gastrectomy for adenocarcinoma: A prospective comparative analysis*. Minerva Chirurgica 2010;65 (3):243-250.

47 Du XH, Li R, Chen L, Shen D, Li SY, Guo Q. *Laparoscopy-assisted D2 radical distal gastrectomy for advanced gastric cancer: initial experience*. Chin Med J (Engl) 2009;122:1404-1407.

48 Huang JL, Wei HB, Zheng ZH, et al. *Laparoscopy-assisted D2 radical distal gastrectomy for advanced gastric cancer*. Dig Surg 2010;27:291-296.

49 Lee SI, Choi YS, Park DJ, Kim HH, Yang HK, Kim MC. *Comparative study of laparoscopy-assisted distal gastrectomy and open distal gastrectomy*. J Am Coll Surg 2006;202:874-880.

50 Orsenigo E, Di Palo S, Tamburini A, Staudacher C. *Laparoscopy-assisted gastrectomy versus open gastrectomy for gastric cancer: A monoinstitutional Western center experience*. Surgical Endoscopy and Other Interventional Techniques 2011;25 (1):140-145.

51 Pugliese R, Maggioni D, Sansonna F, et al. *Total and subtotal laparoscopic gastrectomy for adenocarcinoma*. Surg Endosc 2007;21:21-27.

52 Tanimura S, Higashino M, Fukunaga Y, et al. *Laparoscopic gastrectomy for gastric cancer: experience with more than 600 cases*. Surg Endosc 2008;22:1161-1164.

53 Ziqiang W, Feng Q, Zhimin C, et al. *Comparison of laparoscopically assisted and open radical distal gastrectomy with extended lymphadenectomy for gastric cancer management*. Surg Endosc 2006;20:1738-1743.

54 Bozzetti F, Marubini E, Bonfanti G, Miceli R, Piano C, Gennari L. *Subtotal versus total gastrectomy for gastric cancer: five-year survival rates in a multicenter randomized Italian trial. Italian Gastrointestinal Tumor Study Group*. Annals of Surgery 1999:170-178.

55 Bozzetti F, Marubini E, Bonfanti G, et al. *Total versus subtotal gastrectomy: surgical morbidity and mortality rates in a multicenter Italian randomized trial. The Italian Gastrointestinal Tumor Study Group*. Ann Surg 1997;226:613-620.

56 Csendes A, Burdiles P, Rojas J, Braghetto I, Diaz JC, Maluenda F. *A prospective randomized study comparing D2 total gastrectomy versus D2 total gastrectomy plus splenectomy in 187 patients with gastric carcinoma*. Surgery 2002;131:401-407.

57 Furukawa H, Hiratsuka M, Ishikawa O, et al. *Total gastrectomy with dissection of lymph nodes along the splenic artery: a pancreas-preserving method*. Ann Surg Oncol 2000;7:669-673.

58 Kitamura K, Nishida S, Ichikawa D, et al. *No survival benefit from combined pancreaticosplenectomy and total gastrectomy for gastric cancer*. British Journal of Surgery 1999;86 (1):119-122.

59 Kasakura Y, Fujii M, Mochizuki F, Kochi M, Kaiga T. *Is there a benefit of pancreaticosplenectomy with gastrectomy for advanced gastric cancer?* American Journal of Surgery 2000;179 (3):237-242.

60 Lo SS, Wu CW, Shen KH, Hsieh MC, Lui WY. *Higher morbidity and mortality after combined total gastrectomy and pancreaticosplenectomy for gastric cancer*. World J Surg 2002;26:678-682.

61 Takeuchi K, Tsuzuki Y, Ando T, et al. *Total gastrectomy with distal pancreatectomy and splenectomy for advanced gastric cancer*. Journal of Surgical Research 2001;101 (2):196-201.

62 Imamura H, Kurokawa Y, Kawada J, et al. *Influence of bursectomy on operative morbidity and mortality after radical gastrectomy for gastric cancer: results of a randomized controlled trial*. World J Surg 2011;35:625-630.

63 Lehnert T, Buhl K. *Techniques of reconstruction after total gastrectomy for cancer*. British Journal of Surgery 2004;91 (5):528-539.

64 Gertler R, Rosenberg R, Feith M, Schuster T, Friess H. *Pouch vs. no pouch following total gastrectomy: meta-analysis and systematic review*. Am J Gastroenterol 2009;104:2838-2851.

65 Schwarz A, Buchler M, Usinger K, et al. *Importance of the duodenal passage and pouch volume after total gastrectomy and reconstruction with the Ulm pouch: prospective randomized clinical study*. World Journal of Surgery 1996:60-66.

66 Fein M, Fuchs KH, Thalheimer A, Freys SM, Heimbucher J, Thiede A. *Long-term benefits of Roux-en-Y pouch reconstruction after total gastrectomy: a randomized trial*. Ann Surg 2008;247:759-765.

67 Chareton B, Landen S, Manganas D, Meunier B, Launois B. *Prospective randomized trial comparing Billroth I and Billroth II procedures for carcinoma of the gastric antrum*. J Am Coll Surg 1996;183:190-194.

68 Ishikawa M, Kitayama J, Kaizaki S, et al. *Prospective randomized trial comparing Billroth I and Roux-en-Y procedures after distal gastrectomy for gastric carcinoma*. World J Surg 2005;29:1415-1420.

69 Persiani R, Antonacci V, Biondi A, et al. *Determinants of surgical morbidity in gastric cancer treatment*. J Am Coll Surg 2008;207:13-19.

70 Sah BK, Chen MM, Yan M, Zhu ZG. *Gastric cancer surgery: Billroth I or Billroth II for distal gastrectomy?* BMC Cancer 2009;9:428.

71 Fujita T, Katai H, Morita S, Saka M, Fukagawa T, Sano T. *Short-term outcomes of Roux-en-Y stapled anastomosis after distal gastrectomy for gastric adenocarcinoma*. J Gastrointest Surg 2010;14:289-294.

72 Seufert RM, Schmidt-Matthiesen A, Beyer A. *Total gastrectomy and oesophagojejunostomy--a prospective randomized trial of hand-sutured versus mechanically stapled anastomoses*. Br J Surg 1990;77:50-52.

73 Takeyoshi I, Ohwada S, Ogawa T, et al. *Esophageal anastomosis following gastrectomy for gastric cancer: comparison of hand-sewn and stapling technique*. Hepatogastroenterology 2000;47:1026-1029.

74 Wu MH, Lin MT, Chen WJ. *Effect of perioperative parenteral nutritional support for gastric cancer patients undergoing gastrectomy*. Hepatogastroenterology 2008;55:799-802.

75 Karcz W, Gluszek S, Kot M, Matykiewicz J. *Influence of nutritional treatment on the postoperative course in patients with gastric cancer*. Adv Med Sci 2006;51:278-282.

76 Farreras N, Artigas V, Cardona D, Rius X, Trias M, Gonzalez JA. *Effect of early postoperative enteral immunonutrition on wound healing in patients undergoing surgery for gastric cancer*. Clin Nutr 2005;24:55-65.

77 Klek S, Kulig J, Szczepanik AM, Jedrys J, Kolodziejczyk P. *The clinical value of parenteral immunonutrition in surgical patients*. Acta Chir Belg 2005;105:175-179.

78 Okamoto Y, Okano K, Izuishi K, Usuki H, Wakabayashi H, Suzuki Y. *Attenuation of the systemic inflammatory response and infectious complications after gastrectomy with preoperative oral arginine and omega-3 fatty acids supplemented immunonutrition*. World J Surg 2009;33:1815-1821.

79 Carrere N, Seulin P, Julio CH, Bloom E, Gouzi JL, Pradere B. *Is nasogastric or nasojejunal decompression necessary after gastrectomy? A prospective randomized trial*. World J Surg 2007;31:122-127.

80 Wu CC, Hwang CR, Liu TJ. *There is no need for nasogastric decompression after partial gastrectomy with extensive lymphadenectomy*. Eur J Surg 1994;160:369-373.

81 Yoo CH, Son BH, Han WK, Pae WK. *Nasogastric decompression is not necessary in operations for gastric cancer: prospective randomised trial*. Eur J Surg 2002;168:379-383.

82 Liu XX, Jiang ZW, Wang ZM, Li JS. *Multimodal optimization of surgical care shows beneficial outcome in gastrectomy surgery*. JPEN J Parenter Enteral Nutr 2010;34:313-321.

83 Wang D, Kong Y, Zhong B, Zhou X, Zhou Y. *Fast-track surgery improves postoperative recovery in patients with gastric cancer: a randomized comparison with conventional postoperative care*. J Gastrointest Surg 2010;14:620-627.

84 Moriguchi S, Maehara Y, Akazawa K, Sugimachi K, Nose Y. *Lack of relationship between perioperative blood transfusion and survival time after curative resection for gastric cancer*. Cancer 1990;66:2331-2335.

85 Maeta M, Shimizu N, Oka A, et al. *Perioperative allogeneic blood transfusion exacerbates surgical stress-induced postoperative immunosuppression and has a negative effect on prognosis in patients with gastric cancer*. J Surg Oncol 1994;55:149-153.

86 Choi JH, Chung HC, Yoo NC, et al. *Perioperative blood transfusions and prognosis in patients with curatively resected locally advanced gastric cancer*. Oncology 1995;52:170-175.

87 Heiss MM, Allgayer H, Gruetzner KU, et al. *Prognostic influence of blood transfusion on minimal residual disease in resected gastric cancer patients*. Anticancer Res 1997;17:2657-2661.
88 Fong Y, Karpeh M, Mayer K, Brennan MF. *Association of perioperative transfusions with poor outcome in resection of gastric adenocarcinoma*. Am J Surg 1994;167:256-260.
89 Sanchez-Bueno F, Garcia-Marcilla JA, Perez-Abad JM, et al. *Does perioperative blood transfusion influence long-term prognosis of gastric cancer?* Digestive Diseases and Sciences 1997;42 (10):2072-2076.
90 Hyung WJ, Noh SH, Shin DW, et al. *Adverse effects of perioperative transfusion on patients with stage III and IV gastric cancer*. Ann Surg Oncol 2002;9:5-12.
91 Weitz J, D'Angelica M, Gonen M, et al. *Interaction of splenectomy and perioperative blood transfusions on prognosis of patients with proximal gastric and gastroesophageal junction cancer*. J Clin Oncol 2003;21:4597-4603.
92 Bortul M, Calligaris L, Roseano M, Leggeri A. *Blood transfusions and results after curative resection for gastric cancer*. Suppl Tumori 2003;2:S27-S30.
93 Schardey HM, Joosten U, Finke U, et al. *The prevention of anastomotic leakage after total gastrectomy with local decontamination. A prospective, randomized, double-blind, placebo-controlled multicenter trial*. Ann Surg 1997;225:172-180.
94 Mohri Y, Tonouchi H, Kobayashi M, Nakai K, Kusunoki M. *Randomized clinical trial of single- versus multiple-dose antimicrobial prophylaxis in gastric cancer surgery*. Br J Surg 2007;94:683-688.
95 Hartgrink HH, van de Velde CJ, Putter H, et al. *Neo-adjuvant chemotherapy for operable gastric cancer: long term results of the Dutch randomised FAMTX trial*. Eur J Surg Oncol 2004;30:643-649.
96 Schuhmacher C, Gretschel S, Lordick F, et al. *Neoadjuvant chemotherapy compared with surgery alone for locally advanced cancer of the stomach and cardia: European organisation for research and treatment of cancer randomized trial 40954*. Journal of Clinical Oncology 2010;28 (35):5210-5218.
97 Wang XL, Wu GX, Zhang MD, Guo M, Zhang H, Sun XF. *A favorable impact of preoperative FPLC chemotherapy on patients with gastric cardia cancer*. Oncol Rep 2000;7:241-244.
98 Li W, Qin J, Sun YH, Liu TS. *Neoadjuvant chemotherapy for advanced gastric cancer: a meta-analysis*. World J Gastroenterol 2010;16:5621-5628.
99 Cunningham D, Allum WH, Stenning SP, et al. *Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer*. New England Journal of Medicine 2006;355 (1):11-20.
100 Biffi R, Fazio N, Luca F, et al. *Surgical outcome after docetaxel-based neoadjuvant chemotherapy in locally-advanced gastric cancer*. World J Gastroenterol 2010;16:868-874.
101 Zhang ZX, Gu XZ, Yin WB, Huang GJ, Zhang DW, Zhang RG. *Randomized clinical trial on the combination of preoperative irradiation and surgery in the treatment of adenocarcinoma of gastric cardia (AGC)--report on 370 patients*. Int J Radiat Oncol Biol Phys 1998;42:929-934.
102 Hermans J, Bonenkamp JJ, Boon MC, et al. *Adjuvant therapy after curative resection for gastric cancer: meta-analysis of randomized trials*. J Clin Oncol 1993;11:1441-1447.
103 Liu TS, Wang Y, Chen SY, Sun YH. *An updated meta-analysis of adjuvant chemotherapy after curative resection for gastric cancer*. Eur J Surg Oncol 2008;34:1208-1216.
104 Mari E, Floriani I, Tinazzi A, et al. *Efficacy of adjuvant chemotherapy after curative resection for gastric cancer: a meta-analysis of published randomised trials. A study of the GISCAD (Gruppo Italiano per lo Studio dei Carcinomi dell'Apparato Digerente)*. Ann Oncol 2000;11:837-843.
105 Panzini I, Gianni L, Fattori PP, et al. *Adjuvant chemotherapy in gastric cancer: a meta-analysis of randomized trials and a comparison with previous meta-analyses*. Tumori 2002;88:21-27.
106 Paoletti X, Oba K, Burzykowski T, et al. *Benefit of adjuvant chemotherapy for resectable gastric cancer: a meta-analysis*. JAMA 2010;303:1729-1737.
107 Sun P, Xiang JB, Chen ZY. *Meta-analysis of adjuvant chemotherapy after radical surgery for advanced gastric cancer*. Br J Surg 2009;96:26-33.
108 Earle CC, Maroun JA. *Adjuvant chemotherapy after curative resection for gastric cancer in non-Asian patients: revisiting a meta-analysis of randomised trials*. Eur J Cancer 1999;35:1059-1064.
109 Hu JK, Chen ZX, Zhou ZG, et al. *Intravenous chemotherapy for resected gastric cancer: meta-analysis of randomized controlled trials*. World J Gastroenterol 2002;8:1023-1028.
110 Janunger KG, Hafstrom L, Glimelius B. *Chemotherapy in gastric cancer: a review and updated meta-analysis*. Eur J Surg 2002;168:597-608.
111 Wagner AD. *Chemotherapy in Advanced Gastric Cancer: A Systematic Review and Meta-Analysis Based on Aggregate Data*. J Clin Oncol 2006;24:2903-2909.
112 Macdonald JS, Smalley SR, Benedetti J, et al. *Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction*. The New England journal of medicine 2001:725-730.
113 Blomjous JG, Hop WC, Langenhorst BL, ten Kate FJ, Eykenboom WM, Tilanus HW. *Adenocarcinoma of the gastric cardia. Recurrence and survival after resection*. Cancer 1992;70:569-574.
114 Chan WH, Wong WK, Khin LW, Chan HS, Soo KC. *Significance of a positive oesophageal margin in stomach cancer*. Australian and New Zealand Journal of Surgery 2000;70 (10):700-703.

115 Hallissey MT, Jewkes AJ, Dunn JA, Ward L, Fielding JW. *Resection-line involvement in gastric cancer: a continuing problem*. Br J Surg 1993;80:1418-1420.
116 Jahne J, Piso P, Meyer HJ. *1114 total gastrectomies in the surgical treatment of primary gastric adenocarcinoma--a 30-year single institution experience*. Hepatogastroenterology 2001;48:1222-1226.
117 Nazli O, Derici H, Tansug T, et al. *Survival analysis after surgical treatment of gastric cancer: review of 121 cases*. Hepatogastroenterology 2007;54:625-629.
118 Shiu MH, Moore E, Sanders M, et al. *Influence of the extent of resection on survival after curative treatment of gastric carcinoma. A retrospective multivariate analysis*. Arch Surg 1987;122:1347-1351.
119 Songun I, Bonenkamp JJ, Hermans J, van Krieken JH, van de Velde CJ. *Prognostic value of resection-line involvement in patients undergoing curative resections for gastric cancer*. Eur J Cancer 1996;32A:433-437.
120 Sun Z, Li DM, Wang ZN, et al. *Prognostic significance of microscopic positive margins for gastric cancer patients with potentially curative resection*. Ann Surg Oncol 2009;16:3028-3037.
121 Wanebo HJ, Kennedy BJ, Chmiel J, Steele G, Jr., Winchester D, Osteen R. *Cancer of the stomach. A patient care study by the American College of Surgeons*. Ann Surg 1993;218:583-592.
122 Wang SY, Yeh CN, Lee HL, et al. *Clinical impact of positive surgical margin status on gastric cancer patients undergoing gastrectomy*. Ann Surg Oncol 2009;16:2738-2743.
123 Yu CC, Levison DA, Dunn JA, et al. *Pathological prognostic factors in the second British Stomach Cancer Group trial of adjuvant therapy in resectable gastric cancer*. Br J Cancer 1995;71:1106-1110.
124 Cunningham SC, Kamangar F, Kim MP, et al. *Survival after gastric adenocarcinoma resection: eighteen-year experience at a single institution*. J Gastrointest Surg 2005;9:718-725.
125 Kim SH, Karpeh MS, Klimstra DS, Leung D, Brennan MF. *Effect of microscopic resection line disease on gastric cancer survival*. J Gastrointest Surg 1999;3:24-33.
126 Morgagni P, Garcea D, Marrelli D, et al. *Resection line involvement after gastric cancer surgery: clinical outcome in nonsurgically retreated patients*. World J Surg 2008;32:2661-2667.
127 Siewert JR, Bottcher K, Stein HJ, Roder JD. *Relevant prognostic factors in gastric cancer: Ten-year results of the German Gastric Cancer Study*. Annals of Surgery 1998;228 (4):449-461.
128 Cascinu S, Giordani P, Catalano V, Agostinelli R, Catalano G. *Resection-line involvement in gastric cancer patients undergoing curative resections: implications for clinical management*. Jpn J Clin Oncol 1999;29:291-293.
129 Coburn NG, Swallow CJ, Kiss A, Law C. *Significant regional variation in adequacy of lymph node assessment and survival in gastric cancer*. Cancer 2006;107:2143-2151.
130 Huang CM, Lin JX, Zheng CH, et al. *Prognostic impact of dissected lymph node count on patients with node-negative gastric cancer*. World J Gastroenterol 2009;15:3926-3930.
131 Siewert JR, Bottcher K, Roder JD, Busch R, Hermanek P, Meyer HJ. *Prognostic relevance of systematic lymph node dissection in gastric carcinoma*. British Journal of Surgery 1993;80 (8):1015-1018.
132 Wouters MW, Gooiker GA, van Sandick JW, Tollenaar RA. *The volume-outcome relation in the surgical treatment of esophageal cancer: A systematic review and meta-analysis*. Cancer 2011.
133 Bonenkamp JJ, Hermans J, Sasako M, van de Velde CJH. *Extended lymph-node dissection for gastric cancer*. New England Journal of Medicine 1999;340 (12):908-914.
134 Mortensen FV, Jensen LS, Sorensen HT, Pedersen L. *Cause-specific mortality associated with leukoreduced, buffy coat-depleted, or no blood transfusion after elective surgery for colorectal cancer: a posttrial 15-year follow-up study*. Transfusion 2011;51:259-263.
135 Ajani JA, Barthel JS, Bekaii-Saab T, et al. *Gastric cancer*. J Natl Compr Canc Netw 2010;8:378-409.
136 Dikken JL, van Sandick JW, Swellengrebel HA, et al. *Neo-adjuvant chemotherapy followed by surgery and chemotherapy or by surgery and chemoradiotherapy for patients with resectable gastric cancer (CRITICS)*. BMC Cancer 2011;11:329.
137 Aiken LH, Clarke SP, Cheung RB, Sloane DM, Silber JH. *Educational levels of hospital nurses and surgical patient mortality*. JAMA 2003;290:1617-1623.
138 Birkmeyer JD, Sun Y, Wong SL, Stukel TA. *Hospital volume and late survival after cancer surgery*. Ann Surg 2007;245:777-783.
139 Enzinger PC, Benedetti JK, Meyerhardt JA, et al. *Impact of hospital volume on recurrence and survival after surgery for gastric cancer*. Ann Surg 2007;245:426-434.
140 Ioka A, Tsukuma H, Ajiki W, Oshima A. *Hospital procedure volume and survival of cancer patients in Osaka, Japan: a population-based study with latest cases*. Jpn J Clin Oncol 2007;37:544-553.
141 Sah BK, Zhu ZG, Chen MM, et al. *Effect of surgical work volume on postoperative complication: superiority of specialized center in gastric cancer treatment*. Langenbecks Arch Surg 2009;394:41-47.
142 Kuwabara K, Matsuda S, Fushimi K, et al. *Quantitative assessment of the advantages of laparoscopic gastrectomy and the impact of volume-related hospital characteristics on resource use and outcomes of gastrectomy patients in Japan*. Ann Surg 2011;253:64-70.
143 Bilimoria KY, Talamonti MS, Wayne JD, et al. *Effect of hospital type and volume on lymph node evaluation for gastric and pancreatic cancer*. Arch Surg 2008;143:671-678; discussion 678.
144 Lustosa SA, Saconato H, Atallah AN, Lopes Filho Gde J, Matos D. *Impact of extended lymphadenectomy on morbidity, mortality, recurrence and 5-year survival after gastrectomy for cancer. Meta-analysis of randomized clinical trials*. Acta Cir Bras 2008;23:520-530.

145 McCulloch P, Nita Marcelo E, Kazi H, Gama-Rodrigues J. *Extended versus limited lymph nodes dissection technique for adenocarcinoma of the stomach*. Cochrane Database of Systematic Reviews 2003.
146 Cuschieri A, Fayers P, Fielding J, et al. *Postoperative morbidity and mortality after D1 and D2 resections for gastric cancer: preliminary results of the MRC randomised controlled surgical trial. The Surgical Cooperative Group*. Lancet 1996;347:995-999.
147 Wu CW, Hsiung CA, Lo SS, Hsieh MC, Shia LT, Whang-Peng J. *Randomized clinical trial of morbidity after D1 and D3 surgery for gastric cancer*. Br J Surg 2004;91:283-287.
148 Wu CW, Chiou JM, Ko FS, et al. *Quality of life after curative gastrectomy for gastric cancer in a randomised controlled trial*. British Journal of Cancer 2008;98 (1):54-59.
149 Sano T, Sasako M, Yamamoto S, et al. *Gastric cancer surgery: morbidity and mortality results from a prospective randomized controlled trial comparing D2 and extended para-aortic lymphadenectomy--Japan Clinical Oncology Group study 9501*. J Clin Oncol 2004;22:2767-2773.
150 Kulig J, Popiela T, Kolodziejczyk P, Sierzega M, Szczepanik A. *Standard D2 versus extended D2 (D2+) lymphadenectomy for gastric cancer: an interim safety analysis of a multicenter, randomized, clinical trial*. American Journal of Surgery 2007;193 (1):10-15.
151 Kurokawa Y, Sasako M, Sano T, et al. *Functional outcomes after extended surgery for gastric cancer*. Br J Surg 2011;98:239-245.
152 Yonemura Y, Wu CC, Fukushima N, et al. *Operative morbidity and mortality after D2 and D4 extended dissection for advanced gastric cancer: a prospective randomized trial conducted by Asian surgeons*. Hepatogastroenterology 2006;53:389-394.
153 Ichikura T, Tomimatsu S, Okusa Y, Mochizuki H. *Improved physical condition by limiting lymphadenectomy around the coeliac artery after distal gastrectomy for gastric cancer*. European Journal of Surgery 1999;165 (2):123-132.
154 Lin SZ, Tong HF, Qin YS, Ni ZL, Zhang W. *Prevention and treatment of lymphorrhoea following surgery for gastric cancer*. ANZ J Surg 2010;80:515-518.
155 Hao YX, Yu PW, Zhong H, et al. *Comparison of laparoscopic and open gastrectomy on cancer cells exfoliating from the cancer-invaded serosa*. Surg Laparosc Endosc Percutan Tech 2009;19:201-207.
156 Meyer HJ, Jahne J, Wilke H, Pichlmayr R. *Surgical treatment of gastric cancer: retrospective survey of 1,704 operated cases with special reference to total gastrectomy as the operation of choice*. Semin Surg Oncol 1991;7:356-364.
157 Launois B, Cardin JL, Bardaxoglou E, et al. *Management of cancer of the stomach: total gastrectomy versus sub-total gastrectomy*. Hepatogastroenterology 1991;38:45-52.
158 Stipa S, Di Giorgio A, Ferri M, Botti C. *Results of curative gastrectomy for carcinoma*. J Am Coll Surg 1994;179:567-572.
159 Braga M, Molinari M, Zuliani W, et al. *Surgical treatment of gastric adenocarcinoma: Impact on survival and quality of life. A prospective ten year study*. Hepato-Gastroenterology 1996;43 (7):187-193.
160 de Manzoni G, Verlato G, Roviello F, et al. *Subtotal versus total gastrectomy for T3 adenocarcinoma of the antrum*. Gastric Cancer 2003;6:237-242.
161 Gockel I, Pietzka S, Gonner U, Hommel G, Junginger T. *Subtotal or total gastrectomy for gastric cancer: impact of the surgical procedure on morbidity and prognosis--analysis of a 10-year experience*. Langenbecks Arch Surg 2005;390:148-155.
162 Kim JH, Park SS, Kim J, et al. *Surgical outcomes for gastric cancer in the upper third of the stomach*. World J Surg 2006;30:1870-1876.
163 Jentschura D, Winkler M, Strohmeier N, Rumstadt B, Hagmuller E. *Quality-of-life after curative surgery for gastric cancer: a comparison between total gastrectomy and subtotal gastric resection*. Hepatogastroenterology 1997;44:1137-1142.
164 Svedlund J, Sullivan M, Liedman B, Lundell L. *Long term consequences of gastrectomy for patient's quality of life: the impact of reconstructive techniques*. Am J Gastroenterol 1999;94:438-445.
165 Korenaga D, Orita H, Okuyama T, Moriguchi S, Maehara Y, Sugimachi K. *Quality of life after gastrectomy in patients with carcinoma of the stomach*. Br J Surg 1992;79:248-250.
166 Yang K, Chen XZ, Hu JK, Zhang B, Chen ZX, Chen JP. *Effectiveness and safety of splenectomy for gastric carcinoma: a meta-analysis*. World J Gastroenterol 2009;15:5352-5359.
167 Yu W, Choi GS, Chung HY. *Randomized clinical trial of splenectomy versus splenic preservation in patients with proximal gastric cancer*. Br J Surg 2006;93:559-563.
168 Maruyama K, Sasako M, Kinoshita T, Sano T, Katai H, Okajima K. *Pancreas-preserving total gastrectomy for proximal gastric cancer*. World J Surg 1995;19:532-536.
169 Otsuji E, Yamaguchi T, Sawai K, Okamoto K, Takahashi T. *Total gastrectomy with simultaneous pancreaticosplenectomy or splenectomy in patients with advanced gastric carcinoma*. Br J Cancer 1999;79:1789-1793.
170 Iriyama K, Ohsawa T, Tsuchibashi T, et al. *Results of combined resection of invaded organs in patients with potentially curable, advanced gastric cancer*. Eur J Surg 1994;160:27-30.
171 Martin RC, 2nd, Jaques DP, Brennan MF, Karpeh M. *Extended local resection for advanced gastric cancer: increased survival versus increased morbidity*. Ann Surg 2002;236:159-165.
172 Yonemura Y, Kawamura T, Nojima N, et al. *Postoperative results of left upper abdominal evisceration for advanced gastric cancer*. Hepatogastroenterology 2000;47:571-574.
173 Liedman B, Andersson H, Berglund B, et al. *Food intake after gastrectomy for gastric carcinoma: the role of a gastric reservoir*. The British journal of surgery 1996:1138-1143.

174 Fuchs KH, Thiede A, Engemann R, Deltz E, Stremme O, Hamelmann H. *Reconstruction of the food passage after total gastrectomy: randomized trial*. World J Surg 1995;19:698-705.
175 Lee WJ, Chen TC, Lai IR, Wang W, Huang MT. *Randomized clinical trial of Ligasure versus conventional surgery for extended gastric cancer resection*. Br J Surg 2003;90:1493-1496.
176 Hayashi S, Takayama T, Masuda H, et al. *Bioresorbable membrane to reduce postoperative small bowel obstruction in patients with gastric cancer: a randomized clinical trial*. Ann Surg 2008;247:766-770.
177 Imai E, Ueda M, Kanao K, Miyaki K, Kubota T, Kitajima M. *Surgical site infection surveillance after open gastrectomy and risk factors for surgical site infection*. J Infect Chemother 2005;11:141-145.
178 Inaba T, Okinaga K, Fukushima R, et al. *Prospective randomized study of two laparotomy incisions for gastrectomy: midline incision versus transverse incision*. Gastric Cancer 2004;7:167-171.
179 Kim J, Lee J, Hyung WJ, et al. *Gastric cancer surgery without drains: a prospective randomized trial*. J Gastrointest Surg 2004;8:727-732.
180 Alvarez Uslar R, Molina H, Torres O, Cancino A. *Total gastrectomy with or without abdominal drains. A prospective randomized trial*. Revista espanola de enfermedades digestivas : organo oficial de la Sociedad Espanola de Patologia Digestiva 2005;97 (8):562-569.
181 Kamei T, Kitayama J, Yamashita H, Nagawa H. *Intraoperative blood loss is a critical risk factor for peritoneal recurrence after curative resection of advanced gastric cancer*. World J Surg 2009;33:1240-1246.
182 Yang Z, Zheng Q, Wang Z. *Meta-analysis of the need for nasogastric or nasojejunal decompression after gastrectomy for gastric cancer*. Br J Surg 2008;95:809-816.
183 Lee JH, Hyung WJ, Noh SH. *Comparison of gastric cancer surgery with versus without nasogastric decompression*. Yonsei Med J 2002;43:451-456.
184 Doglietto GB, Papa V, Tortorelli AP, Bossola M, Covino M, Pacelli F. *Nasojejunal tube placement after total gastrectomy: a multicenter prospective randomized trial*. Arch Surg 2004;139:1309-1313.
185 Hsu SD, Yu JC, Chen TW, Chou SJ, Hsieh HF, Chan DC. *Role of nasogastric tube insertion after gastrectomy*. Chirurgische Gastroenterologie Interdisziplinar 2007;23 (3):303-306.
186 Suehiro T, Matsumata T, Shikada Y, Sugimachi K. *Accelerated rehabilitation with early postoperative oral feeding following gastrectomy*. Hepatogastroenterology 2004;51:1852-1855.
187 Bellantone R, Sitges-Serra A, Bossola M, et al. *Transfusion timing and postoperative septic complications after gastric cancer surgery: a retrospective study of 179 consecutive patients*. Arch Surg 1998;133:988-992.
188 Jeong O, Ryu SY, Park YK, Kim YJ. *The effect of low molecular weight heparin thromboprophylaxis on bleeding complications after gastric cancer surgery*. Ann Surg Oncol 2010;17:2363-2369.
189 Skoropad V, Berdov B, Zagrebin V. *Concentrated preoperative radiotherapy for resectable gastric cancer: 20-years follow-up of a randomized trial*. J Surg Oncol 2002;80:72-78.
190 Hallissey MT, Dunn JA, Ward LC, Allum WH. *The second british stomach cancer group trial of adjuvant radiotherapy or chemotherapy in resectable gastric cancer: Five-year follow-up*. Lancet 1994;343 (8909):1309-1312.
191 Bamias A, Karina M, Papakostas P, et al. *A randomized phase III study of adjuvant platinum/docetaxel chemotherapy with or without radiation therapy in patients with gastric cancer*. Cancer Chemother Pharmacol 2010;65:1009-1021.
192 Kwon HC, Kim MC, Kim KH, et al. *Adjuvant chemoradiation versus chemotherapy in completely resected advanced gastric cancer with D2 nodal dissection*. Asia Pac J Clin Oncol 2010;6:278-285.
193 Kosik J, Gil J, Szmigielski S, Beuth J, Pulverer G. *Prevention of hepatic metastases by liver lectin blocking with D-galactose in stomach cancer patients. A prospectively randomized clinical trial*. Anticancer Research 1997;17 (2 B):1411-1414,1415.