A decade in gastric cancer curative surgery: Evidence of progress (1999-2009)

Stefano Rausei, Gianlorenzo Dionigi, Francesca Rovera, Luigi Boni, Caterina Valerii, Luisa Giavarini, Francesco Frattini, Renzo Dionigi

Stefano Rausei, Gianlorenzo Dionigi, Francesca Rovera, Luigi Boni, Caterina Valerii, Luisa Giavarini, Francesco Frattini, Renzo Dionigi, Department of Surgical Sciences, University of Insubria, 21100 Varese, Italy

Author contributions: All the authors contributed to this paper.

Correspondence to: Stefano Rausei, MD, PhD, Department of Surgical Sciences, University of Insubria, Viale L. Borri 57, 21100 Varese, Italy. s.rausei@libero.it

Telephone: +39-332-393229 Fax: +39-332-260260

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Abstract

To investigate the progress in evidence-based surgical treatment of non-metastatic gastric cancer, we reviewed the last ten years’ literature. The data used in this review were identified by searches made on MEDLINE, Current Contents, PubMed, and other references taken from relevant original articles (on prospective and retrospective studies) concerning gastric cancer surgery. Only papers published in English between January 1999 and December 2009 were selected. Data from ongoing studies were obtained in December 2009, from the trials registry of the United States National Institutes of Health (http://www.clinicaltrial.gov). The citations list was presented according to evidence based relevance (i.e., randomized controlled trials, prospective studies, retrospective series). In the last ten years, many challenges have been faced relating to the extension of gastric resection and nodal dissection as well as surgical timing, but we found only limited evidence, regardless of latitude of study. The ongoing phase-III trials may provide answers that will be valid for the coming decades, and which may bring definitive answers for the currently unresolved questions.

Key words: Gastric cancer; Evidence-based surgery; D2 lymphadenectomy; Laparoscopic gastrectomy; Endoscopic treatment; Neoadjuvant therapy

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INTRODUCTION

In the current era of evidence-based medicine, the year 1999 seemed to provide several definitive answers regarding the management and, more specifically, the surgical treatment of gastric cancer. Since then, the extension of gastric resection and nodal dissection as well as surgical timing have achieved clear and convincing definitions due to well-designed, randomized, controlled phase-III trials. In March 1999, almost simultaneously, Cuschieri et al. and Bonenkamp et al. discouraged the routine use of D2 lymph node dissection in patients with gastric cancer because of high morbidity risks without any clear survival benefit. Five months later, Bozzetti et al. stated that in patients with distal gastric cancer, subtotal gastrectomy can achieve the same outcome as total gastrectomy, with the only difference being that the former procedure provides a better quality of life.

Taken together, these conclusions appeared to decrease the relevance of surgical exeresis in gastric cancer treatment. The neoadjuvant therapy approach, suggested by several phase-II trials, indicated a in the same direc-
tion, resulting in further questioning of surgical timing.

However, in April 1999, Songun et al.\textsuperscript{[4]} were obliged to stifle their enthusiasm for the supposed efficacy of preoperative chemotherapy due to an unacceptable tumor progression rate, allowing some surgeons the (short-lived) belief that they still held exclusive rights over the cure.

Over the last decade, many trials concerning gastric cancer surgery have been performed, and many of the earlier conclusions have either been changed or reversed.

More than a decade after the publication of the above-cited “revolutionary” randomized studies, we sought to review the specific literature and to report the progress in evidence-based surgical treatment of non-metastatic gastric cancer.

During the decade 1999-2009, many challenges were addressed, but we found only a limited amount of evidence, regardless of the latitude of our searches.

### SELECTION CRITERIA

The data used in this review were identified by searches made on MEDLINE, Current Contents, PubMed, and other references taken from relevant original articles (prospective and retrospective studies) concerning gastric cancer surgery.

Only papers published in English between January 1999 and December 2009 were selected. Data from ongoing studies were obtained in December 2009, from the trials registry of the United States National Institutes of Health (http://www.clinicaltrial.gov).

### ANALYSIS OF DATA

The authors attributed an evidence category to the retrieved studies according to the well-known classification (Table 1)\textsuperscript{[10,11]} using references taken from relevant articles (on prospective and retrospective studies) concerning gastric cancer surgery. Only papers published in English between January 1999 and December 2009 were selected. Data from ongoing studies were obtained in December 2009, from the trials registry of the United States National Institutes of Health (http://www.clinicaltrial.gov).

### TRADITIONAL CONTROVERSIES

#### Extension of resection

Starting from the publication of the Bozzetti et al. trial, and subsequently confirmed by a number of retrospective studies\textsuperscript{[32,33]}, the aim of achieving adequate gastric resection through 5-cm negative margins contributed to the worldwide spread of the concept of limited gastrectomy, regardless of the histological type of tumor.

However, although evidence on subtotal gastrectomy for distal tumors has now reached a relevant level (evidence level: I A; Table 2)\textsuperscript{[1]}, proximal gastrectomy for cancer of the upper third still remains controversial.

Despite the promising results of some small eastern prospective studies\textsuperscript{[12,13]}, several retrospective analyses\textsuperscript{[16,18]} reported a lack convincing long-term results for this procedure whilst demonstrating a high frequency of complications (anastomotic stenosis and reflux esophagitis) and cancer recurrences. This has significantly affected diffusion of this procedure (evidence level: II B).

Driven by the additional morbidity risks and the poor nutritional status associated with extension of gastric resection\textsuperscript{[19]}, several authors suggested either a wedge resection or a pylorus-preserving sleeve gastrectomy, at least for the treatment of early disease\textsuperscript{[25,24]}. However, there still is a lack of data to support the adoption of these solutions (evidence level: II B).

Similarly, the reports published over the last decade...
found a survival benefit for patients who underwent a D2 resection\[39\]. This finding was later confirmed by two small phase-II prospective studies carried out by Italian and UK groups\[40,41\], both of which concluded that modified D2 gastrectomy (without routine spleno-pancreatectomy) could improve survival for gastric cancer patients, without any significant increase in morbidity or mortality compared to D1 gastrectomy. Therefore, with the new-born concept of the minimum number of removed lymph nodes for staging in the 5th edition of the TNM (UICC, 1997)\[42\], and just five years after the appearance of the results of both the Dutch and MRC trials, the conclusions about lymphadenectomy were evolved rapidly.

Recommendations radically changed in 2006, when data from the first RCT concerning the efficacy of modified D2 lymphadenectomy (named D3 by the authors, according to the first edition of the Japanese classification of gastric cancer)\[43\] were published\[44\]. Wu et al confirmed, in a well-designed study of over 200 gastric cancer patients, that compared with D1 nodal dissection, D2 dissection offers a survival benefit only if performed by well-trained, experienced surgeons (evidence level: I A; Table 2). The last conclusion was derived from the knowledge that an extended modified nodal dissection could be associated with an increase in morbidity (with no mortality) rates that was far from the disturbing rates recorded in previous trials.

Similar concerns have also been expressed by the authors of the JCOG9501 trial relating to the comparison between D2 lymphadenectomy “alone” or associated with para-aortic nodal dissection\[45\]. This study presented clear reassurance on the efficacy of modified D2 gastrectomy (Figure 1), also confirming the trend towards higher morbidity and excluding any survival benefit for more extended lymphadenectomy.

Interestingly, the duration of this controversy induced authors to design even larger trials to confirm a well-known answer (e.g., the NCT00447746 trial from Tata Memorial Centre Mumbai, India) (Table 3)\[46\].

MINIMALLY INVASIVE APPROACH

Because the recent philosophy “from maximum tolerable, to minimum effective therapy” has also gained a footing in gastric cancer management, the (industrial) push towards the minimally invasive approach seems to be unstoppable.

Even though there is no strong evidence concerning the lowest extension limit of gastric resection, we will probably obtain more evidence in the near future from new technological approaches rather than from more conventional methods (i.e., wedge resection or sleeve gastrectomy pylorus-preserving). This will only happen if the slow and rigorous approach of RCTs is able to keep pace with technological evolution.

Meanwhile, we would like stress that the current final goal is the most “effective” therapy rather than necessarily the “minimum” one.

**Extension of lymphadenectomy**

While Bozzetti et al(3) opened the road towards limited surgery for gastric cancer treatment, Cuschieri et al(2)(MRC trial) and Bonenkamp et al(2)(Dutch trial) seem to have stopped the use of extended lymphadenectomy that had begun in the 1970s in eastern countries. These randomized controlled trials (RCTs) revealed no survival benefit for D2 nodal dissection with spleno-pancreatectomy and confirmed an increase in morbidity related to this procedure, thus leading many surgeons to abandon this strategy (evidence level: I A; Table 2).

However, the re-reading of data contained in the Dutch study after a long-term follow-up revealed an improved survival trend for selected patients who had D2 dissection\[46\]. Moreover, a further reanalysis of the trial performed by Bonenkamp and colleagues, which excluded both distal pancreatectomy and splenectomy cases (as these are a significant factor in post-operative morbidity),

suggest that we still have not achieved a definition of surgical overtreatment. Although good evidence has discouraged prophylactic splenectomy in cardiac tumors\(25-27\) (evidence level: I A; Table 2) and although we are currently awaiting the results of the JCOG0110 trial (Table 3)\[28\], retrospective analysis by many authors has led to their recommending the aggressive combined resection of adjacent organs for patients with T4 carcinoma\[29-32\]. However, the possibility of obtaining a curative resection in the presence of a supposed T4 cancer is not always predictable. In fact, although histopathological examination reveals that multi-organ resections are often performed for pT3 tumors, a relatively small proportion of tumors are actually invading adjacent organs\[33\]. Therefore, accurate selection of patients for multi-organ resection based on lymph nodal status has been proposed\[31,32\], similar to the recommendation of the completion of exeresis after a gastrectomy with positive surgical margins\[34-37\]. However, the evidence does not support any of these extreme procedures (evidence level: IV C).

**Figure 1 Survival curves of gastric cancer patients after D2 gastrectomy according to data of phase-III RCTs\[25,44,45\].**

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Endoscopic treatment

Over the last decade, endoscopy has been considered to be an adequate therapeutic option for the cure of early gastric cancer. It has been both included into eastern guidelines for gastric cancer treatment\[48\] and cited in the clinical practice guidelines of the National Comprehensive Cancer Network in the United States\[48\].

Currently, the literature (predominantly coming from the Asian continent) relating to therapeutic endoscopy [endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD)] is very broad\[49-69\] and already includes some review articles aimed at summarizing a number of different techniques, as well as comforting results for the two modalities (EMR, ESR) in terms of resection rates, morbidity and survival\[49,51\].

However, the evidence supporting the use of these modalities is limited, especially considering the complete absence of randomized controlled studies (many retrospective and few prospective series; evidence level: III C).

For this reason, although the scientific community still anticipates a satisfactory survival comparison between EMR (presented in the 1970s) and conventional surgery, several recent reports have provided (from the late 1990s) a similarly positive recommendation for ESD (even if not supported by large samples and long-term outcome data).

The efficacy of removing more advanced lesions without any size limitation is undoubtedly superior with ESD rather than with conventional EMR, even though this technique carries several disadvantages, such as a longer procedure time together with a higher post-operative bleeding and perforation rate.

Therefore, ESD has introduced great changes in the endoscopic treatment of early cancers and extension of its indications has been suggested: from differentiated lesions up to 20 mm in diameter without ulceration in the EMR era, to 30-mm ulcerative or submucosal (less than 500 μm) differentiated lesions in the ESD era\[72\].

One remarkable issue concerns the recruitment criteria for endoscopic treatment, which were designed on the basis of fundamental prognostic considerations, stating the likelihood of the presence of metastatic lymph nodes calculated by observational studies\[73-78\]. As shown above, these criteria have been extended\[72,79\] and, although there are some questions about their suitability\[80\], several authors encourage their further extension\[81-83\]. Moreover, as in primary treatment, in the case of incomplete resection after EMR or ESD, an additional endoscopic procedure (within the limits of the histopathologically verified extended criteria) has been suggested\[84,85\].

Recently, the phase-II JCOG 0607 study set out to verify the safety of the extended criteria, which appear to
be already included in the Japanese guidelines\textsuperscript{87}.

**Laparoscopic resection**

The laparoscopic approach to gastric cancer surgery was adopted in eastern countries from the beginning of the 1990s and presented encouraging results in terms of both feasibility and safety.

However, laparoscopy for gastric cancer treatment still has not reached the same evidence strength as laparoscopic colorectal cancer surgery. The well-known technical difficulties and oncological concerns, delayed the widespread use of this approach in its initial phase.

A considerable number of series and comparative studies have focused on laparoscopic resection for gastric cancer, especially in early and distal disease. Results have suggested that totally laparoscopic distal gastrectomy (as well as laparoscopy-assisted procedure, hand-assisted laparoscopic procedure or, more recently, robot-assisted laparoscopic procedure) is, compared to open gastrectomy, associated with a quicker return of gastrointestinal function, faster discharge from the hospital as well as comparable complications and recurrence rates\textsuperscript{88-94}. These findings have resulted in the inclusion of this modality of treatment in the Japanese guidelines for gastric cancer since 2001\textsuperscript{99}.

However, to date, the English literature does not present any large randomized studies with clear-cut results regarding this issue. In fact, the only four RCTs containing survival data from long-term follow-up\textsuperscript{96-99} recruited less than one hundred patients (pooled: 82; the trial by Huscher et al also included advanced disease). It is because of these small numbers that the evidence supporting laparoscopic treatment is so weak (evidence level: II B), and, as a consequence, widespread adoption of the procedure cannot be recommended.

Nonetheless, this problem should be solved by ongoing phase-III trials (both Korean), which aim at recruiting a ten-fold higher number of patients than previous RCTs\textsuperscript{100,101} (Table 3).

As suggested by some recent reports, even once the safety and efficacy of laparoscopic distal gastrectomy have been demonstrated, there will remain problems regarding evidence for laparoscopic resection\textsuperscript{102-107}. First, the efficacy of laparoscopic gastrectomy in proximal early disease (also laparoscopic gastrectomy and extended lymphadenectomy for advanced tumors) and the territorial line between the indications for either minimally invasive (laparoscopy) or organ conservative surgery (endoscopy) will need to be demonstrated. Second, the possibility of generalizing laparoscopic (as well as endoscopic) results should be verified because all pioneering studies are likely to favor the new method, as their authors are experts in the field.

**Sentinel node navigation**

Although sentinel node navigation aims at surgical cancer staging and not surgical cure, we will examine this “staging modality,” as it was introduced with the purpose of confirming the oncological clearance of the minimally invasive approach for primary tumors (EMR/ESD, laparoscopic or open limited resection). For patients who do not have any clinical demonstration of metastatic lymph nodes, some surgeons have suggested that a sentinel node procedure might avoid the complications resulting from overtreatment by an extended lymphadenectomy\textsuperscript{12,98-112}.

However, the centrifugal nature of the lymphatic flow from the stomach has resulted in skepticism towards the efficacy of this technique associated to gastrectomy, and, to date, no series have demonstrated a false negative rate which is acceptably close zero.

The available literature reports a sensitivity of 72%-93\%, a specificity of 75% and an accuracy of 74%-100\%, but a negative predictive value of 50%\textsuperscript{111,118}. The reasons for these wide ranges will be indicated hereafter.

The first issue resides in the absence of a standardized approach for the identification of the sentinel node (cancer-injected endoscopically or intra-operatively, in either the sub-mucosa or subserosa, using a dye or radioactive tracer; sentinel node identified by direct visualization or by hand-held gamma probe). The second problem arises from the possible presence of lymphatic invasion of early tumors included in the analyses. In such cases there might be a false negative sentinel node because the lymphatic vessels have been completely obstructed by the cancer.

Hence, the usefulness of sentinel node navigation in influencing the patient’s care has not yet been established, and is probably still far from being established (evidence level: III C). Additionally, this issue has never been taken into consideration in a randomized trial setting.

**SURGERY IN MULTIMODAL STRATEGY**

The rationale of the first RCT, published by a Dutch group in 1999, concerning pre-operative chemotherapy was driven by a number of considerations, such as the demonstrated higher morbidity/mortality rates and lack of any survival benefits after extended lymphadenectomy and the poor efficacy of adjuvant regimens in locally advanced diseases\textsuperscript{4}. Hence, this trial attempted, albeit unsuccessfully, to integrate the unsatisfactory surgical results with a pre-operative tumor downstaging therapy aimed at reducing the risk of disease recurrence after surgery.

At the present time, the rationale of neoadjuvant chemotherapy is based on different premises, but still has the same purpose. Although extended lymphadenectomy has added efficacy to gastric cancer surgery\textsuperscript{14,40} and effective post-operative schedules have been introduced\textsuperscript{14,16,17}, worldwide mortality still remains unacceptable for patients with resectable T3 and T4 tumors or other types of resectable gastric cancer involving the lymph nodes\textsuperscript{14,15,16,18,19}. Therefore, many efforts, using a multimodal strategy and a pre-operative approach, have been performed\textsuperscript{5,41,58}.

In 2006, the MAGIC and the FFCD 9703 trials\textsuperscript{2,12,122} started to provide concrete evidence for neoadjuvant chemotherapy, definitively introducing the concept of “delayed
surgery” in gastric cancer treatment.

Issues from pre-operative therapy

Today, gastric cancer surgeons should be able to postpone surgical exeresis in the case of a patient with a resectable locally advanced tumor. Indeed, it is widely recognized that this type of patient might experience an effective survival benefit in response to a neoadjuvant treatment comprising pre-operative chemotherapy with epirubicin, cisplatin and 5-FTU[126,127] (evidence level: I A; Table 2). However, surgeons should also be aware of the concerns arising from pre-operative treatment. In fact, the resection delay (within three to six weeks after completion of the third three-week cycle of chemotherapy) does not exclude patients from the benefits of a potentially curative postponed resection and does not worsen surgical outcomes, even though some patients might be affected by tumor progression.

For these reasons, this issue undoubtedly needs further investigation not only to determine the size of the problem, but also to reduce its incidence, to optimize pre-treatment staging and, finally, to improve the biologic characterization of each cancer. The primary aim is the selection of patients who will benefit from pre-operative treatment. Consequently, the topic of the neoadjuvant approach remains “hot” and is the focus of several ongoing phase-III RCTs (Table 3): the JCOG trial 0501 (Japan Clinical Oncology Group Study 0501 trial-completed, but still awaiting publication of results)[128]; the MAGIC B trial (United Kingdom National Cancer Research Institute ST03 trial -in recruitment phase)[129]; and the CRITICS study (Dutch Colorectal Cancer Group trial -in recruitment phase)[130] (Table 3).

Importantly, the latter study is investigating the efficacy, within the adjuvant setting, of the association of radiotherapy with chemotherapy, simultaneously seeking to confirm the consolidated evidence for pre-operative chemotherapy through the study design. The role of radiotherapy in the neoadjuvant setting has also been tested, and phase-II trials are currently giving encouraging results[130,127] (evidence level: III C). Thus, the role of radiotherapy in the neoadjuvant setting is worth exploring further in clinical phase-III RCTs.

However, we do not want to dwell on the different therapeutic modalities for achieving (pre-operatively, intra-operatively and post-operatively) the curative effect of surgery. Instead, we want to underline the possibility of modifying the timing of surgery by safe postponement of gastrectomy.

The reliability of trial results is further enhanced by application of methods such as independent investigators, blinding techniques and therapy standardization.

Although the basic principles of trial methodology may be considered to be valid for surgical research as well, surgical situations that would require a RCT approach often present several factors [e.g., patients’ preferences (selection bias), surgeons’ preferences and lack of blinding or placebo (treatment bias)] that may complicate or, in some extreme cases, even prevent the conduction of the analysis.

Therefore, surgical research typically comprises either rigorously performed trials that have a great impact on clinical practice or poorly performed trials in which the validity of the result is questionable.

In the present work we referred, on the basis of these premises, to the modified Sackett’s classification of evidence levels[130,131] (Table 1); this only assigns great credibility to large, well-designed RCTs with clear-cut results, avoiding all possible considerations of the complex and not always accurate statistical processing of meta-analyses.

Nonetheless, we must underline some issues that are of crucial importance for understanding the real progress of evidence levels in gastric cancer surgery.

Firstly, over the last decade, rapid changes in technology and their consequent industrial push might have led to a biased approach in RCTs.

Secondly, the design of surgical trials aimed at detecting even minimal differences (and thus requiring large sample sizes) has not only hindered performance but has also limited the possibility of generalization of outcomes.

Finally, the generalization of treatment findings emerging from trials should be discouraged for non-experts. The modern management of gastric cancer could actually require risky surgical solutions as well as a multimodal approach. Better surgical outcomes and reasonable survival times can be achieved in selected high-volume institutions with sufficiently strong experience in gastric cancer therapy.

Meanwhile, the ongoing phase-III trials may provide definitive answers that will hopefully be valid for the coming decades, and may bring definitive answers for the currently unresolved questions.

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