

Reflections on adjuvant treatment of gastric cancer

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Abstract: Gastric cancer constitutes a significant health problem in the world due to its high incidence in certain geographical areas. The basic treatment of this tumor in its localized stages is surgery. Unfortunately, survival is less than 5 years, despite radical surgery. Radical and extensive surgery has proved to be crucial to survival, although there is no agreement on the need for reaching the nodes until there is more than 3 cm of tumor. However, even with the most extensive surgery, survival does not reach more than approximately 35% at 5 years, if we consider all the localized stages. Adjuvant treatment is therefore necessary for this neoplasm. The role of post-operative chemotherapy, as that of radiochemotherapy, is not well established and there is no standard. However, there is relative evidence of the benefit of adjuvant treatment in some chemotherapy studies and in combination with radiotherapy, so that it is an option for treatment in these patients.

Keywords: gastric cancer, adjuvant, chemotherapy, radiotherapy

Introduction

Gastric cancer constitutes an important social and health problem worldwide, due to its high incidence in particular geographical areas. In Europe it ranks fifth after lung, prostate, colorectal and bladder cancer in men, and breast, colorectal, lung and uterine cancer in women. On a global scale it represents 24% of all malignant neoplasia (Ferlay et al 2001). The survival at 5 years has increased slightly from 17% to 22%, with the stage being the determining prognostic factor. The rate is 2% at 5 years for disseminated neoplasia, and approximately 60% in more localized tumors.

Surgery is still the treatment chosen for patients with localized gastric cancer, but adjuvant treatment is necessary as a result of these patients' low overall survival, even after radical R0 D2 surgery. (In Table 1, the concepts of R and D used in this paper are defined.) The survival rate after curative resection is 30%–40%, with the stage and location of the tumor being the major influential factors. A proximal location has the worst prognosis, as can be seen in Table 2 (Meyerhardt and Fuchs 2003). In any case, it is remarkable that even for stage IA, more than 20% of patients are expected to relapse and die within 5 years. The failure of the treatment is produced by a combination of local relapses and distance dissemination, with local relapse showing a very significant percentage. The distribution of relapses is summarized in Table 3, and includes the analysis of four recent series. Loco-regional relapses reach between 30%–50% as a whole, with distance dissemination between 18%–54% according to the series. This high percentage of local relapses favors the inclusion of radiotherapy in the adjuvant treatment of this tumor.

Extent of surgery and adjuvant chemotherapy

The efficacy of the extent of surgery is a controversial aspect with great importance in the indication of adjuvant treatment. Two large studies have been published on this

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Table 1 Definition of “R” and “D”. R refers to the type of resection carried out. D refers to the extent of the lymph node dissection

R0	Curative resection without residual disease
R1	Resection with curative intention but with microscopic residual disease
R2	Palliative resection with macroscopic residual disease
D1	Resection of tumor and adjacent nodes only
D2	Resection including coeliac and perigastric nodes up to >3 cm of the primary T

aspect. The study by the German group (German Gastric Cancer Study group) Roder et al 1993 (record study) showed that patients in stages II and IIIA who had undergone R0 and D2 surgery (>25 nodes resected) gained significant improvement in survival compared with those patients who had undergone standard resection. The Dutch study (Bonenkamp et al 1999) (randomized study) and the Cuschieri study (Cuschieri et al 1999) reached the opposite conclusion – that D2 surgery should not be considered as the standard treatment. In this study, the extent of the surgery (D1 vs. D2) entailed better staging of patients, without showing improvement in survival for the stages. However, it is difficult to ignore that in the German study, the survival at 5 years increased from 26% to 55% in stage II for D2 surgery.

In this context, the role of adjuvant chemotherapy has not been defined. There are other relatively recent studies with significant results, although the majority of these could not be reproduced, or lack statistical power due to the small number of cases (Table 4).

The studies by Cirera et al (1999) and Neri et al (2001) are worth a separate mention. In the study by Neri et al the treatment used was epirubicin, 5-fluorouracil (5-FU) and leucovorin (LV). We can include this as a more common treatment than those used in most studies that make up the meta-analyses published until now. All patients had positive nodes; 88% of patients received the scheduled treatment. The average survival for the group treated was 31 months, almost double that of the control group, which had an average survival of 18 months ($p < 0.01$). The survival at 5 years

Table 2 Survival at 5 years by stage and location of tumor

Stage	Overall	Antrum/pylorus	Cardia/fundus
IA	78%	81%	64%
IB	58%	65%	42%
II	34%	38%	24%
IIIA	20%	23%	13%
IIIB	8%	6%	6%
IV	7%	9%	6%

Table 3 Distribution of gastric cancer relapses

Local	Peritoneal	Distant	Ref.
23%	54%	54%	Schwarz et al 2002
42%–48%	21%–52%	25%–46%	Marrelli et al 2002
29%	72%	18%	Macdonald et al 2001
38%–93%	30%–43%	49%	Gunderson et al 2002

was 30% of treated patients in contrast with 13% of the control group. Although there was toxicity grade 3–4, with 12% of patients having mucositis, 8.7% diarrhoea and 7% leukopenia, the level of toxicity was acceptable and there were no cases of hospitalization. The study by Cirera et al involved 156 patients, all in stage III including cases of N0. In this study, the treatment was very simple and included a single dose of mitomycin (MMC) followed by 3 months of oral tegafur daily. It is important to highlight that all the patients included had undergone R0 D2 surgery. The results were highly significant, with 56% survival at 5 years for the treated group and 31% for the control group ($p = 0.04$). In this case, the price of obtaining the survival benefit was minimal, with only one case of grade 3 toxicity. Although confirmation studies with a greater number of cases are necessary, these data should not be ignored. In the study by Cirera et al the greatest percentage of relapses were local and peritoneal, reaching 33% in the non-treated group. Although no significant results were reached, the study developed by ITMO group (Italian Trials in Medical Oncology) is very interesting. There were 274 patients included in it with T3, T4 or N1, N2. Chemotherapy consisted of two cycles of EAP (etoposide, adriamycin, and cisplatin) followed by two cycles of 5FULV according to Machover’s scheme with leucovorin. Survival at 5 years was 48% for the control group and 52% for the treatment group without significant statistical difference. The highest benefit was for patients N⁺ with more than 6 nodules whose survival was 22% and 42% respectively. The authors also point out the importance of the D2 surgery performed in the study, influencing the high survival achieved in both groups (Bajetta et al 2002).

Some molecular alterations have been described in gastric cancer as indicative factors of different biological behavior and prognosis which may relate to the different results achieved. We quote as an example the microsatellite instability, present in 13%–44% of sporadic gastric cancers which confers better prognosis (dos Santos et al 1996) or some specific somatic changes that can occur in p53 without a clear prognosis or in p16INK4 related to gastroesophageal junction cancers (Wong et al 1997). The anatomical location

Table 4 Adjuvant chemotherapy studies with positive results

Study	Treatment	No. p	Sup %	p	Criticism
GITSG 1982	MeCCNU + 5FU	71		<0.03	Not reproduced in VASOG y ECOG ?
	Control	71			
Neri et al 2001	Epi + 5FU/LV	69	30	<0.01	
	Control	68	13		
Grau et al 1998	MMC	45	44	0.004	Small number of cases. 11 years conscription. No control group
	MMC + tegafur	40	67		
Hagiwara et al 1992	IP carbon-absorbed cisplatin	24	69	<0.005	Small number of cases. Australian study negative.
	Control	25	27		
Kim et al 1992	MMC + 5FU + AraC + OK432	74	45	<0.05	Small number of cases. Not reproduced
	Control	64	23		
Cirera et al 1999	MMC + tegafur	76	56	0.04	?
	Control	72	36		

Abbreviations: FU, fluorouracil; LT, leucovorin; MMC, mitomycin.

has also been described as a prognostic factor. In this sense the work by the ITMO group included this parameter in the multivariate analysis (Cox model) proving to be an independent prognostic factor, being the location in middle and distal third better prognosis than in the upper third ($p:0.033$).

Five meta-analyses have been published. The first, by Hermans et al (1993), reviewed 11 trials (2000 patients) that compared adjuvant treatments with very uneven therapies, including intraperitoneal chemotherapy, radiotherapy and chemotherapy combined with immunotherapy, with surgery as a control arm. They did not show any survival benefit in the combined arm. The second meta-analysis was presented by Earle and Maroun (1999). They compiled 13 clinical trials, including 1990 patients, and found a small but significant survival benefit for patients treated with chemotherapy (odds ratio 0.80, relative risk 0.94). Mari et al (2000) analyzed more than 20 articles taking into account more than 300 patients, and showed an 18% reduction in the risk of death (HR 0.82, $p < 0.001$). Panzini et al (2002) evaluated more than 3000 patients in a total of 17 clinical trials. Their results showed significant survival benefit in patients treated with adjuvant chemotherapy (odds ratio 0.72). Finally Hu et al (2002) reviewed 14 trials involving more than 4500 patients. They found survival benefit in patients treated adjuvantly (odds ratio 0.56). In short, 4 meta-analyses suggest survival benefit, being the most favorable group being that presenting nodular affection.

Another approach to adjuvant treatment of gastric cancer is the perioperative chemotherapy used in the MAGIC trial (Cunningham et al 2006). The study included 503 patients

with gastric or esophagogastric junction adenocarcinoma in stage II or higher, randomized in to control or to receive three pre-operative cycles and three post-operative cycles of chemotherapy with ECF (epirubicine, cisplatin, and infusional 5FU). The extension of surgery (D1,D2) follows the surgeon's criteria. Survival at 5 years, although lower than in other studies, shows significant difference ($p:0.009$) favoring the treatment group with 36% in comparison with the 23% of the control group. A fact of great interest in this study is that in the pre-treated group the average of tumor size, the T and the N are significantly smaller showing the benefit of pre-operative treatment.

Considering this evidence and the lack of a standard, we should consider whether the patient, ie, the ordinary patient outside a clinical trial, should be advised to undergo complementary treatment after apparently radical surgery (R0, D1–D2). If the answer is yes, what is the most suitable treatment? Is chemotherapy enough? Should we always advise radiochemotherapy?

Local relapse and radiotherapy

We have already mentioned the importance of local relapse in this neoplasm. This has motivated the inclusion of radiotherapy in the adjuvant treatment of this tumor, in spite of the technical and practical difficulties that it entails. The most relevant radiochemotherapy studies are summarised in Table 5. Two of these are not comparative, which limits their value (Park et al 2003; Lim et al 2004). In both, D2 surgery was performed and the patients were treated with 5FU/LV + RT (radiotherapy); they reached a survival of 58% and 60%

Table 5 Studies of adjuvant radiochemotherapy

Study	Treatment	P	Sup %	p	Criticism
Lim et al 2004	5FU/LV + RT D2 Surgery	291	58	-	Not comparative
Park et al 2003	5FU/LV + RT D2 Surgery	261	60	-	Not comparative
Macdonald et al 2001 INT-0116	5FU/LV + RT Control D2 Surgery 10% D1 Surgery 36%	281	50%* 41%* *3 years		Low compliance with protocol (64%) 17% abandoned due to toxicity 35% revision of RT plan 3 toxic deaths <i>Poor quality of surgery</i>

Abbreviations: FU, fluorouracil; LT, leucovorin; RT, radiotherapy.

at 5 years. It is worth highlighting that this survival is not different from that reached in some adjuvant chemotherapy studies, such as that by Cirera et al in which there was 56% survival in the treated group at 5 years. The study by Macdonald et al (2001) (INT-0116) compared one treatment arm (5FU/LV + RT) with a group of surgery only. The results of survival and the disease-free interval (DFI) at 3 and 5 years show significant improvement in favor of the treatment group, with a survival of 50% and 40%. (Although the results at 5 years have not been published, they show an 11.6% increase in survival benefit, 40% vs 28.4% ($p < 0.001$), and survival free of relapse increased from 25% to 31% ($p < 0.001$) in the radiochemotherapy arm). These were lower than the results found by Hagiwara et al (1992) and Cirera et al (1999) with chemotherapy alone, comparing 41% and 28.4% in the control group ($p < 0.005$) and with DFI of 48% and 31% as against 31% and 25% ($p < 0.005$). The results of this study have led to post-operative radiochemotherapy being considered by many as standard in the treatment of gastric cancer, in spite of the fact that it is widely considered reprehensible. The most

significant criticism (see Table 4) is convincing. Compliance with the protocol was under 64%, and 26% were abandoned due to toxicity or patient rejection. Due to the complexity of the radiotherapy protocol, in 35% of cases the treatment schedule had to be corrected. The most important criticism was that the surgery was very low quality, with only 10% D2 surgery and 36% D1, ie, more than half the patients received non-curative surgery with D0 resections, a fact that the authors defend as the reality of gastric surgery in the USA. Survival at 3 years for the patients who had undergone D1 or D2 resection in the Dutch study reached 60%, 20% more than in Macdonald's study, by which we can conclude that poor surgery was a poor prognostic factor in the INT-0116 study. What would the results of this study have been with R0 D2 surgery in all patients?

Another aspect for discussion is the real effect of radiotherapy on local relapses. Table 6 shows the percentages of locoregional relapse in studies with surgery alone, chemotherapy alone and radiochemotherapy. We can see that the rates of local relapse are similar in any of these situations.

Table 6 Locoregional relapses according to treatment

Study	P No. rel/(Total no.)	Treatment	Locoregional relapses	Relapse* predictors	p*
Schwarz et al 2002	35/(73)	Surgery R0D2	23% only local 6%	N3 T3/T4	0.005 0.008
Cirera et al 1999	37/(76) 50/(72)	Surgery D2 + CT Surgery D2	26% 33%	—	—
Lim et al 2004	114/(291)	Surgery D2 + CT + RT	19% only local 7%	N3 T3/T4	<0.0001 <0.0001
Park et al 2003	114/(261)	Surgery D2 + CT + RT	29% —	III/IV (M0)	<0.001
Macdonald et al 2001 (INT-0116)	120/(281) 177/(275)	10% D2 Surgery + CT + RT 10% D2 Surgery	19% 29%**	—	**NS

Abbreviations: CT, chemotherapy; RT, radiotherapy.

Two facts are worth mentioning: one, that solely local relapses are scarce in the studies that have been carried out, and secondly, that they do not differentiate between R0 D2 surgery alone and those with adjuvant radiochemotherapy treatment. On the other hand, in the INT-0116 study there is no significant difference in locoregional relapses according to the arm of treatment.

Final comments

Therefore, in general, there are positive data to advise the use of adjuvant treatment in gastric cancer in N3 and T3/T4. There is no evidence that radiotherapy improves the rate of locoregional relapses in patients who undergo R0 D2 surgery. Even in Macdonald's study, there is no significant difference between the two arms, despite D0 surgery in 53% of cases. The optimum treatment has not been established, but as there is probably real potential benefit, it seems reasonable to opt for any of the treatments that have shown positive results, bearing in mind the patient's circumstances and the infrastructures available. For incomplete surgery (R1, R2 or D0), it seems advisable to include radiotherapy in the complementary treatment. In any case, a discussion of the pros and cons with the patient is fundamental to reach what should be a joint decision. However the development of new trials that allow a definitive standard treatment to be established is necessary.

References

- Bajetta E, Buzzoni R, Mariani L, et al. 2002. Adjuvant chemotherapy in gastric cancer: 5-year results of a randomized study by the Italian Trial in Medical Oncology (ITMO) group. *Ann oncol*, 13(2):299–307
- Bonenkamp JJ, Hermans J, Sakako M, et al. 1999. Extended lymph-node dissection for gastric cancer. Dutch Gastric Cancer Group. *N Engl J Med*, 340:908–14
- Cirera LI, Balil A, Batiste-Alentorn E, et al. 1999. Randomized clinical trial of adjuvant mitomycin plus tegafur in patients with resected stage III gastric cancer. *J Clin Oncol*, 17:3810–15
- Cunningham D, Allum WH, Stenning SP, et al. 2006. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med*, 355:11–20.
- Cuschieri A, Weeden S, Fielding J, et al. 1999. Patient survival after D1 and D2 resections for gastric cancer: long-term results of the MRC randomized surgical trial. Surgical cooperative group. *Br J Cancer*, 79:1522–30.
- dos Santos NR, Seruca R, Constancia M, et al. 1996. Microsatellite instability at multiple loci in gastric carcinoma: Clinicopathologic implication and prognosis. *Gastroenterology*, 110:38–44.
- Earle CC, Maroun JA. 1999. Adjuvant chemotherapy after curative resection for gastric cancer in non-Asian patients: Revisiting a meta-analysis of randomized trials. *Eur J Cancer*, 35:1059–64.
- Ferlay J, Bray F, Pisani P, et al. 2001. Cancer Incidence, mortality and prevalence Worldwide, *L You*: IARC Press, IARC cancer base, no. 5
- Grau JJ, Estape J, Fuster J, et al. 1998. Randomized trial of adjuvant chemotherapy with mitomycin plus fluorouracil versus mitomycin alone in resected locally advanced gastric cancer. *J Clin Oncol*, 16:1036–39.
- Gunderson LL. 2002. Gastric cancer – patterns of relapse after surgical resection. *Semin Radiat Oncol*, 12:150–61.
- Hagiwara A, Takahashi T, Kojima O, et al. 1992. Prophylaxis with carbon-absorbed mitomycin against peritoneal recurrence of gastric cancer. *Lancet*, 339:629–63.
- Hermans J, Bonenkamp JJ, Boon MC, et al. 1993. Adjuvant therapy after curative resection for gastric cancer: meta-analysis of randomized trials. *J Clin Oncol*, 11:1441–7.
- Hu JK, Chen ZX, Zhou ZG, et al. 2002. Intravenous chemotherapy for resected gastric cancer: meta-analysis of randomized controlled trials. *World J Gastroenterol*, 8:1023–8.
- Kim JP, Kwon J, Sung T, et al. 1992. Results of surgery on 6589 gastric cancer patients and immunochemosurgery as the best treatment of advanced gastric cancer. *Ann Surg*, 216:269–78.
- Lim DH, Kim DY, Kang MK, et al. 2004. Patterns of failure in gastric carcinoma after D2 gastrectomy and chemoradiotherapy: a radiation oncologist's view. *Br J Cancer*, 91:11–7.
- Macdonald JS, Snalley SR, Benedetti J, et al. 2001. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med*, 345:725–30
- Mari E, Floriani I, Tinazzi A, et al. 2000. Efficacy of adjuvant chemotherapy after curative resection for gastric cancer: a meta-analysis of published randomized trials. A study of the GISCAD. *Ann Oncol*, 11:837–43.
- Marrelli D, Roviello F, de Manzoni G. et al. 2002. Different patterns of recurrence in gastric cancer depending on Lauren's histological type: longitudinal study. *World J Surg*, 26:1160–5.
- Meyerhardt JA, Fuchs CS. 2003. Adjuvant therapy in gastric cancer: Can we prevent recurrences? *Oncology*, 17:714–21.
- Neri B, Cini G, Andreoli F, et al. 2001. Randomized trial of adjuvant chemotherapy versus control after curative resection for gastric cancer: 5-year follow-up. *Br J Cancer* 84:878–80.
- Panzini I, Gianni L, Fattori PP, et al. 2002. Adjuvant chemotherapy in gastric cancer: a meta-analysis of randomized trials and a comparison with previous meta-analyses. *Tumori*, 88:21–7.
- Park SH, Kim DY, Heo JS, et al. 2003. Postoperative chemoradiotherapy for gastric cancer. *Ann Oncol*, 14:1373–7.
- Roder JD, Bottcher K, Siewert JR, et al. 1993. Prognostic factor in gastric carcinoma. Results of the German Gastric Carcinoma Study. *Cancer*, 72(7):2089–97.
- Schwarz RE, Zagala-Nevarez K. 2002. Recurrence patterns after radical gastrectomy for gastric cancer: Prognostic factors and implications for postoperative adjuvant therapy. *Ann Surg Oncol*, 9:394–400.
- [GITSG] The Gastrointestinal Tumor Study Group. 1982: Controlled trial of adjuvant chemotherapy following curative resection for gastric cancer. *Cancer*, 49:1116–22.
- Wong DJ, Barrelet MT, Stoger R et al, 1997. p16INK4 promoter is hypermethylated at a high frequency in esophageal adenocarcinoma. *Cancer Res*, 57:2619–22.

