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TOPIC HIGHLIGHT

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Improving the outcomes in gastric cancer surgery

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Abstract

Gastric cancer remains a significant health problem worldwide and surgery is currently the only potentially curative treatment option. Gastric cancer surgery is generally considered to be high risk surgery and five-year survival rates are poor, therefore a continuous strive to improve outcomes for these patients is warranted. Fortunately, in the last decades several potential advances have been introduced that intervene at various stages of the treatment process. This review provides an overview of methods implemented in pre-, intra- and postoperative stage of gastric cancer surgery to improve outcome. Better preoperative risk assessment using comorbidity index (*e.g.*, Charlson comorbidity index), assessment of nutritional status (*e.g.*, short nutritional assessment questionnaire, nutritional risk screening - 2002) and frailty assessment (Groningen frailty indicator, Edmonton frail scale, Hopkins frailty) was introduced. Also preoperative optimization of patients using prehabilitation has future potential. Implementation of fast-track or enhanced recovery after surgery programs is showing promising results, although future studies have to determine what the exact optimal strategy is. Introduction of laparoscopic surgery has shown improvement of results as well as optimization of lymph node dissection. Hyperthermic intraperitoneal chemotherapy has not shown to be beneficial in peritoneal metastatic disease thus far. Advances in postoperative care include optimal timing of oral diet, which has been shown to reduce hospital stay. In general, hospital volume, *i.e.*, centralization, and clinical audits might further improve the outcome in gastric cancer surgery. In conclusion, progress has been made in improving the surgical treatment of gastric cancer. However, gastric cancer treatment is high risk surgery and many areas for future research remain.

Key words: Gastric cancer; Laparoscopic surgery; Risk assessment; Surgical outcome; Postoperative care

Core tip: In gastric cancer surgery comorbidities, nutritional status and geriatric frailty should be assessed to judge surgical risks in preoperative assessment. Improving postoperative recovery by laparoscopic surgery has improved outcomes for these patients. Enhanced recovery after surgery and fast-track programs should aim to further improve recovery after surgery. Advances have been made, however many areas for future research and improvement remain.

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INTRODUCTION

Gastric cancer constitutes a major health problem worldwide and is one of the leading causes of cancer-related deaths. In the United States gastric cancer compromises only 2% (25500 cases) of all new cancer cases yearly. In South Korea it is the leading form of cancer constituting 20.8% of malignant neoplasms. The number of deaths due to gastric cancer has decreased from 774000 in 1990 to 755000 in 2010 worldwide. It remains however the second leading cause of cancer death after lung cancer[1]. Prognosis of gastric cancer is relatively poor with an overall five-year survival rate for gastric cancer in the United States between 1999 and 2005 of 27%[2]. For localized disease 5-year survival rate was 63%, but only 23% of all gastric cancer cases were diagnosed at this stage[2]. In 2008 gastric cancer was responsible for a disability-adjusted life-year (DALY) rate of 241 per 100000 for males and 146 per 100000 in females worldwide, which is 9.8% and 6.3% of total cancer related DALY-rates respectively[3].

Surgery is the mainstay of treatment for gastric malignancy. In European and other Western countries gastric cancer surgery is regarded to be high risk surgery and there are major differences in outcome between countries[4]. Therefore, knowledge to improve the outcome of gastric cancer treatment is of great importance. As with all operations perioperative planning of this type of surgery is crucial for the clinical outcome of treatment, not only in terms of morbidity but also in functional recovery and hospital stay. Many efforts have been made to improve outcome after surgery for these patients in pre-, intra- and postoperative stage of treatment. Not only surgical efforts have been implemented, medical oncology has also contributed a great deal with neoadjuvant and adjuvant chemotherapeutic regimens for example. However, these advances are beyond the scope of this review.

This paper will provide a structured review of current literature that deals with advances in surgical care for gastric cancer patients in the preoperative-, intra-operative- and postoperative stage. Literature will be discussed this order. MEDLINE database was searched using appropriate search terms for each of the discussed themes. Most relevant and recent literature was used to complete this review. Search terms used for each paragraph are given in Table 1. Lastly, advances in organization of surgical care will be discussed.

ADVANCES IN PREOPERATIVE CARE

Surgical morbidity in gastric cancer surgery is reported to be as high as 39%[5]. In addition, complications after curative surgery for gastric cancer have a negative effect on overall and disease specific survival[6]. Therefore much effort should be made in preventing morbidity and mortality. Needles to say, the preferential moment to assess the risk of morbidity and mortality is during preoperative work-up. Gastric cancer patients in Western countries constitute a group that is especially frail to surgical treatment due to the condition in which patients usually present at time of diagnosis. An example is the reported rate of malnutrition as high as 85%[7]. The on average poor physical state and advanced age as well as disease stage contributes to poorer outcomes in Western countries as compared to Eastern countries such as Japan and South Korea where nationwide screening programs exist to diagnose gastric cancer at an early stage[8].

Preventing morbidity is becoming especially important since multidisciplinary treatment schedules are becoming standard in gastric cancer. Deterioration of general condition or delay because of required rehabilitation time due to serious adverse events (*e.g.*, abdominal sepsis due to anastomotic leakage requiring long-term Intensive Care Unit treatment) may disqualify a patients for his/her treatment.

Surgical risk assessment

Surgical risk assessment can be complex. Several risk scores have been introduced. A globally used risk-score is the American Society of Anesthesiologists (ASA)-Physical status and was first introduced in 1941[9]. To the best knowledge of the authors, ASA physical status as a risk factor has not been extensively investigated in gastric cancer surgery. ASA-physical status is only a component of the overall risk assessment. Moreover, it might also subject to interpretation by the assessor. Different ASA classifications may be ascribed by different assessors depending on which factors are taken into account[9]. The ASA classification as an instrument is also a non-specific. Moreover, it is just a momentary status, without any clues to improve its figure in the future. By definition each cancer patient is having systemic disease and only therefore already ASA 2-classification. Practical applicability of this classification remains a challenge not only in daily practice but also in clinical research. Therefore new classifications have been developed.

The Charlson comorbidity index (CCI) was established as a method for classifying comorbid conditions that determine risks of mortality[10]. CCI was later identified and validated in a surgical setting for prediction of mortality risk in patients undergoing complex gastrointestinal surgery[11]. It was shown in octo- and nonogenarians who underwent radical gastrectomies that these elderly patients had higher morbidity and mortality rates, and this was associated with CCI $\geqslant$ 5[12]. Cancer specific survival was comparable to younger patients[12]. In another cross-sectional study the only independent factor predicting for mortality was the presence of comorbidity not age[13]. In contrast, a German study which included 139 gastric cancer patients did not find a significant correlation between CCI and the occurrence of morbidity and mortality postoperatively[14]. In multivariate analysis age was found as an independent factor for postoperative events.

Several patient factors associated with an impaired outcome after gastric cancer surgery have been reported over the years. In a series of 118 laparoscopic total gastrectomies, male gender was independently associated

Table 1 MEDLINE search terms used per section

Section	MEDLINE search terms	Limits
Introduction	"Cancer", "Mortality", "Global Burden of Disease", "Cancer statistics", "Gastric cancer", "Disability adjusted life years"	Language: English Time period: 2005-2014
Advances in preoperative care		
Risk assessment	"Risk assessment", "ASA classification", "peri operative risk", "Charlson Comorbidity Index", "Gastric cancer", "obesity", "complications", "previous abdominal surgery"	Language: English Time period: 2005-2014
Nutritional status	"Malnutrition", "screening tool", "Surgery", "Gastric cancer"	Language: English Time period: 2005-2014
Sarcopenia	"Gastric cancer", "Sarcopenia", "Surgery"	Language: English Time period: 2005-2014
Frailty	"Fraily surgery", "Complications", "Gastric cancer"	Language: English Time period: 2005-2014
Prehabilitation	"Prehabilitation", "Cancer"	Language: English Time period: 2005-2014
Staging laparoscopy and was cytology	"Gastric cancer", "Staging laparoscopy", "peritoneal cytology", "Hyperthermic Intreperitoneal Chemotherapy"	Language: English Time period: 2005-2014
Advances in intra-operative care		
Laparoscopic surgery (introduction)	"Gastrectomy", "Gastric cancer", "Laparoscopy"	Language: English Time period: 1990-2000
Laparoscopic surgery	"Gastrectomy", "Gastric cancer", "Laparoscopy"	Language: English Time period: 2005-2014 Article type: Review
Lymph node dissection	"D2 resection", "Gastric cancer", "Nodal dissection", "Bursectomy"	Language: English Time period: 1995-2014 Article type: Clinical Trial
Reconstruction technique	"Distal gastrectomy", "Gastric cancer", "Reconstruction", "Billroth", "Reconstruction"	Language: English Time period: 2005-2014
Intra-operative feeding jejunostomy placement	"Gastric cancer", "feeding jejunostomy", "morbidity"	Language: English Time period: 2005-2014
Advances in postoperative care		
Detection and treatment of anastomotic leakage	"Gastrectomy", "anastomotic leak", "risk factors", "gastric cancer", "covered stent"	Language: English Time period: 2005-2014
ERAS and Fast-track programs	"Gastric cancer", "ERAS", "Fast track", "Oral feeding", "Gastrectomy"	Language: English Time period: 2005-2014
Advances in organization of care: centralization and audits	"Case load" or "hospital volume", "gastric cancer", "gastrectomy"	Language: English Time period: 2005-2014

ASA: American Society of Anesthesiologist; ERAS: Enhanced recovery after surgery.

with postoperative morbidity[15]. Overweight patients [*i.e.*, body mass index (BMI) > 25 kg/m^2] are at an increased risk of complications; this was shown in a large prospective series of 1853 patients[16]. This showed increased complication rate (47.9% *vs* 35.8%, $P < 0.001$). Obese patients especially had more anastomotic leakages (11.8% *vs* 5.4%) and wound infections (8.9% *vs* 4.7%). Several other studies have also shown the association between higher BMI and increased postoperative morbidity[17-19]. Although no valid explanation for this finding is reported; it is suggested that in open and laparoscopic surgery, obesity is associated with more technical difficulties[20].

A history of upper abdominal surgery is not a contraindication for laparoscopic gastrectomy. In a series of 22 cases with previous upper abdominal surgery (PUAS) no differences were found for operative time, blood loss or conversion to open surgery when compared to patients without a history PUAS[21]. In a larger series of 50 patients with a history of laparotomy similar results were obtained for laparoscopic assisted gastrectomies[22]. Also, when compared to open surgery in patients with PUAS laparoscopic gastrectomy was performed with comparable postoperative outcome[21].

The literature fairly uniformly states that age should not be factored in clinical decision making, rather comorbid conditions and general condition are far more important factors predicting adverse outcomes. It remains challenging to adequately assess a patient's general condition and decide what factors exclude a patient from surgical treatment. Therefore, we discuss some of the features that are crucial to take into account during preoperative work-up.

Nutritional status

Gastric cancer patients are at a high risk for malnutrition and 30% to 38% of patients are reported to have > 10% weight loss in past six months[23]. A misbalance between energy expenditure and nutritional supplementation is the fundamental physiologic derangement leading to cancer-induced weight loss. Tumor related causes of malnutrition include early satiety and obstruction, but also tumor induced metabolic alterations[7]. Malnutrition is associated with increased morbidity and mortality after gastric cancer surgery[7]. It is highly important to thoroughly screen patients for malnutrition as interventions can be done to preoperatively improve nutritional status and subsequently

Table 2 Malnutrition universal screening tool and short nutritional assessment questionnaire, screening tools for detecting malnutrition

	Points
MUST	
Step 1 Body mass index	
> 20	0
18.5-20	1
< 18.5	2
Step 2 Unintentional weight loss past 3-6 mo	
< 5%	0
5%-10%	1
> 10%	2
Step 3 Acute disease effect	
If patient is acutely ill and there has been or is likely to be no nutritional intake for > 5 d	2
SNAQ	
Did you lose weight unintentionally?	
More than 6 kg in past 6 mo	3
More than 3 kg in past 3 mo	2
No	0
Did you experience a decreased appetite over the last month?	
Yes	1
No	0
Did you use supplemental drinks or tube feeding over the last month?	
Yes	1
No	0

Risk of malnutrition: MUST: 0 = Low risk, 1 = Medium risk, 2 or more = High risk. SNAQ: 0-1 = Low risk, 2 = Medium risk, 3 or more = High risk. MUST: Malnutrition universal screening tool; SNAQ: Short nutritional assessment questionnaire.

surgical outcome. Both malnourishment and weight loss are associated with poor clinical outcome after surgery[24].

Questionnaires: An easy and non-invasive tool to estimate the patient's physical and/or mental condition preoperatively is the use of questionnaires. Several questionnaires have been developed to identify patients at risk for malnutrition. The Short Nutritional Assessment Questionnaire (SNAQ) and Malnutrition Universal Screening Tool (MUST) scores are commonly used nutritional screening tools in surgical patients (Table 2)[25,26]. These questionnaires accurately screen for malnutrition and are obligatory in some Western countries as a part of governmental health care quality programs[27,28]. Although it is easy to apply, evidence for the value of nutritional screening tools to predict postoperative outcome in gastric cancer surgery is scarce. It has been shown that screening for nutritional risk in gastric cancer surgery patients using Nutritional Risk Screening 2002 (NRS 2002) is helpful. Increased scores are associated with more complications and increased length-of-stay[29]. A recently published study in which SNAQ was used to evaluate risks of adverse postoperative events after gastric cancer surgery showed that SNAQ $\geqslant$ 1 was associated with increased severe complications (*i.e.*, Clavien-Dindo grade $\geqslant$ 3a, 35.7% *vs* 17.7%, $P = 0.02$) and in-hospital mortality (OR = 5.1, 95%CI: 1.01-23.8, $P = 0.04$)[30]. The detection of nutritional depletion is important, especially with neo-adjuvant therapies potentially further compromising the nutritional and metabolic status[31]. Questionnaires are subjective methods to assess nutritional status and therefore methods to objectively measure a patient's condition might improve outcomes.

Sarcopenia

Sarcopenia, or the decrease of muscle tissue, is a part of the cachexia syndrome[7]. Presence of sarcopenia has been shown to affect short-term postoperative outcome with increased morbidity and mortality rates in patients undergoing liver resection for colorectal liver metastases[32]. It also predicts adverse long-term outcome in liver and pancreas surgery for malignancy[33,34]. The method for measuring sarcopenia in these studies was to calculate the total muscle or psoas muscle cross-sectional area using a specialized software package (*e.g.*, OsiriX5.5.2, open-source software) on computed tomography (CT) imaging on a set level (*e.g.*, at level of spinous process of lumbar vertebra L3). This could also be a useful method in gastric cancer patients as they all have preoperative staging CT-imaging of the abdomen. But as far as the authors are aware no literature on this subject exists to date. Other objective parameters such as lowered preoperative serum albumin levels have been identified as risk factors for postoperative complications after surgery for gastrointestinal carcinomas[35,36]. But the latter risk factors remain under debate as some authors dispute the role of malnutrition and lowered serum albumin levels as risk factors for impaired outcome after gastric cancer surgery[37].

For future research it is important to establish objective screening tools to detect malnutrition in surgical patients and whether these results are related to perioperative outcomes. More importantly, studies need to be done to establish whether correction of nutritional status results in improved outcome.

Frailty

In Western countries gastric cancer is a disease of the elderly, and therefore geriatric aspects have an important role in these patients. Frailty is defined as a state of increased vulnerability towards stressors in older individuals, leading to increased risk of developing adverse health outcomes. Geriatric frailty is considered by Fried *et al*[38] to be a clinical syndrome in which three of following five aspects are present. These are: unintentional weight loss (10 lbs in the past year), self-reported exhaustion, weakness (grip strength), slow walking speed, and low physical activity. Methods for assessing frailty are numerous. They range from a comprehensive geriatric assessment, which often employs the use of multiple questionnaires and short physical tests (*e.g.*, 4-m walk test, grip strength measurement), to using specific frailty questionnaires (*e.g.*, Edmonton frail scale).

Frailty assessment is an emerging method to aid surgical risk assessment and it rapidly gaining evidence based support[39,40]. It has been shown that scores on the Edmonton frail scale (EFS) > 7, *i.e.*, increased frailty, were

associated with increased complications after non-cardiac surgery (OR = 5.02, 95%CI: 1.55-16.25)[39]. The association between frailty and adverse postoperative outcomes has also been shown in patients undergoing cardiac surgery[41] and patients undergoing various types of elective surgery[42]. Some use tools such as EFS or Hopkins Frailty Score which includes various tests with regards to cognition, ADL function and more (including laboratory tests such as serum albumin)[39,40]. Recently published results from a large prospective study with patients who underwent general, oncologic and urologic procedures confirmed these findings in a larger patient population (n = 189)[43]. They showed that "intermediately frail" or "frail" as judged by the Hopkins Frailty score was an independent predictor for complications. Another example of frailty assessment questionnaire is the Groningen frailty indicator[44]. This questionnaire was used in a retrospective study to evaluate frailty assessment as a predictor for adverse outcome after gastric cancer surgery. In this recent study, incorporating 180 patients, increased GFI was significantly associated with postoperative morbidity and in-hospital mortality[30].

Prehabilitation

A novel strategy for improving outcomes after surgery is by preoperatively correcting the reduced functional, nutritional, physical and neurophysiological state of patients: prehabilitation[45]. This type of intervention might prove to be especially beneficial in elderly patients because they are often compromised in these respects. Most available literature on prehabilitation concerns joint replacement surgery. A pilot study has been published that evaluates multimodality prehabilitation interventions in colorectal surgical patients[46]. This study uses a trimodal approach of preoperative exercise, nutritional intervention (dietary behavior counseling and protein supplementation) and anxiety reduction training (also aimed at increasing compliance of exercise and nutritional intervention). Multimodal approaches have yielded promising preliminary results such as better walking capacity in weeks after surgery and higher physical activity levels after surgery compared to controls[46,47]. Because in Western society gastric cancer is predominantly a disease of the elderly prehabilitation may provide a promising effort for improving outcomes in these patients in the future[48].

Staging laparoscopy and wash cytology

Preoperative staging laparoscopy improves detection of peritoneal metastases not otherwise detected by preoperative ultrasonography or CT imaging[49]. It can therefore prevent an unnecessary explorative laparotomy or change management in up to 60% of cases[50,51]. An expert panel concluded that a staging laparoscopy should be performed for reasons mentioned above, exceptions being early gastric cancer or known metastatic disease[52].

Also, during staging laparoscopy peritoneal wash cytology can be obtained to detect intraperitoneal free cancer cells (IFCC). This has been shown to be a predictor for early recurrence after curative intent surgery[53]. It is even a negative prognostic factor in patients with overt peritoneal metastases in patients with suspected serosal invasion with median survival times of 14.0 and 10.0 mo in patients without and with positive cytology respectively[54].

In patients with overt peritoneal metastases hyperthermic intraperitoneal chemotherapy (HIPEC) together with cytoreductive surgery has been considered as additional treatment. A recent review concluded that HIPEC was not beneficial for these patients[55]. Gastric cancer patients with IFCC may be suitable candidates for new treatment regimens such as neoadjuvant systemic and intraperitoneal chemotherapy before radical surgery are currently under investigation.

ADVANCES IN INTRA-OPERATIVE CARE

One of the most significant and fundamental developments in gastrointestinal surgery last decades has been the introduction of the laparoscopic technique. Large incisions are avoided and surgical trauma is minimized.

Laparoscopic surgery

Introduced in Asia in the early nineties, a laparoscopic approach was first implemented for the treatment of early gastric cancer (EGC)[56]. Early reports comparing open and laparoscopic surgery for EGC showed several advantages of the laparoscopic approach over conventional open surgery. These included, less intra-operative blood loss, less postoperative pain and shorter length-of-stay. Also serum markers indicating postoperative stress were lower, *i.e.*, lower C-reactive protein (CRP) level on day 7, leukocyte count and interleukin-6 levels[57]. There were no significant differences in operation time, number of harvested lymph nodes and postoperative complications[57,58]. A review and meta-analysis evaluating randomized controlled trials (RCT's) and high quality non-randomized controlled trials on laparoscopic *vs* open approach for distal gastrectomy for cancer showed that major complications and mortality rates were similar between procedures and concluded that the laparoscopic approach is safe[59]. However, the majority of patients had EGC and therefore comparison to a Western population case-mix is difficult. Results further showed additional benefits of fewer overall and minor complications, shorter length-of-stay (weighted mean difference, 3.6 d) and less blood loss[59]. Also, longer operation time and lower number of harvested lymph nodes was reported for laparoscopic gastrectomy. Several other reviews and meta-analyses have been published on this subject since (Table 3)[59-63]. The general conclusion of these studies is that laparoscopic approach offers improved recovery after surgery at no compromise of morbidity and mortality.

Laparoscopic approach for performing a total gastrectomy for gastric cancer is technically more demanding and has therefore not gained as much widespread acceptance as the laparoscopic distal gastrectomy. A

Table 3 Summary of recently published meta-analysis examining laparoscopic distal gastrectomy *vs* open distal gastrectomy for gastric cancer

Ref.	Trials included (*n*)	Laparoscopic/open procedures (*n*)	TumOR = characteristics	Operative time (min) (WMD)	Blood loss (mL) (WMD)	Harvested lymph nodes (WMD)	Length-of-stay (WMD)	Complication rates	Mortality
Memon *et al*[62], 2008	4 RCT's	82/80	EGC, GC	+83 ($P < 0.001$)	-104 ($P = 0.02$)	-4.3 ($P < 0.001$)	-3.3 d ($P = 0.14$)	OR = 0.66 ($P = 0.14$)	OR = 0.94 ($P = 0.94$)
Chen *et al*[60], 2009	6 RCT's	323/306	EGC	+87 ($P < 0.001$)	-108 ($P = 0.001$)	-4.9 ($P < 0.001$)	-2.0 d ($P = 0.14$)	RR = 0.61 ($P = 0.01$)	Risk difference 0.01 ($P = 0.32$)
Kodera *et al*[61], 2010	6 RCT's	343/323	EGC, GC	+82 ($P < 0.001$)	-118 ($P < 0.001$)	-4.8 ($P < 0.001$)	NA	OR = 0.46 ($P = 0.003$)	OR = 0.17 ($P = 0.86$)
Ohtani *et al*[63], 2011	5 RCT's	164/162	EGC, GC	+82 ($P < 0.001$)	-122 ($P < 0.001$)	-4.8 ($P < 0.001$)	-2.5 d ($P = 0.04$)	OR = 0.38 ($P = 0.01$)	OR = 0.47 ($P = 0.54$)
Viñuela *et al*[59], 2012	6 RCT's 19 NRCT's	1658/1397	ECG, GC	+48.3 ($P < 0.001$)	-118 ($P < 0.001$)	-3.9 ($P < 0.001$)	-3.6 ($P < 0.001$)	OR = 0.59 ($P < 0.001$)	OR = 0.64 ($P = 0.39$)

RCT: Randomized controlled trial; NRCT: Non-randomized controlled trial; EGC: Early gastric cancer; GC: Gastric cancer (all stages); WMD: Weighted mean difference; NA: Not available.

systematic review and meta-analysis by Chen *et al*[64] showed similar differences between laparoscopic assisted total gastrectomy and open total gastrectomy, *i.e.*, longer operative time, shorter hospital stay, a decrease in medical complications and no difference in operative mortality. It included nine studies comprising 1221 patients (436 laparoscopic procedures and 758 open procedures), but none of the studies were RCT's. All but one study included both EGC and advanced stage disease patients. Nevertheless, the authors concluded that laparoscopic approach for total gastrectomy can be performed safely and with improved outcome in experienced surgical centers[64].

As mentioned, most reported studies report on laparoscopic procedures for EGC. Laparoscopic approach for advanced stage disease has also been shown to be associated with shorter length-of-stay and less blood loss with comparable morbidity and mortality rates[65-67]. Also similar oncological outcomes are reported for laparoscopic surgery in advanced stage disease[68]. A systematic review and meta-analysis on distal gastrectomy for advanced gastric cancer concluded that further prospective controlled studies are needed for a comprehensive comparison.

A critical issue with the laparoscopic approach is oncological adequacy. The evidence for this is still sparse although a few report similar oncological outcomes for laparoscopic procedures at five years[65,66,69].

Lymph node dissection

Differences in treatment outcome between Asian and Western countries remain striking. The debate continues whether this is due to more extensive approach of lymph node dissection advocated by the Japanese Gastric Cancer Association. D2 lymphadenectomy has been shown increased survival in Chinese patients[70]. Initial results from randomized trials performed in the Netherlands and United Kingdom showed an increased morbidity and mortality rate in the D2 group and no survival benefit[71,72]. Fifteen-year follow-up results of the Dutch trial showed that D2 resection was associated with lower regional recurrence (22% in D1 resection and 12% in D2 resection) and gastric-cancer-related death[73]. They advocate a spleen preserving D2 procedure as a safer alternative. Later studies showed however that D2 resections can be performed safely in the West, they had low overall morbidity and mortality rates (3.0% after D1 and 2.2% after D2 gastrectomy, $P = 0.722$)[74]. Additional value of D3 dissection (dissection of hepatoduodenal ligament, superior mesenteric vein and retro-pancreatic area) is disputed. A prospective trial in Taiwan showed a slight 5-year survival benefit for D3 resections 59.5% compared to 53.6% in D1 gastrectomy patients ($P = 0.041$)[70]. Para-aortic nodal dissection was shown to be performed safely in addition to D2 dissection but failed to show a 5-year benefit[75,76].

Another strategy for attempting to improve oncological outcome of gastric cancer surgery was to perform a bursectomy in addition to resection and lymphadenectomy for advanced stage gastric cancer. Several studies did not show a benefit of bursectomy[77,78]. But proponents of this technique argue that it may improve survival and should not be discarded as a futile technique[79]. A phase Ⅲ trial is currently ongoing in Japan that will also evaluate the effectiveness of procedure (see: http://www.jcog.jp/en/trials/index.html).

Reconstruction technique

Roux-en-Y is the accepted standard technique for reconstructing bowel continuity after total gastrectomy. Billroth I and II reconstruction after distal gastrectomy have been the standard for a long time but are associated with increased rates of reflux symptoms and esophagitis[80]. Roux-en-Y reconstruction as an alternative after distal gastrectomy has been thoroughly investigated. Studies have shown beneficial outcomes in terms of less reflux symptoms and less gastric remnant gastritis[81,82]. These findings persist in long-term follow-up[83]. However, patients did not differ in terms of quality of life[84]. Morbidity and mortality were similar between Billroth I and Roux-en-Y technique, but the latter was associated with longer length-of-stay and discontinuance of food intake[85].

Intra-operative feeding jejunostomy placement

Routine intra-operative placement of feeding jejunostomy can potentially decrease malnutrition and improve tolerance of adjuvant chemotherapy[86]. A study with data from a prospectively maintained database including 132 patients showed no advantage of jejunostomy placement and increased complications associated with jejunostomy placement[87]. In a series of 73 patients who received jejunostomy placement, it was shown that 21 patients had jejunostomy specific complications (11 minor and 10 major)[88]. Therefore, routine jejunostomy placement is not recommended and should be reserved for selected patients.

ADVANCES IN POSTOPERATIVE CARE

Detection and treatment of anastomotic leakage

Anastomotic failure or leakage is an important complication of gastric surgery, potentially with detrimental consequences. Risk factors for anastomotic leakage have been identified in several studies. These include: older age (> 65 years), longer operating time, intra-operative errors, increased blood loss and comorbidities[89-91].

When leakage or associated intra-abdominal abscess is suspected clinically by positive peritoneal signs, fever and/or wound infection, further investigation using computed tomography should be prompted. If detected and leakage is minor it can be successfully managed with percutaneous drainage[92,93]. Some authors advocate the use of conservative management techniques for treating anastomotic leakage such as placement of a nasojejunal tube combined with percutaneous drainage of abscess[94]. In this study this approach was associated with lower mortality rates compared to operative intervention. Therefore, reoperation is only required when conservative treatment is ineffective. When reoperation is carried out the anastomosis can be evaluated and if it is in a poor condition reconstruction can be carried out[95].

Endoscopic approach also offers a chance to assess the anastomosis site and endoscopic treatment options for leakage are available. Recent literature describes endoscopic approaches for the management of anastomotic leakage and different techniques can be applied[96]. The authors concluded that defects smaller than 2 cm in size could be successfully managed using endoscopy. Techniques include use of fibrosealant or Histoacryl and also stent insertion. Multiple studies report use of removable covered metal stents to treat anastomotic leaks with relatively good results[97,98]. Main advantage of this approach is that it enables evaluation the anastomosis without the need for invasive surgery. However, this technique requires a well trained and well equipped endoscopy department.

Enhanced recovery after surgery and fast-track programs

Enhanced recovery after surgery (ERAS) programs have been developed and implemented with great success in colorectal surgery[99]. All recommendations by ERAS society for colonic surgery (see also: http://www.eras-society.org/index.php/eras-care-system/eras-protocol) can potentially be implemented in gastric cancer patients, *i.e.*, early removal of urinary catheter, prevention of postoperative ileus, postoperative analgesia, and early mobilization and resumption of normal diet[100]. Important to note is that ERAS protocols not only include recommendations on postoperative care, but also preoperative measures (*e.g.*, counseling) and intra-operative measures (*e.g.*, avoidance of salt and water overload and use of short acting anesthetic agents). In recent years efforts have been made to develop, implement and evaluate the effect of similar programs in gastric cancer surgery. Studies on the timing of oral intake after gastrectomy for gastric cancer are sparse. Small studies that exist have evaluated early oral feeding as safe and feasible[101]. This study started liquid intake on days 1-2 and soft diet on postoperative day 3. Similar studies showed significant shorter hospital stay (*e.g.*, 5.7 d *vs* 9.2 d) and earlier return of bowel function[102-104]. Although the strategies for early oral feeding were different, ranging from oral diet on day one to liquid diet on day two followed by soft diet from day three until discharge, their findings were that it is safe and potentially leads to shorter hospital-stay.

A randomized comparison between fast-track surgery and conventional care in gastric cancer patients (n = 45 and n = 47 respectively) showed less stress response in the fast-track surgery group[105]. This was measured by serum tumor necrosis factor-alfa, CRP and interleukin-6 levels. Also, fast-track patients had a shorter hospital stay and higher quality of life with no increase in complications. Yamada *et al*[106] compared ERAS (n = 91) with conventional care (n = 100) after gastrectomy and found that ERAS was associated with less postoperative pain and analgesics use. There was no difference in complication rates between ERAS and conventional care. They did not find a significant difference in mean length-of-stay.

Implementation of a fast-track or ERAS program was also investigated as an addition to laparoscopic procedures[107-109]. A consecutive series of 32 patients showed

that it was safe and had similar postoperative results[107]. In addition, a randomized clinical trial with 22 fast-track and 22 conventional care patients showed a shorter length of stay for fast-track patients (5 d *vs* 8 d, $P < 0.001$) but no difference was noted for postoperative pain[108]. Chen Hu *et al*[109] found that the laparoscopic assisted procedure with the addition of a fast-track approach resulted in shortest length-of-stay.

ADVANCES IN ORGANIZATION OF CARE: CENTRALIZATION AND AUDITS

In Western countries the incidence of gastric cancer is relatively low. Annual hospital volume can therefore be low in institutions in non-centralized regions. Centralization offers a chance to increase volumes in selected centers. Increased hospital volume leads to better treatment results in gastric cancer surgery[110]. More recent studies support this idea and show that increased volumes are associated with lower short-term mortality and improved survival[111,112]. Other literature suggests that hospital volume is not a determinant for disease-free survival or overall survival in gastric cancer surgery survivors (*i.e.*, perioperative mortality excluded)[113]. Although the optimal number of procedures is not clearly defined in literature, expert panel based recommendations state that an annual volume of more than 15 for an institution and more than 6 for the individual surgeon are held to be appropriate[52]. They also state that the necessity of these volumes is undetermined.

In several countries clinical auditing has been initiated in various fields of surgery. It is considered an important tool for quality assessment and the identification of factors needing improvement. Furthermore, clinical audits provide a unique dataset for research as well. For gastric cancer surgery, a nationwide audit has been initiated in the Netherlands, the Dutch upper GI cancer audit (DUCA) (http://duca.clinicalaudit.nl/). The DUCA has become a performance index for gastric cancer surgeons as it was also adopted as a quality indicator for the health care inspectorate. It is expected that postoperative mortality and anastomotic leakage rates will decrease but few reports have been published in the Netherlands so far. From 2011 to 2012 30-d mortality decreased from 8.8% to 6.7% (see: http://www.clinicalaudit.nl/jaarrapportage/#dica_rapportages_duca). Whether these improvements are directly related to the introduction of the audit has to be determined. At least, it can be stated that the DUCA has effectuated increased awareness of and insight in aspects of improvement.

Clinical audits have revealed several interesting findings with respect to postoperative complications. Hospitals with higher mortality rates had only slightly higher incidences of postoperative complications. But in high volume centers these patients with a serious complication had less chance dying than in high-mortality centers. This phenomenon is addressed as failure to rescue and was not only described for gastrectomy but also for other gastro-intestinal operations[114]. Data from the American College of Surgeons National Surgical Quality Improvement Program showed that although complication incidences did not vary between hospitals, mortality rates, largely contributed to death after major complications, significantly varied, indicating that timely recognition and treatment of complications deserves greater attention[115]. Future research should aim at identifying and improving the fundamental aspects causing failure to rescue.

CONCLUSION

Surgical risk assessment is complex and difficult. In preoperative assessment of gastric cancer patients age should not be a criterion on which treatment decisions are be made. Rather, presence of comorbidities, nutritional status and geriatric frailty should be assessed and taken into account. Future studies should further determine the role geriatric frailty and nutritional status assessment has in the preoperative evaluation of gastric cancer surgery patients, especially in Western counties, as these patients are more often at an advanced age.

Improving postoperative recovery by using fast-track and ERAS protocols has yielded improved results. The timing of oral intake is still at debate, but early oral feeding (postoperative days 1-3) seems to be feasible and safe. Further studies have to verify this and investigate its effect on morbidity, length-of-stay and quality of life/patient satisfaction. Also optimal fast-track/ERAS programs have to be developed to further improve outcome and quality of care for these patients.

Introduction of laparoscopic surgery has improved short-term postoperative outcome for gastric cancer patients. Oncological safety remains an area of debate, but available literature suggest that oncological safety is not compromised.

In conclusion, although advances have been made in pre-, intra- and postoperative stage of gastric cancer surgery to improve the outcome of these patients, there still remain many areas for improvement and future research.

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