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.

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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.

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. 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[5].

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* 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[8,13]. 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 Hermanek 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[29]. 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[15].

Although the accuracy of T staging has been much improved for EUS (current range: 78%-92%[14,15]) 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[19,25]. 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[9,21,25]. 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 sensitivity (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 $\leq 5$ 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\[38,39\].

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 RESSECTION**

**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 esophagogastrrectomy (transhiatral or transhiatral). 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 lymphangiinvasion, 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\[52-54\]. 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 intramuscosally or submucosally well-differentiated tumors of less than 3 cm and poorly intramusculo-sally 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. Independent factors of a worse prognosis, such as N3 tumors and large diameter tumors (> 10 cm), have to be excluded before performing extended resection. 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. 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 \( \geq 60\% \) after 5 years. Retrospective studies from Japan, and later from Korea, 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.

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. Several Western reports have confirmed that extended lymphadenectomy, similar to that recommended in the General Rules, can be safely performed with improvements in survival.

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

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. 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, 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. Moreover, the study showed that the morbidity of extended lymphadenectomy, although not lethal, is substantial even in experienced hands. 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 \( \geq 25 \text{ kg/m}^2 \) and age > 65 years was a notable concern.

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.”

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, Kampschoer et al. 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. The so-called “Maruyama Index of Unresected Disease” (MI), when retrospectively...
used, was able to quantify the adequacy of lymphadenec-
tomy. 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 dissec-
tion[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 bi-
oppy is negative. These anatomical peculiarities have led to the concept of a “sentinel lymphatic basin”[106], which
indicates the lymph node stations to which sentinel nodes
belong. Dissection of these stations can provide an ac-
ceptable safety net for the clinical application of these
procedures, and minimize the possibility of leaving me-
tastasis behind. Preliminary studies have shown that these
sentinel node techniques are an acceptable procedure for
pathological T1 tumors with a diameter of < 40 mm, al-
though 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 postop-
erative chemoradiation therapy (United States INT-0116
trial)[115], postoperative single-drug chemotherapy (Japanese
ACTS-GC trial)[116] and perioperative three-drug combina-
tion chemotherapy (European MAGIC trial)[117]. Since the
publication of these trials, surgery alone is no longer con-
sidered 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 chemorad 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 nonstandardized timing and regimens of adjuvant therapy that are now considered as outdated[128]. At the same time, results from pivotal studies on postoperative chemoradio-
therapy 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 postopera-
tive chemoradiotherapy: 45 Gy radiotherapy at 1.8 Gy/d,
given 5 d/wk for 5 wk, with modified doses of fluoro-
uracil and leucovorin on the first 4 d and last 3 d of rad-
iotherapy; Two 5-d cycles of fluorouracil and leucovorin
were given after, and one cycle was given before chemora-
diotherapy[135]. Although clinically significant toxicity was
recorded after chemoradiotherapy, the overall and relapse-
free survival results of the surgery-alone arm were sig-
nificantly worse than those of the adjuvant chemoradio-
therapy 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 inter-
pretation 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[136] recently has shown that chemo-
radiotherapy 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[137].

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)[119]. 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 differ-
ence 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 immunoncology 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[108], Nocardia rubra cell wall skeleton[142], Bacillus Calmette-Guerin (BCG)[143] and polyadenyl-copolyuridylic acid[144] 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 fluorinated 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 immunoncology 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[140]. 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 antibiotic 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[135-137]. 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 untreated patients[142,143]. These preliminary observations encouraged the introduction of preoperative chemotherapy protocols for potentially resectable, locally advanced gastric cancer (Table 1)[147,148-149]. 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)[140]. 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 incorrectness 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[140,147].

Since the late 1990s, ambitious European phase III
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). Only the MAGIC trial (started in the United Kingdom in 1994) and the FFCD 9703 trial (started in France in 1996) have been completed. 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.

Based on the results of the SWOG 9008/INT-0116 trial, 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. 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 chemo-radiotherapy in terms of complete pathological response (up to 30% in some series) and increased long-term survival without an increase in morbidity or mortality.

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 capcitabine, with or without the endothelial growth factor antibody, bevacizumab; the CRITICS trial (Chemoradiotherapy after Induction Chemotherapy In Cancer of the Stomach), a phase III study that is randomizing between preoperative chemotherapy (three courses of epirubicin/cisplatin/capcitabine) and gastric surgery with...

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**Table 1: Trials of preoperative chemotherapy in gastric cancer**

| Author      | Phase  | Selection criteria            | Preoperative | Postoperative | Pts  | R0 (%) | Pathological CR (%) | Median survival (mo) |
|-------------|--------|------------------------------|--------------|---------------|------|--------|---------------------|----------------------|
| Ajani et al., 1991 | II     | M0 Resectable (+ GEJ)        | EFP × 2      | EFP × 3       | 25   | 72     | 0                   | 15                   |
| Leichman et al., 1992 | II     | M0 Resectable               | FPL × 2      | IP FUdR × P cisplatin × 2 | 38   | 88     | 8                   | > 17                  |
| Kang et al., 1992 | II RCT | M0 Loc. advanced            | EFP × 3      | EFP × 3-6     | 53   | 79     | 8                   | 43                   |
| Ajani et al., 1993 | II     | M0 Resectable               | EAP × 3      | EAP × 2       | 48   | 90     | 0                   | 16                   |
| Rouzier et al., 1994 | II     | M0 Loc. advanced (+ GEJ)    | FP × 6       | None          | 30   | 78     | 0                   | 16                   |
| Kelsen et al., 1996 | II     | M0 Loc. advanced            | FAMTX × 3    | IP F × F      | 56   | 77     | NS                  | 15                   |
| Crookes et al., 1997 | II     | M0 Resectable (+ GEJ)       | FPL × 2      | IP FUdR × IP cisplatin × 2 | 59   | 71     | 9                   | 52                   |
| Songun et al., 1999 | II     | T2-T4; M0                   | FAMTX × 4    | None          | 27   | 75     | NS                  | 18                   |
| Schuhmacher et al., 2001 | II     | III-IV; M0 (+ GEJ)          | EAP          | None          | 42   | 86     | 0                   | 19                   |
| D’Ugo et al., 2006 | II     | T3-T4 anyN; T < 2 N; M0     | FP × 3 or ECF × 3 | EFP × 3 or ECF × 3 | 34   | 82     | 3                   | > 28                  |
| Cunningham et al., 2006 | II RCT| II-IV; M0 (+ GEJ)           | ECF × 3      | ECF × 3       | 250  | 74     | NS                  | 18                   |
| Boige et al., 2007 | II RCT | Resectable (+ GEJ)          | FP × 3 or ECF × 3 | None          | 253  | 68     | -                   | 30                   |
| Schuhmacher et al., 2009 | II RCT| Loc. advanced T3-T4Nsm0     | FP × 3       | None          | 111  | 73     | NS                  | NS                   |
| Kinoshita et al., 2009 | II     | Schirrous Resectable        | TS-1 × 2     | None          | 55   | 80.8   | 0                   | NS                   |

*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; EEP: Etoposide, fluorouracil, and cisplatin; ECF: Epirubicin, 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.*
limited lymph node dissection followed by postoperative chemotherapy (another three courses of epirubicin/cisplatin/capecitabine) or chemoradiotherapy[17], and the JCOG trial 0501 [Japan Clinical Oncology Group Study 0501 trial] and KYUH-UH-A-GC04-03 Kyoto trial, which are testing preoperative oral fluoropyrimidine S-1 together with cisplatin for postoperative oral fluoropyrimidine S-1[17].

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 tailor 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 regiments 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.

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