Can Surgical Treatment Results in Gastric Cancer Be Improved?

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ABSTRACT
Patients with gastric cancer have a poor prognosis. Surgery is the only treatment modality offering hope for cure. However, even after curative surgery, the five-year survival rate is still about 30%. Even though the incidence of early gastric cancer is up to 40% of all cases (surgically curable) in Japan, in Western countries most of the patients are diagnosed at an advanced stage, when curative surgery is no longer possible. Most patients die of locoregional recurrence or distant metastasis. Therefore, every attempt should be made to increase early diagnosis and to find additional prognostic factors which can be determined preoperatively. Operations with extended lymphadenectomy are associated with higher morbidity and mortality rates, while a possible survival benefit is not proven in Western countries. The five-year survival results of two large prospectively randomized, controlled trials (the Dutch Gastric Cancer Trial and the British Medical Research Council Trial) comparing limited lymphadenectomy (D1) to extended lymphadenectomy (D2) are still being awaited. In light of increased morbidity and mortality rates associated with extended lymphadenectomy, the limits of surgical possibilities for the treatment of gastric cancer seem to be reached. Adjuvant radiotherapy and chemotherapy are demonstrated to not give an additional survival advantage compared to surgery only. Development of more active combination chemotherapy regimens and results in locally advanced gastric cancer are encouraging. Therefore, to evaluate the place of preoperative chemotherapy in potentially operable gastric cancer, two randomized trials have been initiated in the Netherlands and Great Britain. Gastric cancer should be considered a malignancy which requires a multidisciplinary approach of a specialized team consisting of committed specialists. New treatment modalities should only be applied to patients in clinical trial settings with dedicated clinicians. The Oncologist 1996;1:36-40

INTRODUCTION
Despite declining incidence and associated decline in mortality, the prognosis of patients with gastric cancer has not improved substantially during the last three decades in Western countries [1]; the overall five-year survival rate is 10% [2]. Only a curative operation offers hope for cure, but even after a successful curative resection, the five-year survival rate is still poor (about 30%) [2-4]. Survival of patients with gastric cancer is dependent on the stage at the time of diagnosis. Unfortunately, most of the patients are diagnosed at an advanced stage, when a curative resection is no longer possible. Local-regional extension of the tumor is the most important limiting factor for curative surgery. After curative surgery, about 80% of the patients die within a short period of time from locoregional recurrence (87%) and/or distant metastasis (30%) [5]. This clearly demonstrates the shortcomings of preoperative staging and surgical technique. In contrast with these results are the survival rates reported from Japan during the last 30 years. The five-year survival rate increased from 44% (1963-1966) to 62% (1971-1985) [6]. Although Japanese investigators stress the importance of early diagnosis and the role of regional lymph nodes, and propagate gastrectomy with extended lymphadenectomy (D2 and D3 resection) as standard treatments, possible causes for the difference in five-year survival rates between Japan and the West are still debated. To establish the best form of surgery and to assess the value of any (neo-) adjuvant treatment, we can only rely on prospective randomized trials. The factors which may be altered to improve surgical treatment results and thus survival are discussed in the following paragraphs.

EARLY DETECTION AND STAGING
Due to population screening programs in Japan, the incidence of early gastric cancer is up to 40% of all cases.
Although it is argued that screening in low incidence areas (Western countries) is not cost-effective, Hallissey et al. [7] have demonstrated that we can diagnose gastric cancer early, too, but not so often as in Japan. In this program, patients over 40 years of age presenting with dyspepsia for the first time were referred for early endoscopy. The methods in this study increased the proportion of early gastric cancer from 1% to 26%. The proportion of potentially curative resections was 63%. Also in the Dutch Gastric Cancer Trial, in which no specific measures were taken for early diagnosis, the proportion of early gastric cancer was 25% (unpublished data), while 71% of the patients had curative resections in intent. Owing to earlier experiences, it is not expected that the number of cases of early gastric cancer will further increase despite our sophisticated diagnostic tools [8].

Even though the computerized tomography scan is used extensively for the diagnosis and staging of gastric cancer, it is not reliable for the assessment of local-regional extension (infiltration depth of the primary tumor and regional lymph node involvement). Endoscopic ultrasonography seems reliable for the assessment of the infiltration depth (T stage); concordance with pathologic T stage was 86% [9]. Laparoscopy and cytological examination of the abdominal washing are demonstrated to increase the accuracy of staging by detection of peritoneal carcinomatosis and free tumor cells, which are usually missed by other diagnostic means [10].

**Surgical Treatment**

An analysis of Japanese and Dutch patient data led to the conclusion that among known and unknown factors, the extended lymphadenectomy could play an important role [11]. In Japan, the D2 resection has been the standard treatment for many years for gastric cancer. However, the place of neither the extent of gastrectomy or lymphadenectomy is clear, because until recently no results were available from prospective randomized trials. Even today, only six prospective randomized trials are being conducted in this field: four trials studying the place of extended lymphadenectomy and two trials studying the place of total gastrectomy “de principe.” The first results of a randomized trial, in which D1 resection (gastrectomy with limited lymphadenectomy) was compared to D2 (gastrectomy with extended lymphadenectomy) came in 1988 from South Africa [12]. In this trial, D2 resection was associated with a greater blood transfusion requirement, increased morbidity and a longer hospital stay, while there was no survival advantage. The fact that only 11% of the randomized patients were eligible made the interpretation of these results very difficult. More than six years later, this time from Hong Kong, a second trial warned against extended lymphadenectomy [13]. In this trial, comparing D1 subtotal gastrectomy to D3 total gastrectomy for patients with antral carcinoma, increased morbidity (intra-abdominal sepsis) associated with extended dissection was demonstrated again. Although the patients in the D1 group had a significantly better survival rate than the patients in the D3 group, a straightforward interpretation of this finding for use in general practice is not possible. This is because not only the number of analyzed patients was small, but also subtotal gastrectomy combined with limited lymphadenectomy (D1) was compared to total gastrectomy combined with extended lymphadenectomy (D3), while the extent of lymphadenectomy, as well as the place of total and subtotal gastrectomy, are still debated in gastric cancer surgery. Two other prospectively randomized trials, one in the Netherlands by the Dutch Gastric Cancer Group (DGCG) and the other in Great Britain by the Medical Research Council (MRC) comparing D1 to D2 dissection were completed in 1993. In the DGCG trial, 711 patients (of the 1078 patients randomized over 3.5 years) underwent a curative resection in intent. In the British MRC trial, 400 patients were included. Strict quality control measures were taken in the DGCG trial to guarantee the intended difference between the two resection types [14]. “Contamination” (dissection of lymph nodes outside the indicated area) and “noncompliance” (incomplete lymph node dissection) were defined and acknowledged as possible confounders of the outcome. Also a beneficial effect of extended lymph node dissection by stage migration was assessed in this trial [15]. Both of these trials with a large number of patients demonstrated that extended lymphadenectomy is associated with significantly higher morbidity and mortality rates compared to limited lymphadenectomy, while the five-year survival results are still being awaited [14, 16].

Total and subtotal gastrectomy “de principe” for antral carcinoma were compared in a randomized manner in two trials. Gouzi et al. (France) [17] found no difference in postoperative mortality and survival rates. But in another study by Bocetti et al. (Italy) [18], increased morbidity and mortality were found in patients undergoing total gastrectomy in interim-analysis, while survival results are also being awaited.

Despite numerous retrospective comparisons of limited and extended lymphadenectomies, in which a survival advantage was found in patients undergoing extended lymphadenectomy for gastric cancer, a beneficial effect on survival remains to be demonstrated in prospectively randomized trials. Although retrospective studies are very important, their results cannot and should not be used in general practice because of a strong case selection bias. In the German multicenter observation study [19], a totally different definition for D1 and D2 resection than dictated by the Japanese Research Society for Gastric Cancer (JRSGC) was also used: as a cut-off point for the distinction between D1 and D2, merely a lymph node count of 25 was used, irrespective of the level of the lymph nodes.
**MULTIMODALITY TREATMENT**

Gastric cancer used to be known as a relatively chemotherapy- and radiotherapy-insensitive tumor, especially in advanced stages. Due to local-regional management difficulties posed by surgery only, the value of radiotherapy and chemotherapy has been studied worldwide, mainly in phase I and II studies. Until now, there was no evidence for an improved survival by using adjuvant radiotherapy, as was demonstrated by two randomized clinical trials, although local control did improve [20, 21]. Also, local treatment with intraperitoneal chemotherapy after gastrectomy in patients with gastric cancer at high risk of recurrence did not show any survival advantage [22-24]. In a meta-analysis of 14 randomized trials of adjuvant chemotherapy after a curative resection (published between 1980 and 1992), only a marginal beneficial effect on survival could be found [25]. However, the employed chemotherapeutic regimens are now considered to be suboptimal. After an initial report of a 42% response rate (RR), the most frequently studied combination FAM (5-fluorouracil [5-FU], adriamycin, mitomycin-C) gave an overall RR of 33% in patients with local recurrent or metastatic disease, while complete remissions were rare (less than 3%) [26, 27].

In 1979, Cadman showed that prior treatment with methotrexate improved the efficacy of 5-FU [28]. Klein et al. designed the FAMTX-combination, which included the administration of moderately high doses of methotrexate followed by 5-FU after an interval of 1 h, and of doxorubicin on day 15 every four weeks. The administration of doxorubicin on day 15 was required for the destruction of tumor cells, recruited into cycle in the G1-phase by 5-FU given on day 1. The results of this biochemical modulation were reported in 1986 in a study of 100 patients [29]. In this study, 59 patients responded, including 12 complete remissions. The median survival of all patients was nine months and there were three treatment-related deaths. In a prospective randomized trial by the European Organization for the Research and Treatment of Cancer, in which FAMTX was compared to FAM, FAMTX gave a higher response rate (41% versus 9%; \( p < 0.0001 \)) and a longer survival (42 versus 29 weeks; \( p < 0.004 \)), demonstrating the superiority of the methotrexate-containing regimen. FAMTX was also recommended as the golden standard for all future advanced gastric carcinoma trials [30]. The combination FEMTX and FEMTX-P are used as well, in which adriamycin is replaced by its analogue epiadriamycin, with or without cisplatin. Epiadriamycin was demonstrated to have equivalent tumor activity compared to adriamycin, but was less cardiotoxic, allowing higher doses than with adriamycin. In a phase II trial, FEMTX-P gave an overall objective tumor response of 47% and a 68% response of the primary tumor [31].

Another development was the demonstration of a synergistic effect of cisplatin and etoposide, leading to the combination EAP (etoposide, adriamycin and cisplatin). Wilke et al. [5] used EAP for locally advanced gastric cancer and 5/34 (14%) of the patients showed a pathologic complete response, while 15/34 (44%) of the patients could have a curative resection. With EAP, an overall RR of 53% was achieved, but it was associated with a 10%-14% treatment-related mortality rate [32-34]. In a randomized trial comparing EAP to FAMTX, the effectiveness of both combinations was comparable, whereas the EAP regimen showed unacceptably high toxicity [32]. Even though EAP seemed promising initially, its use is dissuaded due to unacceptably high toxicity. In a phase II trial in the UK, objective tumor response was seen in 71% of the 128 patients with measurable disease, 12% of whom had a complete response with ECF, the combination of 5-FU as continuous infusion, cisplatin and epirubicin [35]. The overall median survival was eight months, while treatment-related deaths occurred in 4.3% of the patients. Even though practical use of the schedule is difficult because of the prolonged (21 weeks) infusion which is required for the continuous administration of 5-FU, there was no measurable reduction in quality of life during chemotherapy; the toxicity was moderate, while 67% of the patients with dysphagia had complete resolution of this symptom.

The development of more active combinations (e.g., FAMTX, EAP, ECF) and insights into timing of administering chemotherapy seem to have opened new possibilities for the treatment of gastric cancer. In other solid tumors (e.g., carcinoma of the breast and osteosarcoma), it has already been established that preoperative chemotherapy increases the curative resectability rate, achieving complete remissions in some cases [36, 37]. Based on the results of recent phase II trials for advanced gastric cancer, preoperative chemotherapy especially seems to have an effect on resectability.

**DISCUSSION**

The answer to the question “Can surgical treatment results of gastric cancer be improved?” is yes! Despite declining incidence, gastric cancer is and will remain an important health problem worldwide and surgery is still the only treatment offering hope for cure. With higher than ever resection rates and high morbidity and mortality rates associated with extended procedures (D2 to even D4 and total gastrectomy), the limits of what can be achieved with surgery alone seem to be reached. Randomized trials with a large number of patients demonstrated that extended lymphadenectomy (D2 and D3) is associated with significantly more morbidity and mortality compared to the D1 resection. Multicenter trials do give a good reflection of the present situation because they are the closest to the real situation. Also, in Japan, where gastric cancer surgery is
performed by gastric cancer surgeons only, extended lymphadenectomy is associated with as high morbidity rates as in the West, but without increased mortality. These facts cannot be fully explained by patient- or tumor-related factors [38, 39]. The development of pancreas and spleen-preserving techniques by the Japanese justify a more refined surgical approach: pancreatectomy and splenectomy “de principe” should be abandoned for “de nécessité” [40, 41]. In case of surgery, bigger does not always mean better: the extent of resection should be adjusted according to the stage of disease, which requires better patient selection. Therefore, accurate preoperative and peroperative staging is essential. There is also a need for other prognostic factors, which can be determined preoperatively and not postoperatively only. Altered protein expression (immunohistochemistry studies) seems to be a promising new tool which can provide additional information for accurate staging and thus patient selection for surgery.

Final survival results from the DGCG trial and the British MRC trial will not be available before 1997. Until these results are obtained, the place of extended lymph node dissections in Western patients is not clear. It is well known that the effectiveness of surgery depends on the extent of disease and adequacy of surgery (R0 resection): microscopically tumor-positive resection margins in otherwise curative surgery reduces survival significantly [42, 43]. We also have to pay attention to perioperative care and not only find out which patients should be treated surgically, but also by whom [44]. Of paramount importance also is the quality of life (well-being) of the patient after surgical intervention, especially after total gastrectomy. Lack of appetite and hunger, reduced food intake and reduced absorption result in malnutrition and weight loss. Even though several modes of reconstruction exist (e.g., Roux-Y, Hunt-Lawrence-Rodino pouch, omega loops), the ideal mode has yet to be found, because they all have similar results [45, 46].

Preoperative (neoadjuvant) systemic chemotherapy seems a promising approach. By giving systemic treatment, both the primary tumor as well as distant (micro)metastases can be handled, which may lead to downstaging. Therefore, it is expected that more patients can have resections, either for cure or for palliation, leading to an improvement of the survival rates and the quality of life. The value of neoadjuvant chemotherapy in resectable gastric cancer is currently under investigation in the Netherlands (Preoperative Chemotherapy for Operable Gastric Cancer [POCOM] trial with four cycles FAMTX) and UK (MRC Adjuvant Gastric Infusional Chemotherapy [MAGIC] trial with ECF).

Other treatment modalities and diagnostic tools should be explored without losing sight of more basic principles in performing radical operations. It should be clear by now that gastric cancer requires a multidisciplinary approach of a specialized team consisting of committed specialists in every area (endoscopy, intensive care, surgery, radiotherapy, pathology, medical-oncology). Until it is proven which treatment modality is the best, promising treatment modalities should be applied only to patients in (good quality) controlled clinical trial settings with dedicated clinicians. Trials are the only way for developing/standardizing treatment without exposing our patients to unproven and thus potentially dangerous treatment fads.

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