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EDITORIAL

R0 resection in the treatment of gastric cancer: Room for improvement

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Abstract

Gastric carcinoma is one of the most frequent malignancies in the world and its clinical behavior especially depends on the metastatic potential of the tumor. In particular, lymphatic metastasis is one of the main predictors of tumor recurrence and survival, and current pathological staging systems reflect the concept that lymphatic spread is the most relevant prognostic factor in patients undergoing curative resection. This is compounded by the observation that two-thirds of gastric cancer in the Western world presents at an advanced stage, with lymph node metastasis at diagnosis. All current therapeutic efforts in gastric cancer are directed toward individualization of therapeutic protocols, tailoring the extent of resection and the administration of preoperative and postoperative treatment. The goals of all these strategies are to improve prognosis towards the achievement of a curative resection (R0 resection) with minimal morbidity and mortality, and better postoperative quality of life.

Key words: Gastric cancer; R0 resection; Total gastrectomy; Lymph node dissection; Adjuvant therapy; Preoperative therapy

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INTRODUCTION

Despite an incidence rate that has steadily declined over the past few decades, gastric carcinoma is one of the most frequent malignancies worldwide. An estimated 934 000 new cases are diagnosed each year, with the highest incidence rate in Northeast Asia, intermediate incidence rates in Europe and South America, and the lowest incidence rates in North America, Africa, South Asia, and Oceania[1,2].

Early dissemination of the disease through the lymphatic system, blood, and peritoneum has limited optimal surgery as a cure, except in patients with early-stage cancers. In Japan and Korea, the introduction of screening for gastric cancer has been shown to improve early detection, and almost half of newly diagnosed patients are detected at an early stage[3-6]. Due to the lower disease incidence rate, this strategy has not been deemed cost-

effective in Europe or North America. Consequently, two-thirds of gastric cancers in the Western world present at an advanced stage, with lymph node metastasis at the time of diagnosis[7].

The mainstay of treatment is radical surgery, but even with optimal surgical resection, the prognosis remains dismal in Western countries. Numerous attempts have been undertaken to improve clinical outcomes. To date, most therapeutic efforts are directed toward an individualization of therapeutic protocols, tailoring the extent of surgery and integrating it with the administration of preoperative and/or postoperative treatment. The goal of such strategies is to improve prognosis towards the achievement of a curative resection with minimal morbidity and mortality and better postoperative quality of life.

R0 RESECTION: DEFINITIONS

Curative resection refers to the absence of tumor after surgical treatment, and in the Western world, it meets the R0 resection definition provided by Hermanek *et al*[8] more than 15 years ago. R0 resection indicates a microscopically margin-negative resection, in which no gross or microscopic tumor remains in the primary tumor bed. R1 resection indicates the removal of all macroscopic disease, but microscopic margins are positive for tumor. R2 indicates gross residual disease with gross residual tumor that was not resected (primary tumor, regional nodes, and macroscopic margin involvement).

If this definition holds, R0 resection should represent a surgical cure, with a high survival rate and low recurrence. Considering the low survival rate after R0 surgical treatment in the Western case-mix, it is clear that the R0 definition needs to be revised, especially in locally advanced cases[9-11]. It is likely that there is a tendency to misclassify a number of cases as R0 resection, which inexorably will recur, which suggests that a curative treatment was not actually achieved.

The reason that the definition of Hermaneck is not in accordance with this scenario may be because it is mainly concerned with the primary tumor site, and not examining in detail the three pathways of tumor dissemination: portal blood stream to the liver, peritoneal surfaces and lymphatic dissemination. With these methods of dissemination, it is often beyond the surgeon's ability to achieve loco-regional control of the cancer. It may be difficult or impossible for the surgeon to reduce the incidence of metastases to the liver, as well as to contain the peritoneal seeding of cancer cells, or the removal of all extra-regional metastatic lymph nodes.

In the eastern world, Japanese guidelines have given a different definition to the curative gastric resection based on both surgical and histopathological details[12]. Resection A: no residual disease, with a high cure probability. It implies resections satisfying all of the following conditions: tumor without serosal invasion; N0 treated by D1, D2, or D3 lymph node dissections, or tumor with first-level lymph node treated by D2 or D3 resection; no distant, peritoneal or liver metastases, negative cytological examination of peritoneal fluid and proximal and distal margins > 10 mm. Resection B: no histopathologic residual disease but not fulfilling criteria for resection A. Resection C: definite residual disease.

These strict criteria emphasize that once the tumor penetrates the serosa or invades adjacent organs, it begins to spread by routes other than the regional lymphatic system. Specifically, tumor metastasis can occur through the peritoneum, extra-regional lymph nodes and the portal-hepatic blood, which consequently diminishes the probability of a cure. Such a definition would imply that more than two-thirds of patients are considered non-curatively treated by surgery in the Western world, which underestimates the role of surgery at these stages.

Today, both definitions seem inadequate: they merely indicate the absence or presence of residual tumor cells in the tumor bed after surgical treatments or provide an estimation of the probability of cure with surgery. In reality, the surgeons must consider themselves responsible not only for resection of the large mass of the primary cancer and overt lymph node metastases in the tumor bed, but also for dealing with microscopic and distant residual disease.

R0 RESECTION AND PREOPERATIVE IMAGING: WHAT CAN WE ANTICIPATE?

Although surgical pathology provides the most accurate information on tumor extent, clinical preoperative staging is crucial to select the appropriate treatment strategy. Today, clinical staging has been improved by technical enhancement in endoscopic ultrasound (EUS), computed tomography (CT), positron emission tomography (PET), combined PET-CT scan, magnetic resonance imaging (MRI) and laparoscopic staging. Presently, EUS and CT are widely used for preoperative staging[13].

Although the accuracy of T staging has been much improved for EUS (current range: 78%-92%)[14-20] and CT (current range: 69%-89%)[17,21-27], N staging accuracy is still poor (63%-78% in EUS[14-20], 51%-78% in CT[17,21-27]). MRI has had limited use in the staging of gastric cancer, primarily as a result of difficulties with motion artifacts, cost, time required for examination, and lack of an appropriate oral contrast agent[28,29]. However, in recent studies, overall T staging accuracy has been reported to be between 71.4% and 82%, which is similar to CT[29]. In N staging, several studies have shown that the accuracy of MRI nodal staging is inferior to CT staging with both techniques tending to understage nodal status[28,29]. Moreover, MRI has showed a greater sensitivity than CT in detecting liver, bone, and peritoneal dissemination[29].

Generally, PET is not routinely performed in the clinical staging of gastric cancer. From clinical studies focusing on PET, it is concluded that, for N staging, PET has a significantly higher specificity (92%) but lower sensibility (56%) compared to CT in the detection of local lymph node involvement[30-32]. Recent reports have confirmed the limited role of PET in the preoperative staging of gastric cancer, but it must be pointed out

that combined PET-CT can significantly improve overall staging accuracy compared to PET and CT alone[33,34].

Due to the inaccuracy of CT for the detection of ≤ 5 mm macrometastases on the peritoneal surface or liver, staging laparoscopy is recommended as the next step in the evaluation of patients with locoregional disease. Staging laparoscopy can detect metastatic disease or modified preoperative therapeutic strategy in 23%-54% of patients, thus confirming its crucial role in staging gastric carcinoma[35-37]. Moreover, there is some evidence that laparoscopy permits a more accurate staging of extraserosal tumors, whereas EUS might sometimes lead to misinterpretation of T3 invasion, when edema distorts the interface between the stomach and adjacent tissues[18,38,39].

In addition, staging laparoscopy facilitates cytological examination of abdominal lavage fluid. Cytology of peritoneal fluid or lavage may reveal the presence of free intraperitoneal gastric cancer cells, which identifies patients with an otherwise occult microscopic carcinomatosis. Recent evidence has suggested that patients with positive findings on peritoneal cytology have a poor prognosis, similar to that of patients with macroscopic stage Ⅳ disease[40].

SURGICAL DEBATES OF R0 RESECTION

R0 resection: Total vs subtotal gastrectomy, what else?

Some issues about the extent of gastric resection seem to have been settled. Total gastrectomy should be avoided if adequate free resection margins can be obtained with subtotal gastrectomy: a gross surgical margin of at least 5 cm for the intestinal type or 8-10 cm for the diffuse type[41-44]. Many authors agree on the necessity of total gastrectomy if the cancer encroaches on an imaginary line between the angula incisura of the lesser curvature and the "bare" area on the greater curvature between the gastroepiploic vessels and the short gastric vessels[44]. This is because the lymph drainage from such a tumor feeds into the splenic hilum and flows along the splenic artery, as well as passing proximally and distally.

Proximal tumors and tumors of the gastroesophageal junction (GEJ) deserve different considerations. These tumors are traditionally classified according to the Siewert classification system, which takes into account the center of the tumor and the variable involvement of the esophagus and stomach: type Ⅰ, esophageal adenocarcinoma of the distal esophagus, with the center located between 1 and 5 cm above the GEJ; type Ⅱ, true adenocarcinoma of the cardia located within 1 cm above and 2 cm below the GEJ; and type Ⅲ, subcardial adenocarcinoma located between 2 and 5 cm below the GEJ. Surgical treatment of these tumors usually requires an extended total gastrectomy with resection of variable portions of the distal esophagus. The extent of resection of the distal esophagus depends on the extent of the tumor spread[45].

Generally, patients with type Ⅰ tumors are best treated by esophagectomy with gastric pull-up to the neck or by esophagogastrectomy (transthoracic or transhiatal). Type Ⅱ and Ⅲ tumors can be resected by gastrectomy with frozen-section-guided resection of the distal esophagus (transhiatally extended gastrectomy)[46]. Although total gastrectomy has been the procedure of choice in these tumors, some authors have advocated proximal gastrectomy as a surgical option, and in a retrospective study conducted by the Memorial Sloan Kettering Cancer Center, proximal gastrectomy has been reported to have similar mortality rate, hospital stay, and recurrence and survival rates[47]. Even if the R0 resection rate does not differ between groups, other authors have reported poor functional and quality of life results in patients undergoing proximal resection[48-50]. Although it is difficult to make definitive conclusions in the absence of a prospective randomized trial, it does appear that total gastrectomy remains the procedure of choice in these patients.

R0 resection: The "circumferential/lateral" margin

The progression of the cancer through the stomach wall to the adjacent structures makes one aware of the concept of circumferential/lateral margins and provides the rationale for conservative and extended surgery.

If diagnosed at an early stage, it may be possible to obtain a margin-negative resection without traditional gastrectomy (subtotal, proximal or total gastrectomy). When margin-free resection is warranted, the only limiting factor is the risk of lymph node metastasis. For patients with a well- to moderately well-differentiated tumor of less than 2 cm in size, with no submucosal invasion or lymphangioinvasion, local excision by endoscopic mucosal resection (EMR) has been the preferred treatment in Japan for the past 15 years, since the risk of lymph node metastases is thought to be very low[51].

Although a prospective randomized trial is lacking in the literature, results of a systematic review of cohort studies have shown that EMR has favorable disease-specific survival, incidence of local recurrence and complications, compared with surgery[52,53]. Endoscopic submucosal dissection (ESD) is a newly developed technique that can remove large tumors in one piece. In a comparison with EMR, resection that removes tumors in one piece was more frequent in an ESD group and resulted in a better 3-year recurrence-free rate, despite a higher complication rate[54,55].

Currently, indications for ESD, according to Japanese guidelines, are only for well-differentiated intramucosal (T1a) tumors. However, a large-scale study analyzing lymph node metastasis of early cancer has expanded the criteria for endoscopic treatment of early gastric cancer, which is based on tumor characteristics with a very low risk of lymph node metastasis[56]. This study showed that patients with intramucosally or submucosally well-differentiated tumors of less than 3 cm and poorly intramucosally differentiated tumors of less than 2 cm have a very low risk of lymph node metastasis.

The results of both the United Kingdom Medical Research Council and the Dutch trials, along with more recently randomized controlled trials, large retrospective series and meta-analysis[57-63] have reported a significantly worse prognosis, higher mortality, higher complication

rate, and longer hospital stay in patients who have undergone gastrectomy with prophylactic splenectomy or pancreaticosplenectomy.

Theoretically, in patients with T4 gastric adenocarcinoma, extended resection is required to improve the R0 resection rate. With careful patient selection, gastrectomy with additional organ resection can be done with acceptable morbidity and low mortality. Improvements in preoperative evaluation to confirm T3 and T4 disease are needed because postoperative histopathological examination has revealed that multi-organ resections are often performed for pT3 tumors, with a relatively small proportion of pT4 tumors[64,65]. Independent factors of a worse prognosis, such as N3 tumors and large diameter tumors (> 10 cm), have to be excluded before performing extended resection[66,67]. Based upon these issues, the cautious clinical behavior is to reconsider any clinically defined T4 tumor on a case by case basis before planning extended multi-organ resection.

R0-resection: When can the lymph node dissection be considered margin-negative?

The extent of lymphadenectomy continues to represent the main area for surgical research in gastric cancer, and the surgical strategy of choice is still a matter for debate. Lymphatic metastasis is one of the main predictors of tumor recurrence, and survival and current pathological staging systems reflect the concept that lymphatic spread is the most relevant prognostic factor in patients resected with curative intent[68-73]. Recurrence rates attributed to residual lymph node metastasis around the celiac artery have led to the concept that complete clearance of the metastatic lymph nodes by extended dissection (D2) may prolong survival. In Japan, where gastric cancer is far more common than in Western countries, a standardized lymph node dissection has been developed over the past 40 years and is used nationwide with therapeutic benefit and long-term survival rates of $\geqslant$ 60% after 5 years. Retrospective studies from Japan, and later from Korea[74], involving more than 10 000 patients, have suggested that extended lymph node dissection combined with gastrectomy increases 5-year survival rate from 50% to 62%, compared to a 5-year survival rate of 15%-30%, as a result of limited resections in the United States[75-79].

The importance of adequate lymph node dissection as part of a potentially curative resection has led to the development and publication of "The General Rules for the Gastric Cancer Study in Surgery and Pathology", which was definitively published in English in 1996[12]. Several Western reports have confirmed that extended lymphadenectomy, similar to that recommended in the General Rules, can be safely performed with improvements in survival[80-85].

In the Western world, the challenge has been to show whether these results could be generalized for unselected patients. To date, four prospective randomized trials of Japanese-defined D1 *vs* D2 lymph node dissection and two meta-analysis studies have been conducted[86-92].

All of these studies have documented limited survival benefits with unacceptable morbidity and mortality that is probably associated with pancreaticosplenectomy, low case volume, and a lack of specialist training[93,94]. Moreover, some authors have suggested that extended lymph node dissection combined with rigorous pathological evaluation results in improved staging rather than therapeutic benefit. Through accurate staging, patients with advanced stage cancer are well categorized, and any comparisons with series of non-standardized lymph node dissection, or under-staged patients, are therefore inaccurate. These results have made many Western surgeons reluctant to perform extended lymph node dissection routinely in an effort to obtain better regional disease control, and possibly, some survival advantage. Nevertheless, there is some evidence that extended lymph node dissection may offer a definite chance for a cure in a subset of patients with pN2 disease[88], even if these patients cannot be distinguished preoperatively.

At the same time, in the eastern World, where D2 lymph node dissection is not a matter of debate, the challenge has been to demonstrate that super-extended lymph node dissection offers a better chance of a cure in gastric cancer treated with curative intent. The Taipei single-institution study that has compared D1 and D3 dissection has demonstrated a significant overall survival benefit in extended lymph node dissection, but no significant improvements in disease-free survival or in per-protocol analysis[90]. Moreover, the study showed that the morbidity of extended lymphadenectomy, although not lethal, is substantial even in experienced hands[95]. Finally, a multi-institutional, randomized and controlled trial by the Japan Clinical Oncology Group (JCOG-9501) has failed to demonstrate a survival benefit when super-extended (D2 + para-aortic node) lymph node dissection was performed. Moreover, in this randomized trial, the rate of postoperative morbidity in patients with a body mass index of $\geqslant$ 25 kg/m^2 and age > 65 years was a notable concern[96].

Geographical differences notwithstanding, all of these results agree with Cady's paradigm "...the therapeutic effect of cancer surgery is akin to that of a drug with a threshold or plateau effect: dose response up to a certain plateau, and then no further therapeutic effect beyond this point, only more complications"[97].

From a practical point of view, it is hard to believe that unresected overt nodal metastases in the tumor bed will not worsen prognosis. Likewise, it is hard to believe that resection of more negative lymph nodes will improve it. Tailoring lymph node dissection on the basis of actual lymph node involvement could be a key point for performing appropriate lymph node dissection and avoiding high rates of postoperative morbidity.

In the late 1980s, Kampschöer *et al*[98] developed software that was designed to match cases with characteristics similar to a given case. With seven demographic and clinical inputs, all identifiable preoperatively or intraoperatively, the program was able to predict the statistical likelihood of nodal disease for each of the 16 main nodal stations around the stomach[98-100]. The so-called "Maruyama Index of Unresected Disease" (MI), when retrospectively

used, was able to quantify the adequacy of lymphadenectomy. Such a novel measure was defined as the sum of Maruyama Program predictions for lymph node stations (Japanese stations 1-12) left *in situ* by the surgeon[101,102]. In a large United States adjuvant chemoradiation study, MI proved to be a strong predictor of survival that was independent from the level of lymph node dissection[103]. Furthermore, a blinded retrospective analysis of Dutch D1 *vs* D2 trial data has suggested that low-MI surgery is associated with significantly increased survival, regardless of lymph node dissection[104]. The MI aims to define an R+ lymph node dissection, and it appears that surgeons might have a better impact on single patient survival by pursuing a low MI operation (low probability of lymph node metastases left *in situ*) instead of relying exclusively on D-level guidance.

When the probability of lymph node metastasis is considered low, sentinel node dissection can be considered as another approach to customize lymph node dissection[105-107]. The sentinel nodes are the first sites of lymph node metastasis from a primary tumor and theoretically predict the involvement of more distant lymph nodes. To date, selective sentinel node dissection, detectable using the injection of either dyes or radioactive tracers, represents a standard procedure for melanoma and breast cancer with low probability of lymph node metastasis. In early gastric cancer, the risk of lymph node metastases is 2%-5% for patients with mucosal cancer and 11%-20% for those with submucosal cancer[108]. Sentinel node mapping results in gastric cancer have been variable since the lymphatic drainage from the stomach is very complicated and multidirectional, with an incidence of skip metastasis ranging from 5% to 10%[109]. Moreover, early reports have demonstrated that the loco-regional lymph node station contains truly positive nodes, even when the sentinel biopsy is negative. These anatomical peculiarities have led to the concept of a "sentinel lymphatic basin"[110], which indicates the lymph node stations to which sentinel nodes belong. Dissection of these stations can provide an acceptable safety net for the clinical application of these procedures, and minimize the possibility of leaving metastasis behind. Preliminary studies have shown that these sentinel node techniques are an acceptable procedure for pathological T1 tumors with a diameter of < 40 mm, although long-term follow-up data are still required[111-114].

R0 RESECTION: IS IT MERELY A SURGICAL TARGET?

Along with these classical surgical topics, in the past 20 years, three different modalities of adjuvant (pre- and postoperative) therapy have been proven to be effective by large-scale randomized trials. These include postoperative chemoradiation therapy (Unites States INT-0116 trial)[115], postoperative single-drug chemotherapy (Japanese ACTS-GC trial)[116] and perioperative three-drug combination chemotherapy (European MAGIC trial)[117]. Since the publication of these trials, surgery alone is no longer considered the standard treatment for patients with resectable locally advanced forms of gastric cancer, and the concept of radical resection needs to take into account the fact that R0 resection is not an exclusively surgical target.

Postoperative therapy: Recovery of R0 resection

Many studies and several meta-analyses with a focus on adjuvant postoperative chemotherapy have been conducted[118-127]. Summarizing their results, we can state that there is insufficient evidence, at present, to recommend postoperative chemotherapy as standard adjuvant treatment in Western patients. At present, these results should be cautiously managed, since these studies included very different patient populations, surgical procedures, and non-standardized timing and regimens of adjuvant therapy that are now considered as outdated[128]. At the same time, results from pivotal studies on postoperative chemoradiotherapy are inconclusive and conflicting because of the relatively small number of patients recruited[129-133].

In the United States, between 1991 and 1998, a study from the SWOG-Intergroup 0116 trial randomly assigned 556 patients to surgery only and surgery plus postoperative chemoradiotherapy: 45 Gy radiotherapy at 1.8 Gy/d, given 5 d/wk for 5 wk, with modified doses of fluorouracil and leucovorin on the first 4 d and last 3 d of radiotherapy. Two 5-d cycles of fluorouracil and leucovorin were given after, and one cycle was given before chemoradiotherapy[115]. Although clinically significant toxicity was recorded after chemoradiotherapy, the overall and relapse-free survival results of the surgery-alone arm were significantly worse than those of the adjuvant chemoradiotherapy arm. Chemoradiotherapy significantly improved median survival from 27 to 36 mo. Distant relapse was the most common pattern of recurrence in the adjuvant group (33% *vs* 18%), whereas local recurrence was more common in the surgery-only group (29% *vs* 19%). In this trial, < 10% of patients received formal D2 dissection, whereas 54% underwent D0 dissection. A common interpretation of these results is that adjuvant therapy may be useful in high-risk patients treated with inadequate lymph node dissection, because, through radiotherapy, it can eliminate residual lymph node metastasis, which would have been removed by D2 resection. A Korean non-randomized study[134] recently has shown that chemoradiotherapy after Japanese D2 resection improves survival. Currently, promising results from a randomized study conducted by the same group (SMC-IRB 2004-08-10 trial) are anticipated[135].

In 2007, the most convincing evidence on the benefits of adjuvant therapy was reported by the Japanese ACTS-GC trial (Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer)[116]. In this trial, 1059 patients with stage Ⅱ or Ⅲ gastric cancer who had undergone curative D2 gastrectomy were randomized to observation or 1-year administration of oral S-1. The study was terminated at the first interim analysis due to a highly significant difference in survival that favored chemotherapy. The incidence rate of loco-regional, lymphatic and peritoneal relapse was significantly lower in the chemotherapy arm than in the surgery-alone arm, although the rate of distant metastases

did not differ between the two arms. This study reported a survival-associated advantage with adjuvant chemotherapy within the context of surgery performed according to Japanese standards.

New ongoing trials investigating adjuvant therapy (CLASSIC trial, SMC-IRB 2004-08-10, CALGB-80101) are expected to show the true efficacy and survival benefits in the near future[135-137].

In the past 30 years, Japanese and Korean researchers have performed a number of trials that have investigated the use of immunochemotherapy as adjuvant treatment after curative resection of gastric cancer. A variety of immunotherapeutic agents, such as protein-bound polysaccharide (polysaccharide K extracted from mycelia of *Coriolus versicolor*; PSK)[138,139], *Streptococcus pyogenes* preparation (OK-432)[140,141], polysaccharide sizofiran[142], *Nocardia rubra* cell wall skeleton[143], Bacillus Calmette-Guerin (BCG)[144] and polyadenylic-polyuridylic acid[145] have been used in addition to chemotherapy.

Results from randomized trials that have compared adjuvant chemo-immunotherapy with surgery alone or with other chemotherapeutic schedules have been contradictory because of a lack of robust evidence in clinical practice[146]. However, interesting results have been derived from two recent meta-analyses about OK-432 and PSK[147,148].

The benefit of combined adjuvant chemotherapy and immunotherapy with OK-432 (a lyophilized preparation of a low virulence group A *S. pyogenes*), in patients with curatively resected gastric cancer was assessed by Sakamoto *et al*[147] in a meta-analysis of data derived from 1522 patients enrolled in six randomized clinical trials. In these trials, adjuvant chemotherapy, usually consisting of induction with mitomycin C plus long-term oral fluordinated pyrimidines, was compared with the same chemotherapy plus OK-432. The 3-year survival rate for all eligible patients in the six trials was 67.5% in the chemo-immunotherapy group *vs* 62.6% in the chemotherapy-only group. The 3-year overall survival odds ratio was 0.81 (95% CI: 0.65-0.99). The beneficial treatment effect was shown to be statistically significant ($P < 0.044$). The results of this meta-analysis were interpreted by the authors to suggest that chemo-immunotherapy after surgery with OK-432 can improve the survival of patients with successfully resected gastric cancer.

The effect of adjuvant immunochemotherapy with PSK after curative resection of gastric cancer by means of a meta-analysis of eight randomized trials has been assessed by Oba *et al*[148]. In this analysis, the estimated overall HR was 0.88 (95% CI: 0.79-0.98, $P = 0.018$) with no significant heterogeneity between the treatment effects observed in different studies. The authors have concluded that the addition of PSK to standard chemotherapy offers significant advantages in survival over chemotherapy alone for patients with curative resections of gastric cancer.

Also for postoperative chemo-immunotherapy, there is a necessity for clear evidence in future studies; particularly, the clinical use of immunostimulating factors should be tested in large randomized trials.

Pre-/perioperative therapy: Induction of R0 resection

The rationale for preoperative therapy is based on several theoretical assumptions. Preoperative antiblastic therapy might reduce the risk of proliferation and allow for *in vivo* chemosensitivity tests, thus facilitating the choice of the most appropriate postoperative regimen. Furthermore, the preoperative approach has two distinct advantages: increased compliance due to an undoubtedly better performance status in patients who are not burdened with surgical complications, nutritional impairment, or damaged vascularization of the tumor bed. The twofold goal of eliminating hidden micrometastases along with tumor down-staging might increase the probability of a truly curative complete resection with delayed surgery.

Investigation of the efficacy and possible uses of chemotherapy in patients with advanced gastric cancer began in the late 1970s[149-151]. Encouraging results, however, were not reported until the early 1990s, when two independent studies in patients with non-resectable disease found that chemotherapy led to subsequent resection in 40%-50% of patients, with an increase in total median survival of 18 mo, compared with unresected patients[152,153]. These preliminary observations encouraged the introduction of preoperative chemotherapy protocols for potentially resectable, locally advanced gastric cancer (Table 1)[117,154-166]. However, the results of these first trials are questionable, mainly because of their methodological limitations. By following an inaccurate preoperative staging process, several authors have recruited patients on non-homogeneous criteria, commonly recruiting patients with locally advanced gastric cancer and others with disease of unclear stages, without a fixed distinction between resectable and non-resectable tumors. In addition to non-homogeneous methods of recruitment, other sources of bias in early trials included the use of different chemotherapeutic regimens, non-standardized surgery or surgery of questionable quality, and missing or poorly detailed response criteria.

In 1993, the Dutch Gastric Cancer Group started the first randomized controlled trial of exclusively preoperative chemotherapy for gastric cancer (cardia tumors were excluded)[161]. The regimen used was FAMTX (fluorouracil, doxorubicin, and methotrexate), which was, at that time, the gold standard of treatment for adenocarcinoma of the stomach. This trial had many accrual problems and was prematurely stopped after an interim analysis showed that FAMTX was unlikely to achieve the goal of a 15% increase in curative resectability after preoperative chemotherapy. Several biases have been outlined for this study, particularly the inaccuracy of the staging procedure with optional use of CT and laparoscopy, and inadequate extension of lymphadenectomy. The investigators reported a high rate of tumor progression during treatment (36%) along with a reduction in curative resections (56% *vs* 62%) and a decreased median survival (18 mo *vs* 30 mo), compared with untreated patients. Even if all of the statistical differences in this study were insignificant, both the short-term and long-term results were discouraging[161,167].

Since the late 1990s, ambitious European phase Ⅲ

Table 1 Trials of preoperative chemotherapy in gastric cancer

Author	Phase	Selection criteria	Preoperative	Postoperative	Pts	R0 (%)[1]	Pathological CR (%)	Median survival (mo)
Ajani *et al*[154], 1991	Ⅱ	M0 *Resectable* (+ GEJ)	EFP × 2	EFP × 3	25	72	0	15
Leichman *et al*[155], 1992	Ⅱ	M0 *Resectable*	FPL × 2	IP FUDR + P cisplatin × 2	38	88	8	> 17
Kang *et al*[156], 1992	Ⅲ RCT	M0 *Loc. advanced*	EFP × 3	EFP × 3-6	53	79	8	43
			None		54	61	-	30
Ajani *et al*[157], 1993	Ⅱ	M0 *Resectable*	EAP × 3	EAP × 2	48	90	0	16
Rougier *et al*[158], 1994	Ⅱ	M0 *Loc. advanced* (+ GEJ)	FP × 6	None	30	78	0	16
Kelsen *et al*[159], 1996	Ⅱ	M0 *Loc. advanced*	FAMTX × 3	IP FP + F	56	77	NS	15
Crookes *et al*[160], 1997	Ⅱ	M0 *Resectable* (+ GEJ)	FPL × 2	IP FUDR + IP cisplatin × 2	59	71	9	52
Songun *et al*[161], 1999	Ⅱ RCT	T2-T4; M0	FAMTX × 4	None	27	75	NS	18
			None		29	75	-	30
Schuhmacher *et al*[162], 2001	Ⅱ	Ⅲ-Ⅳ; M0 (+ GEJ)	EAP	None	42	86	0	19
D'Ugo *et al*[163], 2006	Ⅱ	T3-T4 anyN; T ≤ 2 N+; M0	EEP × 3 or ECF × 3	EEP × 3 or ECF × 3	34	82	3	> 28
Cunningham *et al*[117], 2006	Ⅲ RCT	Ⅱ-Ⅳ; M0 (+ GEJ)	ECF × 3	ECF × 3	250	74	NS	18
			None	None	253	68	-	30
Boige *et al*[164], 2007	Ⅲ RCT	*Resectable* (+ GEJ)	FP × 3	FP × 3	113	84	NS	NS
			None	None	111	73	-	
Schuhmacher *et al*[165], 2009	Ⅲ RCT	*Loc. advanced* T3-T4NxM0	FP × 2	None	72	81.9	NS	> 36
			None		72	66.7		
Kinoshita *et al*[166], 2009	Ⅱ	Schirrous *Resectable*	TS-1 × 2	None	55	80.8	0	NS

[1]The "R0" resection rate was calculated only among resection procedures. Pts: Number of patients recruited R0, curative (R0) resections; CR: Complete response; GEJ: Gastroesophageal junction; EFP: Etoposide, fluorouracil, and cisplatin; FPL: Fluorouracil, cisplatin, and leucovorin; IP: Intraperitoneal; FUDR: 5-fluoro-2'-deoxyuridine; RCT: Randomized controlled trial; EAP: Etoposide, doxorubicin, and cisplatin; FP: Fluorouracil and cisplatin; FAMTX: Fluorouracil, doxorubicin, and methotrexate; F: Fluorouracil; NS: Not stated; EEP: Etoposide, epirubicin and cisplatin; ECF: Epirubicin, cisplatin, and fluorouracil.

trials have been designed to provide a definitive demonstration of the efficacy of preoperative treatments. The adoption of strict selection criteria made the selection of patients so difficult that some studies were stopped prematurely (EORTC 40954 and SWS-SAKK-43/99 trials)[165,168]. Only the MAGIC trial (started in the United Kingdom in 1994) and the FFCD 9703 trial (started in France in 1996) have been completed[117,164]. These two studies have yielded substantial evidence supporting the efficacy of perioperative chemotherapy for an increased survival rate (36% *vs* 23%, estimated at 5 years for MAGIC, 38% *vs* 24% estimated at 5 years for FFCD 9703, Table 1), along with a significantly higher curative resection rate in the treated group *vs* the surgery-alone group (79% *vs* 70%, $P = 0.03$ for MAGIC, 84% *vs* 73% in arm 2, $P = 0.04$ for FFCD 9703) without an increase in perioperative morbidity or mortality.

The possible increase in the actual R0-resection rate has been an important goal of preoperative chemotherapy. In a phase Ⅱ study of a perioperative chemotherapy protocol, the achievement of R0 resection in response to preoperative chemotherapy was shown to be the most significant prognostic indicator by univariate and multivariate analysis. Furthermore, R0 resection was the only independent variable in determining the probability of long-term survival in locally advanced gastric carcinoma. The overall survival for all curatively resected patients is higher when compared to historical series treated with surgery alone for locally advanced gastric cancer[163,169].

Based on the results of the SWOG 9008/INT-0116 trial[115], the integration of chemotherapy with radiation applied in the preoperative phase has gained much interest. Some benefits of preoperative radiotherapy for gastric cancer have been reported by a pivotal randomized single-center Chinese study by Zhang *et al*[170]. This study recruited 317 patients with adenocarcinoma of the cardia that were randomly assigned to radiotherapy followed by surgery, or surgery alone. This study indicated a significant 5-year survival benefit for patients treated with neoadjuvant radiotherapy as compared with surgery alone (30.1% *vs* 19.8%, respectively), with an improved rate of complete curative resection after radiotherapy (80% *vs* 62%). Recently, published phase Ⅱ studies have verified the efficacy of chemoradiotherapy in terms of complete pathological response (up to 30% in some series) and increased long-term survival without an increase in morbidity or mortality[171-174].

All of the above results suggest that R0 resection is not an exclusive surgical target in locally advanced gastric cancer, but that it can be facilitated or achieved by preoperative therapy (induction of R0 resection).

Many answers are expected from ongoing trials exploring ways of improving preoperative treatment strategies for resectable gastric cancer: the MAGIC B trial (United Kingdom National Cancer Research Institute ST03 trial) of perioperative epirubicin, cisplatin, and capecitabine, with or without the endothelial growth factor antibody, bevacizumab[175]; the CRITICS trial (Chemo-Radiotherapy after Induction chemoTherapy In Cancer of the Stomach), a phase Ⅲ study that is randomizing between preoperative chemotherapy (three courses of epirubicin/cisplatin/capecitabine) and gastric surgery with

limited lymph node dissection followed by postoperative chemotherapy (another three courses of epirubicin/cisplatin/capecitabine) or chemoradiotherapy[176]; and the JCOG trial 0501 (Japan Clinical Oncology Group Study 0501 trial) and KYUH-UHA-GC04-03 Kyoto trial, which are testing preoperative oral fluoropyrimidine S-1 together with cisplatin *vs* postoperative oral fluoropyrimidine S-1[177].

CONCLUSION

In gastric cancer, radical resection (R0 resection) offers the best chance for a cure because it is defined as the complete surgical removal of any residual cancer cells in the tumor bed. However, distant and loco-regional failure rates in most radically resected patients with positive lymph nodes or involvement of the serosa contradict this statement.

All current therapeutic efforts in resectable gastric cancer are directed toward the individualization of therapeutic protocols, which tailors the extent of resection and the administration of pre- and postoperative treatment. A paradigm shift has rapidly advanced in the past 10 years: three pivotal studies in three different areas of the world (United States, Europe and Japan) have demonstrated that multimodal treatments improve the prognosis for patients with resectable gastric cancer. The common target of all of these strategies is to improve prognosis towards the achievement of a true curative resection (R0 resection) with minimal morbidity and mortality.

In gastric cancer, surgical research has always proceeded slowly, and standardization is still far from being settled. Geographical differences in epidemiology and treatment approaches and a lack of surgical gold standards have diverted attention from the pursuit of a multimodal approach. In other solid neoplasms worldwide, the multimodal approach has already been validated. In the near future, we expect the same to occur for gastric cancer, provided that the published evidence that is needed to reach this goal is further improved and developed. The result of treatment for locally advanced gastric cancer is the sum of the effect of local tumor control by surgery, with or without radiotherapy and/or systemic chemotherapy. The role of each treatment modality varies according to the stage of the disease, individual patient risk, surgical volume, available chemotherapy regimens and quality of radiotherapy. Evidence of the effect of different combinations of treatments should be established for each clinical circumstance, and surgeons should play a key role in this.

REFERENCES

1 **Kamangar F**, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. *J Clin Oncol* 2006; **24**: 2137-2150
2 **Jemal A**, Siegel R, Ward E, Hao Y, Xu J, Murray T, Thun MJ. Cancer statistics, 2008. *CA Cancer J Clin* 2008; **58**: 71-96
3 **Kubota H**, Kotoh T, Masunaga R, Dhar DK, Shibakita M, Tachibana M, Kohno H, Nagasue N. Impact of screening survey of gastric cancer on clinicopathological features and survival: retrospective study at a single institution. *Surgery* 2000; **128**: 41-47
4 **Noguchi Y**, Yoshikawa T, Tsuburaya A, Motohashi H, Karpeh MS, Brennan MF. Is gastric carcinoma different between Japan and the United States? *Cancer* 2000; **89**: 2237-2246
5 **Whiting JL**, Sigurdsson A, Rowlands DC, Hallissey MT, Fielding JW. The long term results of endoscopic surveillance of premalignant gastric lesions. *Gut* 2002; **50**: 378-381
6 **Dan YY**, So JB, Yeoh KG. Endoscopic screening for gastric cancer. *Clin Gastroenterol Hepatol* 2006; **4**: 709-716
7 **Hundahl SA**, Phillips JL, Menck HR. The National Cancer Data Base Report on poor survival of U.S. gastric carcinoma patients treated with gastrectomy: Fifth Edition American Joint Committee on Cancer staging, proximal disease, and the "different disease" hypothesis. *Cancer* 2000; **88**: 921-932
8 **Hermanek P**, Wittekind C. Residual tumor (R) classification and prognosis. *Semin Surg Oncol* 1994; **10**: 12-20
9 **Marrelli D**, De Stefano A, de Manzoni G, Morgagni P, Di Leo A, Roviello F. Prediction of recurrence after radical surgery for gastric cancer: a scoring system obtained from a prospective multicenter study. *Ann Surg* 2005; **241**: 247-255
10 **Roukos DH**, Lorenz M, Karakostas K, Paraschou P, Batsis C, Kappas AM. Pathological serosa and node-based classification accurately predicts gastric cancer recurrence risk and outcome, and determines potential and limitation of a Japanese-style extensive surgery for Western patients: a prospective with quality control 10-year follow-up study. *Br J Cancer* 2001; **84**: 1602-1609
11 **D'Angelica M**, Gonen M, Brennan MF, Turnbull AD, Bains M, Karpeh MS. Patterns of initial recurrence in completely resected gastric adenocarcinoma. *Ann Surg* 2004; **240**: 808-816
12 **Japanese Gastric Cancer Association**. Japanese Classification of Gastric Carcinoma - 2nd English Edition - *Gastric Cancer* 1998; **1**: 10-24
13 **Kwee RM**, Kwee TC. Imaging in local staging of gastric cancer: a systematic review. *J Clin Oncol* 2007; **25**: 2107-2116
14 **Wang JY**, Hsieh JS, Huang YS, Huang CJ, Hou MF, Huang TJ. Endoscopic ultrasonography for preoperative locoregional staging and assessment of resectability in gastric cancer. *Clin Imaging* 1998; **22**: 355-359
15 **Mancino G**, Bozzetti F, Schicchi A, Schiavo M, Spinelli P, Andreola S. Preoperative endoscopic ultrasonography in patients with gastric cancer. *Tumori* 2000; **86**: 139-141
16 **Xi WD**, Zhao C, Ren GS. Endoscopic ultrasonography in preoperative staging of gastric cancer: determination of tumor invasion depth, nodal involvement and surgical resectability. *World J Gastroenterol* 2003; **9**: 254-257
17 **Willis S**, Truong S, Gribnitz S, Fass J, Schumpelick V. Endoscopic ultrasonography in the preoperative staging of gastric cancer: accuracy and impact on surgical therapy. *Surg Endosc* 2000; **14**: 951-954
18 **Bhandari S**, Shim CS, Kim JH, Jung IS, Cho JY, Lee JS, Lee MS, Kim BS. Usefulness of three-dimensional, multidetector row CT (virtual gastroscopy and multiplanar reconstruction) in the evaluation of gastric cancer: a comparison with conventional endoscopy, EUS, and histopathology. *Gastrointest Endosc* 2004; **59**: 619-626
19 **Shimoyama S**, Yasuda H, Hashimoto M, Tatsutomi Y, Aoki F, Mafune K, Kaminishi M. Accuracy of linear-array EUS for preoperative staging of gastric cardia cancer. *Gastrointest Endosc* 2004; **60**: 50-55
20 **Ganpathi IS**, So JB, Ho KY. Endoscopic ultrasonography for gastric cancer: does it influence treatment? *Surg Endosc* 2006; **20**: 559-562
21 **D'Elia F**, Zingarelli A, Palli D, Grani M. Hydro-dynamic CT preoperative staging of gastric cancer: correlation with pathological findings. A prospective study of 107 cases. *Eur Radiol* 2000; **10**: 1877-1885
22 **Habermann CR**, Weiss F, Riecken R, Honarpisheh H, Bohnacker S, Staedtler C, Dieckmann C, Schoder V, Adam G. Preoperative staging of gastric adenocarcinoma: comparison of helical CT and endoscopic US. *Radiology* 2004; **230**: 465-471

23 **Takao M**, Fukuda T, Iwanaga S, Hayashi K, Kusano H, Okudaira S. Gastric cancer: evaluation of triphasic spiral CT and radiologic-pathologic correlation. *J Comput Assist Tomogr* 1998; **22**: 288-294
24 **Hundt W**, Braunschweig R, Reiser M. Assessment of gastric cancer: value of breathhold technique and two-phase spiral CT. *Eur Radiol* 1999; **9**: 68-72
25 **Shimizu K**, Ito K, Matsunaga N, Shimizu A, Kawakami Y. Diagnosis of gastric cancer with MDCT using the water-filling method and multiplanar reconstruction: CT-histologic correlation. *AJR Am J Roentgenol* 2005; **185**: 1152-1158
26 **Chen CY**, Hsu JS, Wu DC, Kang WY, Hsieh JS, Jaw TS, Wu MT, Liu GC. Gastric cancer: preoperative local staging with 3D multi-detector row CT--correlation with surgical and histopathologic results. *Radiology* 2007; **242**: 472-482
27 **Hur J**, Park MS, Lee JH, Lim JS, Yu JS, Hong YJ, Kim KW. Diagnostic accuracy of multidetector row computed tomography in T- and N staging of gastric cancer with histopathologic correlation. *J Comput Assist Tomogr* 2006; **30**: 372-377
28 **Sohn KM**, Lee JM, Lee SY, Ahn BY, Park SM, Kim KM. Comparing MR imaging and CT in the staging of gastric carcinoma. *AJR Am J Roentgenol* 2000; **174**: 1551-1557
29 **Motohara T**, Semelka RC. MRI in staging of gastric cancer. *Abdom Imaging* 2002; **27**: 376-383
30 **Stahl A**, Ott K, Weber WA, Becker K, Link T, Siewert JR, Schwaiger M, Fink U. FDG PET imaging of locally advanced gastric carcinomas: correlation with endoscopic and histopathological findings. *Eur J Nucl Med Mol Imaging* 2003; **30**: 288-295
31 **Chen J**, Cheong JH, Yun MJ, Kim J, Lim JS, Hyung WJ, Noh SH. Improvement in preoperative staging of gastric adenocarcinoma with positron emission tomography. *Cancer* 2005; **103**: 2383-2390
32 **Rosenbaum SJ**, Stergar H, Antoch G, Veit P, Bockisch A, Kühl H. Staging and follow-up of gastrointestinal tumors with PET/CT. *Abdom Imaging* 2006; **31**: 25-35
33 **Dassen AE**, Lips DJ, Hoekstra CJ, Pruijt JF, Bosscha K. FDG-PET has no definite role in preoperative imaging in gastric cancer. *Eur J Surg Oncol* 2009; **35**: 449-455
34 **Lim JS**, Yun MJ, Kim MJ, Hyung WJ, Park MS, Choi JY, Kim TS, Lee JD, Noh SH, Kim KW. CT and PET in stomach cancer: preoperative staging and monitoring of response to therapy. *Radiographics* 2006; **26**: 143-156
35 **D'Ugo DM**, Pende V, Persiani R, Rausei S, Picciocchi A. Laparoscopic staging of gastric cancer: an overview. *J Am Coll Surg* 2003; **196**: 965-974
36 **Lowy AM**, Mansfield PF, Leach SD, Ajani J. Laparoscopic staging for gastric cancer. *Surgery* 1996; **119**: 611-614
37 **Burke EC**, Karpeh MS, Conlon KC, Brennan MF. Laparoscopy in the management of gastric adenocarcinoma. *Ann Surg* 1997; **225**: 262-267
38 **Karpeh MS Jr**, Brennan MF. Gastric carcinoma. *Ann Surg Oncol* 1998; **5**: 650-656
39 **Kelly S**, Harris KM, Berry E, Hutton J, Roderick P, Cullingworth J, Gathercole L, Smith MA. A systematic review of the staging performance of endoscopic ultrasound in gastro-oesophageal carcinoma. *Gut* 2001; **49**: 534-539
40 **Bentrem D**, Wilton A, Mazumdar M, Brennan M, Coit D. The value of peritoneal cytology as a preoperative predictor in patients with gastric carcinoma undergoing a curative resection. *Ann Surg Oncol* 2005; **12**: 347-353
41 **Siewert JR**, Fink U, Sendler A, Becker K, Böttcher K, Feldmann HJ, Höfler H, Mueller J, Molls M, Nekarda H, Roder JD, Stein HJ. Gastric Cancer. *Curr Probl Surg* 1997; **34**: 835-939
42 **Bozzetti F**, Bonfanti G, Bufalino R, Menotti V, Persano S, Andreola S, Doci R, Gennari L. Adequacy of margins of resection in gastrectomy for cancer. *Ann Surg* 1982; **196**: 685-690
43 **Bozzetti F**. Principles of surgical radicality in the treatment of gastric cancer. *Surg Oncol Clin N Am* 2001; **10**: 833-854, ix
44 **Khatri VP**, Douglass HO Jr. D2.5 dissection for gastric carcinoma. *Arch Surg* 2004; **139**: 662-669; discussion 669
45 **Feith M**, Stein HJ, Siewert JR. Adenocarcinoma of the esophagogastric junction: surgical therapy based on 1602 consecutive resected patients. *Surg Oncol Clin N Am* 2006; **15**: 751-764
46 **von Rahden BH**, Stein HJ, Siewert JR. Surgical management of esophagogastric junction tumors. *World J Gastroenterol* 2006; **12**: 6608-6613
47 **Harrison LE**, Karpeh MS, Brennan MF. Total gastrectomy is not necessary for proximal gastric cancer. *Surgery* 1998; **123**: 127-130
48 **Braga M**, Molinari M, Zuliani W, Foppa L, Gianotti L, Radaelli G, Cristallo M, Di Carlo V. Surgical treatment of gastric adenocarcinoma: impact on survival and quality of life. A prospective ten year study. *Hepatogastroenterology* 1996; **43**: 187-193
49 **Buhl K**, Schlag P, Herfarth C. Quality of life and functional results following different types of resection for gastric carcinoma. *Eur J Surg Oncol* 1990; **16**: 404-409
50 **Díaz De Liaño A**, Oteiza Martínez F, Ciga MA, Aizcorbe M, Cobo F, Trujillo R. Impact of surgical procedure for gastric cancer on quality of life. *Br J Surg* 2003; **90**: 91-94
51 **Nakajima T**. Gastric cancer treatment guidelines in Japan. *Gastric Cancer* 2002; **5**: 1-5
52 **Bennett C**, Wang Y, Pan T. Endoscopic mucosal resection for early gastric cancer. *Cochrane Database Syst Rev* 2009; CD004276
53 **Kim JJ**, Lee JH, Jung HY, Lee GH, Cho JY, Ryu CB, Chun HJ, Park JJ, Lee WS, Kim HS, Chung MG, Moon JS, Choi SR, Song GA, Jeong HY, Jee SR, Seol SY, Yoon YB. EMR for early gastric cancer in Korea: a multicenter retrospective study. *Gastrointest Endosc* 2007; **66**: 693-700
54 **Gotoda T**, Yamamoto H, Soetikno RM. Endoscopic submucosal dissection of early gastric cancer. *J Gastroenterol* 2006; **41**: 929-942
55 **Oda I**, Saito D, Tada M, Iishi H, Tanabe S, Oyama T, Doi T, Otani Y, Fujisaki J, Ajioka Y, Hamada T, Inoue H, Gotoda T, Yoshida S. A multicenter retrospective study of endoscopic resection for early gastric cancer. *Gastric Cancer* 2006; **9**: 262-270
56 **Gotoda T**, Yanagisawa A, Sasako M, Ono H, Nakanishi Y, Shimoda T, Kato Y. Incidence of lymph node metastasis from early gastric cancer: estimation with a large number of cases at two large centers. *Gastric Cancer* 2000; **3**: 219-225
57 **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
58 **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
59 **Sano T**, Yamamoto S, Sasako M. Randomized controlled trial to evaluate splenectomy in total gastrectomy for proximal gastric carcinoma: Japan clinical oncology group study JCOG 0110-MF. *Jpn J Clin Oncol* 2002; **32**: 363-364
60 **Kitamura K**, Nishida S, Ichikawa D, Taniguchi H, Hagiwara A, Yamaguchi T, Sawai K. No survival benefit from combined pancreaticosplenectomy and total gastrectomy for gastric cancer. *Br J Surg* 1999; **86**: 119-122
61 **Kodera Y**, Yamamura Y, Shimizu Y, Torii A, Hirai T, Yasui K, Morimoto T, Kato T, Kito T. Lack of benefit of combined pancreaticosplenectomy in D2 resection for proximal-third gastric carcinoma. *World J Surg* 1997; **21**: 622-627; discussion 627-628
62 **Wang JY**, Huang TJ, Chen FM, Huang CJ, Huang YS, Hsieh JS. A comparative study of pancreatectomy and pancreas-preserving gastrectomy in advanced gastric carcinomas. *Hepatogastroenterology* 2004; **51**: 1229-1232
63 **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
64 **Colen KL**, Marcus SG, Newman E, Berman RS, Yee H, Hiotis SP. Multiorgan resection for gastric cancer: intraoperative

and computed tomography assessment of locally advanced disease is inaccurate. *J Gastrointest Surg* 2004; **8**: 899-902
65 **Martin RC 2nd**, Jaques DP, Brennan MF, Karpeh M. Achieving RO resection for locally advanced gastric cancer: is it worth the risk of multiorgan resection? *J Am Coll Surg* 2002; **194**: 568-577
66 **Jeong O**, Choi WY, Park YK. Appropriate selection of patients for combined organ resection in cases of gastric carcinoma invading adjacent organs. *J Surg Oncol* 2009; **100**: 115-120
67 **Kunisaki C**, Akiyama H, Nomura M, Matsuda G, Otsuka Y, Ono HA, Nagahori Y, Takahashi M, Kito F, Shimada H. Surgical outcomes in patients with T4 gastric carcinoma. *J Am Coll Surg* 2006; **202**: 223-230
68 **Roder JD**, Böttcher K, Siewert JR, Busch R, Hermanek P, Meyer HJ. Prognostic factors in gastric carcinoma. Results of the German Gastric Carcinoma Study 1992. *Cancer* 1993; **72**: 2089-2097
69 **Adachi Y**, Kamakura T, Mori M, Baba H, Maehara Y, Sugimachi K. Prognostic significance of the number of positive lymph nodes in gastric carcinoma. *Br J Surg* 1994; **81**: 414-416
70 **Wu CW**, Hsieh MC, Lo SS, Tsay SH, Li AF, Lui WY, P'eng FK. Prognostic indicators for survival after curative resection for patients with carcinoma of the stomach. *Dig Dis Sci* 1997; **42**: 1265-1269
71 **Yokota T**, Ishiyama S, Saito T, Teshima S, Narushima Y, Murata K, Iwamoto K, Yashima R, Yamauchi H, Kikuchi S. Lymph node metastasis as a significant prognostic factor in gastric cancer: a multiple logistic regression analysis. *Scand J Gastroenterol* 2004; **39**: 380-384
72 **Seto Y**, Nagawa H, Muto T. Impact of lymph node metastasis on survival with early gastric cancer. *World J Surg* 1997; **21**: 186-189; discussion 190
73 **Kim JP**, Lee JH, Kim SJ, Yu HJ, Yang HK. Clinicopathologic characteristics and prognostic factors in 10 783 patients with gastric cancer. *Gastric Cancer* 1998; **1**: 125-133
74 **Kim JP**. Current status of surgical treatment of gastric cancer. *J Surg Oncol* 2002; **79**: 79-80
75 **Otsuji E**, Toma A, Kobayashi S, Okamoto K, Hagiwara A, Yamagishi H. Outcome of prophylactic radical lymphadenectomy with gastrectomy in patients with early gastric carcinoma without lymph node metastasis. *Cancer* 2000; **89**: 1425-1430
76 **Shimada S**, Yagi Y, Honmyo U, Shiomori K, Yoshida N, Ogawa M. Involvement of three or more lymph nodes predicts poor prognosis in submucosal gastric carcinoma. *Gastric Cancer* 2001; **4**: 54-59
77 **Maruyama K**, Okabayashi K, Kinoshita T. Progress in gastric cancer surgery in Japan and its limits of radicality. *World J Surg* 1987; **11**: 418-425
78 **Nakamura K**, Ueyama T, Yao T, Xuan ZX, Ambe K, Adachi Y, Yakeishi Y, Matsukuma A, Enjoji M. Pathology and prognosis of gastric carcinoma. Findings in 10,000 patients who underwent primary gastrectomy. *Cancer* 1992; **70**: 1030-1037
79 **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
80 **Jatzko GR**, Lisborg PH, Denk H, Klimpfinger M, Stettner HM. A 10-year experience with Japanese-type radical lymph node dissection for gastric cancer outside of Japan. *Cancer* 1995; **76**: 1302-1312
81 **Volpe CM**, Koo J, Miloro SM, Driscoll DL, Nava HR, Douglass HO Jr. The effect of extended lymphadenectomy on survival in patients with gastric adenocarcinoma. *J Am Coll Surg* 1995; **181**: 56-64
82 **Siewert JR**, Böttcher K, Roder JD, Busch R, Hermanek P, Meyer HJ. Prognostic relevance of systematic lymph node dissection in gastric carcinoma. German Gastric Carcinoma Study Group. *Br J Surg* 1993; **80**: 1015-1018
83 **Pacelli F**, Doglietto GB, Bellantone R, Alfieri S, Sgadari A, Crucitti F. Extensive versus limited lymph node dissection for gastric cancer: a comparative study of 320 patients. *Br J Surg* 1993; **80**: 1153-1156
84 **Viste A**, Svanes K, Janssen CW Jr, Maartmann-Moe H, Søreide O. Prognostic importance of radical lymphadenectomy in curative resections for gastric cancer. *Eur J Surg* 1994; **160**: 497-502
85 **de Manzoni G**, Verlato G, Guglielmi A, Laterza E, Genna M, Cordiano C. Prognostic significance of lymph node dissection in gastric cancer. *Br J Surg* 1996; **83**: 1604-1607
86 **Cuschieri A**, Weeden S, Fielding J, Bancewicz J, Craven J, Joypaul V, Sydes M, Fayers P. Patient survival after D1 and D2 resections for gastric cancer: long-term results of the MRC randomized surgical trial. Surgical Co-operative Group. *Br J Cancer* 1999; **79**: 1522-1530
87 **Dent DM**, Madden MV, Price SK. Randomized comparison of R1 and R2 gastrectomy for gastric carcinoma. *Br J Surg* 1988; **75**: 110-112
88 **Hartgrink HH**, van de Velde CJ, Putter H, Bonenkamp JJ, Klein Kranenbarg E, Songun I, Welvaart K, van Krieken JH, Meijer S, Plukker JT, van Elk PJ, Obertop H, Gouma DJ, van Lanschot JJ, Taat CW, de Graaf PW, von Meyenfeldt MF, Tilanus H, Sasako M. Extended lymph node dissection for gastric cancer: who may benefit? Final results of the randomized Dutch gastric cancer group trial. *J Clin Oncol* 2004; **22**: 2069-2077
89 **Robertson CS**, Chung SC, Woods SD, Griffin SM, Raimes SA, Lau JT, Li AK. A prospective randomized trial comparing R1 subtotal gastrectomy with R3 total gastrectomy for antral cancer. *Ann Surg* 1994; **220**: 176-182
90 **Wu CW**, Hsiung CA, Lo SS, Hsieh MC, Chen JH, Li AF, Lui WY, Whang-Peng J. Nodal dissection for patients with gastric cancer: a randomised controlled trial. *Lancet Oncol* 2006; **7**: 309-315
91 **McCulloch P**, Nita ME, Kazi H, Gama-Rodrigues J. Extended versus limited lymph nodes dissection technique for adenocarcinoma of the stomach. *Cochrane Database Syst Rev* 2004; CD001964
92 **Yang SH**, Zhang YC, Yang KH, Li YP, He XD, Tian JH, Lv TH, Hui YH, Sharma N. An evidence-based medicine review of lymphadenectomy extent for gastric cancer. *Am J Surg* 2009; **197**: 246-251
93 **Bonenkamp JJ**, Songun I, Hermans J, Sasako M, Welvaart K, Plukker JT, van Elk P, Obertop H, Gouma DJ, Taat CW. Randomised comparison of morbidity after D1 and D2 dissection for gastric cancer in 996 Dutch patients. *Lancet* 1995; **345**: 745-748
94 **Cuschieri A**, Fayers P, Fielding J, Craven J, Bancewicz J, Joypaul V, Cook P. 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
95 **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
96 **Kodera Y**, Sasako M, Yamamoto S, Sano T, Nashimoto A, Kurita A. Identification of risk factors for the development of complications following extended and superextended lymphadenectomies for gastric cancer. *Br J Surg* 2005; **92**: 1103-1109
97 **Cady B**. Basic principles in surgical oncology. *Arch Surg* 1997; **132**: 338-346
98 **Kampschöer GH**, Maruyama K, van de Velde CJ, Sasako M, Kinoshita T, Okabayashi K. Computer analysis in making preoperative decisions: a rational approach to lymph node dissection in gastric cancer patients. *Br J Surg* 1989; **76**: 905-908
99 **Bollschweiler E**, Boettcher K, Hoelscher AH, Sasako M, Kinoshita T, Maruyama K, Siewert JR. Preoperative assessment of lymph node metastases in patients with gastric cancer: evaluation of the Maruyama computer program. *Br J Surg* 1992; **79**: 156-160
100 **Siewert JR**, Kelsen D, Maruyama K, Feussner H, Omote K,

Etter M, Hoos A. Gastric Cancer: Diagnosis and Treatment. An interactive training program. 1st ed. Berlin: Springer Electronic Media, 2000
101 **Guadagni S**, de Manzoni G, Catarci M, Valenti M, Amicucci G, De Bernardinis G, Cordiano C, Carboni M, Maruyama K. Evaluation of the Maruyama computer program accuracy for preoperative estimation of lymph node metastases from gastric cancer. *World J Surg* 2000; **24**: 1550-1558
102 **Hundahl SA**. Low maruyama index surgery for gastric cancer. *Scand J Surg* 2006; **95**: 243-248
103 **Hundahl SA**, Macdonald JS, Benedetti J, Fitzsimmons T. Surgical treatment variation in a prospective, randomized trial of chemoradiotherapy in gastric cancer: the effect of undertreatment. *Ann Surg Oncol* 2002; **9**: 278-286
104 **Peeters KC**, Hundahl SA, Kranenbarg EK, Hartgrink H, van de Velde CJ. Low Maruyama index surgery for gastric cancer: blinded reanalysis of the Dutch D1-D2 trial. *World J Surg* 2005; **29**: 1576-1584
105 **Kitagawa Y**, Fujii H, Mukai M, Kubota T, Ando N, Watanabe M, Ohgami M, Otani Y, Ozawa S, Hasegawa H, Furukawa T, Kumai K, Ikeda T, Nakahara T, Kubo A, Kitajima M. The role of the sentinel lymph node in gastrointestinal cancer. *Surg Clin North Am* 2000; **80**: 1799-1809
106 **Tsioulias GJ**, Wood TF, Morton DL, Bilchik AJ. Lymphatic mapping and focused analysis of sentinel lymph nodes upstage gastrointestinal neoplasms. *Arch Surg* 2000; **135**: 926-932
107 **Hiratsuka M**, Miyashiro I, Ishikawa O, Furukawa H, Motomura K, Ohigashi H, Kameyama M, Sasaki Y, Kabuto T, Ishiguro S, Imaoka S, Koyama H. Application of sentinel node biopsy to gastric cancer surgery. *Surgery* 2001; **129**: 335-340
108 **Yasuda K**, Shiraishi N, Suematsu T, Yamaguchi K, Adachi Y, Kitano S. Rate of detection of lymph node metastasis is correlated with the depth of submucosal invasion in early stage gastric carcinoma. *Cancer* 1999; **85**: 2119-2123
109 **Tokunaga M**, Ohyama S, Hiki N, Fukunaga T, Yamada K, Sano T, Yamaguchi T. Investigation of the lymphatic stream of the stomach in gastric cancer with solitary lymph node metastasis. *World J Surg* 2009; **33**: 1235-1239
110 **Miwa K**, Kinami S, Taniguchi K, Fushida S, Fujimura T, Nonomura A. Mapping sentinel nodes in patients with early-stage gastric carcinoma. *Br J Surg* 2003; **90**: 178-182
111 **Orsenigo E**, Tomajer V, Di Palo S, Albarello L, Doglioni C, Masci E, Viale E, Staudacher C. Sentinel node mapping during laparoscopic distal gastrectomy for gastric cancer. *Surg Endosc* 2008; **22**: 118-121
112 **Park DJ**, Lee HJ, Lee HS, Kim WH, Kim HH, Lee KU, Choe KJ, Yang HK. Sentinel node biopsy for cT1 and cT2a gastric cancer. *Eur J Surg Oncol* 2006; **32**: 48-54
113 **Saikawa Y**, Otani Y, Kitagawa Y, Yoshida M, Wada N, Kubota T, Kumai K, Sugino Y, Mukai M, Kameyama K, Kubo A, Kitajima M. Interim results of sentinel node biopsy during laparoscopic gastrectomy: possible role in function-preserving surgery for early cancer. *World J Surg* 2006; **30**: 1962-1968
114 **Tajima Y**, Yamazaki K, Masuda Y, Kato M, Yasuda D, Aoki T, Kato T, Murakami M, Miwa M, Kusano M. Sentinel node mapping guided by indocyanine green fluorescence imaging in gastric cancer. *Ann Surg* 2009; **249**: 58-62
115 **Macdonald JS**, Smalley SR, Benedetti J, Hundahl SA, Estes NC, Stemmermann GN, Haller DG, Ajani JA, Gunderson LL, Jessup JM, Martenson JA. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med* 2001; **345**: 725-730
116 **Sakuramoto S**, Sasako M, Yamaguchi T, Kinoshita T, Fujii M, Nashimoto A, Furukawa H, Nakajima T, Ohashi Y, Imamura H, Higashino M, Yamamura Y, Kurita A, Arai K. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. *N Engl J Med* 2007; **357**: 1810-1820
117 **Cunningham D**, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, Scarffe JH, Lofts FJ, Falk SJ, Iveson TJ, Smith DB, Langley RE, Verma M, Weeden S, Chua YJ, MAGIC Trial Participants. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med* 2006; **355**: 11-20
118 **Hermans J**, Bonenkamp JJ, Boon MC, Bunt AM, Ohyama S, Sasako M, Van de Velde CJ. Adjuvant therapy after curative resection for gastric cancer: meta-analysis of randomized trials. *J Clin Oncol* 1993; **11**: 1441-1447
119 **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
120 **Mari E**, Floriani I, Tinazzi A, Buda A, Belfiglio M, Valentini M, Cascinu S, Barni S, Labianca R, Torri V. 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
121 **Janunger KG**, Hafström L, Nygren P, Glimelius B. A systematic overview of chemotherapy effects in gastric cancer. *Acta Oncol* 2001; **40**: 309-326
122 **Gianni L**, Panzini I, Tassinari D, Mianulli AM, Desiderio F, Ravaioli A. Meta-analyses of randomized trials of adjuvant chemotherapy in gastric cancer. *Ann Oncol* 2001; **12**: 1178-1180
123 **Hu JK**, Chen ZX, Zhou ZG, Zhang B, Tian J, Chen JP, Wang L, Wang CH, Chen HY, Li YP. Intravenous chemotherapy for resected gastric cancer: meta-analysis of randomized controlled trials. *World J Gastroenterol* 2002; **8**: 1023-1028
124 **Janunger KG**, Hafström L, Glimelius B. Chemotherapy in gastric cancer: a review and updated meta-analysis. *Eur J Surg* 2002; **168**: 597-608
125 **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
126 **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
127 **Zhao SL**, Fang JY. The role of postoperative adjuvant chemotherapy following curative resection for gastric cancer: a meta-analysis. *Cancer Invest* 2008; **26**: 317-325
128 **Lim L**, Michael M, Mann GB, Leong T. Adjuvant therapy in gastric cancer. *J Clin Oncol* 2005; **23**: 6220-6232
129 **Gastrointestinal Tumor Study Group**. A comparison of combination chemotherapy and combined modality therapy for locally advanced gastric carcinoma. *Cancer* 1982; **49**: 1771-1777
130 **Moertel CG**, Childs DS Jr, Reitemeier RJ, Colby MY Jr, Holbrook MA. Combined 5-fluorouracil and supervoltage radiation therapy of locally unresectable gastrointestinal cancer. *Lancet* 1969; **2**: 865-867
131 **Dent DM**, Werner ID, Novis B, Cheverton P, Brice P. Prospective randomized trial of combined oncological therapy for gastric carcinoma. *Cancer* 1979; **44**: 385-391
132 **Moertel CG**, Childs DS, O'Fallon JR, Holbrook MA, Schutt AJ, Reitemeier RJ. Combined 5-fluorouracil and radiation therapy as a surgical adjuvant for poor prognosis gastric carcinoma. *J Clin Oncol* 1984; **2**: 1249-1254
133 **Bleiberg H**, Goffin JC, Dalesio O, Buyse M, Pector JC, Gignoux M, Roussel A, Samana G, Michel J, Gerard A. Adjuvant radiotherapy and chemotherapy in resectable gastric cancer. A randomized trial of the gastro-intestinal tract cancer cooperative group of the EORTC. *Eur J Surg Oncol* 1989; **15**: 535-543
134 **Kim S**, Lim DH, Lee J, Kang WK, MacDonald JS, Park CH, Park SH, Lee SH, Kim K, Park JO, Kim WS, Jung CW, Park YS, Im YH, Sohn TS, Noh JH, Heo JS, Kim YI, Park CK, Park K. An observational study suggesting clinical benefit for adjuvant postoperative chemoradiation in a population of over 500 cases after gastric resection with D2 nodal dissection for adenocarcinoma of the stomach. *Int J Radiat Oncol Biol Phys*

2005; **63**: 1279-1285
135 **Samsung Medical Center**. Phase III Randomized trial of adjuvant XP chemotherapy and XP/RT for resected gastric adenocarcinoma. Available from: URL: http://clinicaltrial.gov/ct2/show/NCT00323830?term=SMC+IRB2004-08-10&rank=1
136 **Sanofi-Aventis** (Medical Affairs Study Director). Capecitabine and oxaliplatin adjuvant study in stomach cancer (CLASSIC). Available from: URL: http://clinicaltrial.gov/ct2/show/NCT00411229?term=CLASSIC+gastric+cancer&rank=2
137 **Fuchs C**, Tepper JE, Niedwiecki D, Hollis D, Haller DG, Dragovich T, Alberts SR, Bjarnason G, Mayer RJ. Postoperative adjuvant chemoradiation for gastric or gastroesophageal adenocarcinoma using epirubicin, cisplatin, and infusional (CI) 5-FU (ECF) before and after CI 5-FU and radiotherapy (RT): Interim toxicity results from Intergroup trial CALGB 80101. ASCO Gastrointestinal Cancers Symposium, 26-28 January 2006, San Francisco, California. A-61, 2006
138 **Nakazato H**, Koike A, Saji S, Ogawa N, Sakamoto J. Efficacy of immunochemotherapy as adjuvant treatment after curative resection of gastric cancer. Study Group of Immunochemotherapy with PSK for Gastric Cancer. *Lancet* 1994; **343**: 1122-1126
139 **Maehara Y**, Moriguchi S, Sakaguchi Y, Emi Y, Kohnoe S, Tsujitani S, Sugimachi K. Adjuvant chemotherapy enhances long-term survival of patients with advanced gastric cancer following curative resection. *J Surg Oncol* 1990; **45**: 169-172
140 **Kim JP**, Kwon OJ, Oh ST, Yang HK. Results of surgery on 6589 gastric cancer patients and immunochemosurgery as the best treatment of advanced gastric cancer. *Ann Surg* 1992; **216**: 269-278; discussion 278-279
141 **Maehara Y**, Okuyama T, Kakeji Y, Baba H, Furusawa M, Sugimachi K. Postoperative immunochemotherapy including streptococcal lysate OK-432 is effective for patients with gastric cancer and serosal invasion. *Am J Surg* 1994; **168**: 36-40
142 **Fujimoto S**, Furue H, Kimura T, Kondo T, Orita K, Taguchi T, Yoshida K, Ogawa N. Clinical outcome of postoperative adjuvant immunochemotherapy with sizofiran for patients with resectable gastric cancer: a randomised controlled study. *Eur J Cancer* 1991; **27**: 1114-1118
143 **Ochiai T**, Sato H, Sato H, Hayashi R, Asano T, Isono K, Suzuki T, Nagata M, Enomoto K, Gunji Y, Okuyama K, Tanaka T. Randomly controlled study of chemotherapy versus chemoimmunotherapy in postoperative gastric cancer patients. *Cancer Res* 1983; **43**: 3001-3007
144 **Ochiai T**, Sato H, Hayashi R, Asano T, Sato H, Yamamura Y. Postoperative adjuvant immunotherapy of gastric cancer with BCG-cell wall skeleton. 3- to 6-year follow up of a randomized clinical trial. *Cancer Immunol Immunother* 1983; **14**: 167-171
145 **Jeung HC**, Moon YW, Rha SY, Yoo NC, Roh JK, Noh SH, Min JS, Kim BS, Chung HC. Phase III trial of adjuvant 5-fluorouracil and adriamycin versus 5-fluorouracil, adriamycin, and polyadenylic-polyuridylic acid (poly A:U) for locally advanced gastric cancer after curative surgery: final results of 15-year follow-up. *Ann Oncol* 2008; **19**: 520-526
146 **Kim R**, Yoshida K, Toge T. Current status and future perspectives of post-operative adjuvant therapy for gastric carcinoma. *Anticancer Res* 2002; **22**: 283-289
147 **Sakamoto J**, Teramukai S, Nakazato H, Sato Y, Uchino J, Taguchi T, Ryoma Y, Ohashi Y. Efficacy of adjuvant immunochemotherapy with OK-432 for patients with curatively resected gastric cancer: a meta-analysis of centrally randomized controlled clinical trials. *J Immunother* 2002; **25**: 405-412
148 **Oba K**, Teramukai S, Kobayashi M, Matsui T, Kodera Y, Sakamoto J. Efficacy of adjuvant immunochemotherapy with polysaccharide K for patients with curative resections of gastric cancer. *Cancer Immunol Immunother* 2007; **56**: 905-911
149 **Fujimoto S**, Akao T, Itol B, Koshizuka I, Koyano K. A study of survival in patients with stomach cancer treated by a combination of preoperative intra-arterial infusion therapy and surgery. *Cancer* 1976; **37**: 1648-1653
150 **Bonatsos C**, Aust J, Meisner D, Poisez B, Comis R. Preoperative chemotherapy for patients with locally advanced gastric carcinoma. *Proc ASCO* 1985; **4**: 83
151 **Stephens FO**, Adams BG, Crea P. Intra-arterial chemotherapy given preoperatively in the management of carcinoma of the stomach. *Surg Gynecol Obstet* 1986; **162**: 370-374
152 **Wilke H**, Preusser P, Fink U, Gunzer U, Meyer HJ, Meyer J, Siewert JR, Achterrath W, Lenaz L, Knipp H. Preoperative chemotherapy in locally advanced and nonresectable gastric cancer: a phase II study with etoposide, doxorubicin, and cisplatin. *J Clin Oncol* 1989; **7**: 1318-1326
153 **Plukker JT**, Mulder NH, Sleijfer DT, Grond J, Verschueren RC. Chemotherapy and surgery for locally advanced cancer of the cardia and fundus: phase II study with methotrexate and 5-fluorouracil. *Br J Surg* 1991; **78**: 955-958
154 **Ajani JA**, Ota DM, Jessup JM, Ames FC, McBride C, Boddie A, Levin B, Jackson DE, Roh M, Hohn D. Resectable gastric carcinoma. An evaluation of preoperative and postoperative chemotherapy. *Cancer* 1991; **68**: 1501-1506
155 **Leichman L**, Silberman H, Leichman CG, Spears CP, Ray M, Muggia FM, Kiyabu M, Radin R, Laine L, Stain S. Preoperative systemic chemotherapy followed by adjuvant postoperative intraperitoneal therapy for gastric cancer: a University of Southern California pilot program. *J Clin Oncol* 1992; **10**: 1933-1942
156 **Kang YK**, Choi DW, Kim CW, Lee JI, Hong WS, Paik NS. The effect of neoadjuvant chemotherapy on the surgical outcome of locally advanced gastric adenocarcinoma: interim report of a randomized controlled trial. *Proc ASCO* 1992; **11**: 173
157 **Ajani JA**, Mayer RJ, Ota DM, Steele GD, Evans D, Roh M, Sugarbaker DJ, Dumas P, Gray C, Vena DA. Preoperative and postoperative combination chemotherapy for potentially resectable gastric carcinoma. *J Natl Cancer Inst* 1993; **85**: 1839-1844
158 **Rougier P**, Lasser P, Ducreux M, Mahjoubi M, Bognel C, Elias D. Preoperative chemotherapy of locally advanced gastric cancer. *Ann Oncol* 1994; **5** Suppl 3: 59-68
159 **Kelsen D**, Karpeh M, Schwartz G, Gerdes H, Lightdale C, Botet J, Lauers G, Klimstra D, Huang Y, Saltz L, Quan V, Brennan M. Neoadjuvant therapy of high-risk gastric cancer: a phase II trial of preoperative FAMTX and postoperative intraperitoneal fluorouracil-cisplatin plus intravenous fluorouracil. *J Clin Oncol* 1996; **14**: 1818-1828
160 **Crookes P**, Leichman CG, Leichman L, Tan M, Laine L, Stain S, Baranda J, Casagrande Y, Groshen S, Silberman H. Systemic chemotherapy for gastric carcinoma followed by postoperative intraperitoneal therapy: a final report. *Cancer* 1997; **79**: 1767-1775
161 **Songun I**, Keizer HJ, Hermans J, Klementschitsch P, de Vries JE, Wils JA, van der Bijl J, van Krieken JH, van de Velde CJ. Chemotherapy for operable gastric cancer: results of the Dutch randomised FAMTX trial. The Dutch Gastric Cancer Group (DGCG). *Eur J Cancer* 1999; **35**: 558-562
162 **Schuhmacher CP**, Fink U, Becker K, Busch R, Dittler HJ, Mueller J, Siewert JR. Neoadjuvant therapy for patients with locally advanced gastric carcinoma with etoposide, doxorubicin, and cisplatinum. Closing results after 5 years of follow-up. *Cancer* 2001; **91**: 918-927
163 **D'Ugo D**, Persiani R, Rausei S, Biondi A, Vigorita V, Boccia S, Ricci R. Response to neoadjuvant chemotherapy and effects of tumor regression in gastric cancer. *Eur J Surg Oncol* 2006; **32**: 1105-1109
164 **Boige V**, Pignon J, Saint-Aubert B, Lasser P, Conroy T, Bouché O, Segol P, Bedenne L, Rougier P, Ychou M. Final results of a randomized trial comparing preoperative 5-fluorouracil (F)/cisplatin (P) to surgery alone in adenocarcinoma of stomach and lower esophagus (ASLE): FNLCC ACCORD07-FFCD 9703 trial. *J Clin Oncol* 2007; **25** (18S): 4510
165 **Schuhmacher C**, Schlag P, Lordick F, Hohenberger W,

Heise J, Haag C, Gretschel S, Mauer ME, Lutz M, Siewert JR. Neoadjuvant chemotherapy versus surgery alone for locally advanced adenocarcinoma of the stomach and cardia: Randomized EORTC phase III trial #40954. *J Clin Oncol* (Meeting Abstracts) 2009; **27** (15S): 4510

166 **Kinoshita T**, Sasako M, Sano T, Katai H, Furukawa H, Tsuburaya A, Miyashiro I, Kaji M, Ninomiya M. Phase II trial of S-1 for neoadjuvant chemotherapy against scirrhous gastric cancer (JCOG 0002). *Gastric Cancer* 2009; **12**: 37-42

167 **Hartgrink HH**, van de Velde CJ, Putter H, Songun I, Tesselaar ME, Kranenbarg EK, de Vries JE, Wils JA, van der Bijl J, van Krieken JH. Neo-adjuvant chemotherapy for operable gastric cancer: long term results of the Dutch randomised FAMTX trial. *Eur J Surg Oncol* 2004; **30**: 643-649

168 **Swiss Group for Clinical Cancer Research**. Combination Chemotherapy and Surgery in Treating Patients With Locally Advanced Stomach Cancer. Available from: URL: http://www.clinicaltrial.gov/ct2/results?term=SWS-SAKK-43%2F99&rank=1

169 **Persiani R**, D'Ugo D, Rausei S, Sermoneta D, Barone C, Pozzo C, Ricci R, La Torre G, Picciocchi A. Prognostic indicators in locally advanced gastric cancer (LAGC) treated with preoperative chemotherapy and D2-gastrectomy. *J Surg Oncol* 2005; **89**: 227-336; discussion 237-238

170 **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

171 **Xiong HQ**, Gunderson LL, Yao J, Ajani JA. Chemoradiation for resectable gastric cancer. *Lancet Oncol* 2003; **4**: 498-505

172 **Ajani JA**, Winter K, Okawara GS, Donohue JH, Pisters PW, Crane CH, Greskovich JF, Anne PR, Bradley JD, Willett C, Rich TA. Phase II trial of preoperative chemoradiation in patients with localized gastric adenocarcinoma (RTOG 9904): quality of combined modality therapy and pathologic response. *J Clin Oncol* 2006; **24**: 3953-3958

173 **Ajani JA**, Mansfield PF, Janjan N, Morris J, Pisters PW, Lynch PM, Feig B, Myerson R, Nivers R, Cohen DS, Gunderson LL. Multi-institutional trial of preoperative chemoradiotherapy in patients with potentially resectable gastric carcinoma. *J Clin Oncol* 2004; **22**: 2774-2780

174 **Fujitani K**, Ajani JA, Crane CH, Feig BW, Pisters PW, Janjan N, Walsh GL, Swisher SG, Vaporciyan AA, Rice D, Welch A, Baker J, Faust J, Mansfield PF. Impact of induction chemotherapy and preoperative chemoradiotherapy on operative morbidity and mortality in patients with locoregional adenocarcinoma of the stomach or gastroesophageal junction. *Ann Surg Oncol* 2007; **14**: 2010-2017

175 **Medical Research Council**. Combination chemotherapy with or without bevacizumab in treating patients with previously untreated stomach cancer or gastroesophageal junction cancer that can be removed by surgery. Available from: URL: http://clinicaltrial.gov/ct2/show/NCT00450203?term=ST03+trial&rank=2

176 **Dutch Colorectal Cancer Group**. Randomized phase III trial of adjuvant chemotherapy or chemoradiotherapy in resectable gastric cancer (CRITICS). Available from: URL: http://clinicaltrials.gov/ct2/show/NCT00407186?term=CRITICS+trial&rank=1

177 **Japan Clinical Oncology Group**. A trial of neoadjuvant TS-1 and cisplatin for type 4 and large type 3 gastric cancer. Available from: URL: http://clinicaltrial.gov/ct2/show/NCT00252161?term=JCOG+trial+0501&rank=1

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