Pergamon

European Journal of Cancer, Vol. 35, No. 4, pp. 558–562, 1999

Printed in Great Britain
0959-8049/99/$ - see front matter

PII: S0959-8049(98)00429-8

Original Paper

Chemotherapy for Operable Gastric Cancer: Results of the Dutch Randomised FAMTX Trial

I. Songun,[1] H.J. Keizer,[2] J. Hermans,[3] P. Klementschitsch,[4] J.E. de Vries,[5] J.A. Wils,[6] J. van der Bijl,[7] J.H.J.M. van Krieken[8] and C.J.H. van de Velde[1] for the Dutch Gastric Cancer Group (DGCG)*

[1]Department of Surgery; [2]Department of Clinical Oncology; [3]Medical Statistics, Leiden University Medical Centre, PO Box 9600, 2300 RC Leiden; [4]Department of Surgery, De Weezenlanden Hospital; [5]Department of Surgery, St. Sophia Hospital, Zwolle; [6]Department of Oncology, St. Laurentius Hospital, Roermond; [7]Department of Surgery, St. Gregorius Hospital, Brunssum; and [8]Department of Pathology, Leiden University Medical Centre, Leiden, The Netherlands

The aim of this trial was to investigate whether pre-operative chemotherapy leads to a 15% higher curative resectability rate in patients with operable gastric cancer. In this randomised trial, patients were allocated to receive either four courses of chemotherapy using 5-fluorouracil, doxorubicin and methotrexate (FAMTX) prior to surgery or to undergo surgery only. Patients younger than 75 years of age with a good physical and mental condition and a histologically proven adenocarcinoma of the stomach without clinical or radiographic (computed tomography scan) evidence of distant metastases were eligible for this trial. Early gastric cancer or cardia carcinoma were excluded. The response to chemotherapy was evaluated after two and four courses. In case of progressive disease (PD) after two courses, patients were operated upon as soon as possible. Otherwise complete response (CR) partial response (PR) or stable disease (SD), two more courses were scheduled. The standard surgical procedure was a limited lymphadenectomy (D1) with staging biopsy of the para-aortic lymph nodes. Between September 1993 and February 1996, 56 eligible and evaluable patients were entered: 27 were randomised to receive FAMTX before surgery and 29 to undergo surgery only. In the FAMTX + surgery treatment group, 15/27 (56%) had curative resections versus 18/29 (62%) in the surgery only arm. There was no difference in the frequency of TNM stages I + II in both treatment arms: 15/27 versus 15/29. Due to PD and/or toxicity, 12 patients (44%) could not complete the planned four courses of FAMTX. Response evaluation after chemotherapy was possible in 25 patients: 2 CR, 6 PR, 8 SD and 9 PD. The difference in curative resectability rate was 6.5% (95% confidence interval −32 to +19%) in favour of surgery only. Downstaging for stages I + II did not occur. PD was more often the reason for not completing the planned four courses than toxicity. More active regimens than FAMTX are required for future randomised trials. © **1999 Elsevier Science Ltd. All rights reserved.**

Key words: gastric cancer, chemotherapy, FAMTX, surgery, resectability, prognosis
Eur J Cancer, Vol. 35, No. 4, pp. 558–562, 1999

INTRODUCTION

GASTRIC CANCER has a poor prognosis, despite a slowly declining incidence and an associated decline in mortality rate. Surgery is the only treatment modality offering hope for a cure. In Western countries, most patients are diagnosed at an advanced stage, when curative surgery is no longer possible. However, even after curative surgery, the 5 year survival is still approximately 30% [1–3] and most patients die of locoregional recurrence or distant metastasis, illustrating the shortcomings of pre-operative staging and surgical

*See Appendix for the participating hospitals.
Correspondence to C.J.H. van de Velde, e-mail: velde@surgery.azl.nl
Received 1 Jul. 1998; revised 10 Nov. 1998; accepted 2 Dec. 1998.

technique. 'More radical' operations with extended lymphadenectomy (D2–D4) are associated with higher morbidity and mortality rates compared with limited lymphadenectomy, and a possible survival benefit is not proven in Western countries. The 5-year survival results of two large prospectively randomised, controlled trials (the Dutch Gastric Cancer Trial and the British MRC Trial) comparing extended lymphadenectomy (D2) with limited lymphadenectomy (D1) are still awaited, but preliminary results show no difference in survival rates between both treatment arms (data not shown). In both trials a significant increase in morbidity and hospital mortality rates was found with extended lymphadenectomy [4, 5]. These facts suggest that the limits of surgical possibilities for improving the treatment results in patients with gastric cancer seem to have been reached.

In order to improve survival following surgery, many phase II trials with limited numbers of patients have been performed to investigate the value of adjuvant therapy. In a meta-analysis of 14 randomised trials of adjuvant (post-operative) chemotherapy with regimens that are now considered suboptimal, only a small, but statistically significant, additional survival advantage was found in favour of the adjuvant chemotherapy compared with surgery only [6, 7]. In some pilot studies, gastric cancer before resection showed a promising responsiveness to chemotherapy [8–12].

More active combination chemotherapy regimens, e.g. EAP (etoposide, 5-fluorouracil (5-FU) and methotrexate), FAMTX (5-FU, doxorubicin and methotrexate), FEMTX-P (5-FU, epidoxorubicin, methotrexate and cisplatin) and ECF (epidoxorubicin, cisplatin and continuous infusion of 5-FU), have been developed and their results in locally advanced and metastatic gastric cancer have shown response rates of 41–71%. In some cases, even a complete response could be achieved [9, 13–16]. With FEMTX-P, it was reported that the primary tumour had a higher response rate compared with its metastases [17], suggesting that earlier stages are more chemosensitive than advanced stages. The development of these more active chemotherapy regimens and insights into the timing of the administration of chemotherapy against the background of poor surgical results have opened new possibilities for the treatment of gastric cancer.

In order to evaluate the effect of pre-operative chemotherapy in potentially operable gastric cancer, a randomised trial was conducted in The Netherlands. Out of the four potentially suitable options, the DGCG (Dutch Gastric Cancer Group) decided on FAMTX in 1993, because of its repeatedly demonstrated steady response rates, lower toxicity compared with EAP [2, 3, 9, 18–21] lower costs and lower toxicity compared with FEMTX-P (FAMTX is less toxic due to the omission of cisplatin [8, 22]). Moreover, at that time FAMTX was considered the golden standard for future randomised trials [10, 14, 18].

The major aim of the trial was to study the hypothesis that pre-operative chemotherapy would give rise to a 15% higher curative resectability rate compared with surgery only. The results of this randomised multicentre trial are presented here.

PATIENTS AND METHODS

Patients younger than 75 years of age with a good physical and mental condition and histologically proven adenocarcinoma of the stomach were eligible for this trial with informed consent.

Exclusion criteria were clinical and radiological (computed tomography scan, CT) evidence of distant metastases, prior treatment, early gastric cancer (T1), cardia carcinoma, malignancy in history (other than carcinoma *in situ* of the uterine cervix and basal cell carcinoma of the skin), leucocyte count below 4×10^9/l, platelet count below 100×10^9/l, creatinine clearance below 60 ml/min and serum bilirubin above 25 μmol/l, cardiac problems (e.g. myocardial infarction, cardiac insufficiency) and WHO performance status 3 or 4.

Diagnosis and staging of the tumour was carried out by history taking, physical examination, gastroscopy and biopsy of the tumour (for histological diagnosis), radiographical examination of the stomach and chest and ultrasound of the liver. CT scan of the abdomen and laparoscopic staging were optional. No exclusion was based on stage, among others due to the difficulty of determining stage pre-operatively.

All participating hospitals had the approval of their Medical Ethics Committee.

Eligible patients were randomised to receive four courses of FAMTX prior to surgery or to undergo surgery only. Patients in the chemotherapy arm had to be hospitalised for at least 3 days. On day 0 (the day before administration of methotrexate, patients were hydrated during 24 h with 3 l isotonic (1.4%) sodium bicarbonate. Urine pH had to be higher than 7, otherwise patients received hypertonic sodium bicarbonate until the pH was above 7. On day 1, 1500 mg methotrexate/m^2 body surface and 1500 mg 5-FU/m^2 body surface were administered intravenously (i.v.) in 1 h, with 1 h in between methotrexate and 5-FU. On days 2 and 3, 30 mg leucovorin was administered every 6 h (i.v. or oral). If the methotrexate level was higher than 2.0×10^{-6} after 24 h or higher than 2.5×10^{-7} after 48 h, the dose of leucovorin was increased to 60 mg every 6 h and prophylactic haematological growth factors was started, because of possible toxicity. On day 15, doxorubicin was administered i.v. at a dose of 30 mg/m^2 body surface. Day 29 was day 1 of the following course and the cycle was repeated to a maximum of four courses.

The response to chemotherapy was evaluated after two courses. In case of progressive disease (PD), patients were operated upon as soon as possible. Otherwise complete response (CR), partial response (PR) or stable disease (SD), two more courses were given.

The standard surgical procedure was a limited lymphadenectomy (D1) with staging biopsy of the para-aortic lymph nodes.

Designing this trial, the expectation was that pre-operative chemotherapy should lead to a 15% better curative resectability: 75% versus 60%. With a two-sided significance level of 0.05 and a power of 0.90, requiring 225 patients in each arm, the expected entry period was 3 years, based on experience with the previous gastric cancer trial. In view of the rather limited experience with pre-operative chemotherapy, an interim analysis was planned after entry of 100 patients. Besides curative resectability, downstaging and toxicity were also important short-term evaluation criteria and (disease free) survival a long-term criterion.

RESULTS

Between September 1993 and January 1996, 59 patients were randomised: 29 were allocated to receive FAMTX before surgery and 30 to undergo surgery only. Because of

this slow accrual of patients the National Health Council ('Ziekenfondsraad') stopped further financial support of the trial. The trial committee then decided to study the evidence of the available data in order to judge whether continuation of the trial would be justified. Several patients, mainly in the FAMTX arm, were not yet evaluable at that time. The results with respect to curative resectability for the evaluable patients in that analysis were: 9/19 (47%) in the pre-operative chemotherapy group versus 16/27 (59%) in the surgery only group. This difference of −12%, with a 95% confidence interval from −41% to +17%, nearly discounted the hypothesis of the trial: +15% in favour of FAMTX + surgery. Based on these results, combined with the accrual problems, the trial committee concluded that there was strong evidence that the FAMTX regimen was unlikely to achieve the aimed goal and suggested to the participating hospitals that the trial be stopped. This proposal was accepted by the DGCG.

The final analysis presented below is based on the complete data of all 59 entered patients: 29 allocated to receive FAMTX before surgery and 30 to undergo surgery only. Of these patients, 2 in the FAMTX + surgery and 1 in the surgery only arm were ineligible (1 of the patients had a lymphoma, 1 had metastases and 1 had a cardia carcinoma). The eligible patients consisted of 32 male and 24 female patients, with a mean age of 60 years (range 34–75). The minimum follow-up was 12 months.

Of the 56 eligible patients, the result with respect to curative resectability *pre-operatively* was 18/27 (67%) in the FAMTX + surgery arm and 19/29 (66%) in the surgery only arm (Table 1).

After pathological examination of the resection specimen, in the chemotherapy arm only 15 of the 18 patients having curative resection in intent had an R0 resection (radical excision, clear resection lines and no tumour cells in cytological examination of the abdominal washings). In the surgery only arm, 18 of the 19 patients had an R0 resection. Therefore, the *postoperative* curative resectability rate was 15/27 (56%) in the chemotherapy arm and 18/29 (62%) in the surgery only arm. This difference (FAMTX + surgery minus surgery only) of −6% had a 95% confidence interval from −32 to +19%.

Table 1. *Results of curative resectability and TNM stage distribution in eligible patients* (n = *56)*

	n	FAMTX + surgery *n* (%)	Surgery *n* (%)
Total	56	27	29
Resectability			
Pre-operative			
Curative	37	18 (67)	19 (66)
Palliative	7	2 (7)	5 (17)
No resection	12	7 (26)	5 (17)
Postoperative			
Curative	33	15 (56)	18 (62)
Palliative	11	5 (19)	6 (21)
No resection	12	7 (26)	5 (17)
TNM stage postoperative			
I	14	9 (33)	5 (17)
II	16	6 (22)	10 (35)
III	9	4 (15)	5 (17)
IV	17	8 (30)	9 (31)

The postoperative TNM stage distribution in both treatment arms was equal for stages I and II together; in the chemotherapy arm stage I tumours were a little more frequent than in the surgery only arm: $n = 9$ (33%) versus $n = 5$ (17%) (Table 1).

Of the 27 patients allocated to receive four courses of FAMTX prior to surgery, 12 (44%) could not complete all four courses: 5 patients had to stop because of toxicity (2 patients had leucopenia, 1 patient had deterioration of WHO performance, 1 patient had diarrhoea, mucositis and vomiting grade ≥ 3 and 1 patient had dysphagia grade 3) and 7 patients because of PD (5 patients had local growth of the tumour, 1 patient developed bone metastases and 1 patient liver metastasis). 11 patients received haemopoietic growth factor.

The clinical response rates and resectability in patients completing all four courses and patients stopping earlier are summarised in Table 2. Of the 15 patients who had completed all four courses, 5 patients (33%) could not have a resection. Of the 12 patients stopping earlier, 2 patients had a palliative resection and another 2 patients could not have a resection.

In Table 3, overall toxicity is summarised over all courses as well as the maximal toxicity per patient. WHO grade 3 or 4 toxicity was seen most frequently as hair loss in 24 courses, vomiting in 19 courses and leucopenia in 15 courses. For the maximal toxicity per patient, hair loss, vomiting and leucopenia were the most frequent.

Postoperative mortality was seen in 2 patients in the FAMTX arm and in 1 patient in the surgery only arm. After a minimum of 12 months follow-up for the patients still alive, recurrence was seen in 5 patients in both treatment arms. Median survival was equal in both groups: 13.1 months versus 12.8 months for FAMTX + surgery and surgery only, respectively.

DISCUSSION

In this prospective, randomised trial, we compared four courses of pre-operative FAMTX chemotherapy followed by surgery with surgery alone for operable gastric adenocarcinoma. Of the 25 patients receiving pre-operative chemotherapy, in which clinical response was assessed, 32% had a clinical response (2 CRs and 6 PRs), while 36% (9/25) had PD during the courses, mainly locoregional. The overall clinical response rate in our trial is comparable with the lower results of the reported data in the literature [9, 13, 14, 17, 18]. However, the results in the literature are based on response rates in advanced gastric cancer cases. Therefore, we

Table 2. *Association between the number of courses given and response* (n = 25 *evaluated*) *and resectability* (n = 27)

	Total	< Four courses	Four courses
Response			
Complete response	2	1	1
Partial response	6	2	4
Stable disease	8	1	7
Progressive disease	9	7	2
Pre-operative resectability			
Curative	18	8	10
Palliative	2	2	0
No resection	7	2	5

Table 3. FAMTX toxicity

	Courses ($n = 87$)					Patients ($n = 27$)				
	WHO toxicity grades					Maximal WHO toxicity				
Toxicity	0	1	2	3	4	0	1	2	3	4
Haematological										
Leucopenia	20	17	29	11	4	1	3	7	5	2
Thrombopenia	66	4	2	0	1	14	1	1	0	1
Gastrointestinal										
Vomiting	39	20	8	18	1	8	6	5	7	1
Mucositis	65	15	4	2	1	14	7	3	2	1
Diarrhoea	74	8	1	2	2	17	5	1	2	2
Nephrotoxicity	84	1	0	0	0	26	1	0	0	0
Pulmonary	85	2	0	0	0	25	2	0	0	0
Skin	78	8	1	0	0	22	4	1	0	0
Hair loss	31	16	13	24	0	5	6	4	11	1
Infection	80	4	0	1	0	21	4	0	1	0
Cardiotoxicity	87	0	0	0	0	27	0	0	0	0
Neurotoxicity	86	1	0	0	0	26	1	0	0	0
Allergic	83	3	0	0	0	25	1	0	0	0
Other toxicity	53	17	13	2	1	11	6	7	2	1

expected the response rates to be higher in operable gastric cancer as could be expected from the results of Roelofs and colleagues [17] with a modified chemotherapy regimen (FEMTX-P instead of FAMTX); in this study the response rate of the primary tumour was higher than that of the metastases, suggesting that early stages would be more chemosensitive. In our study, not only was the response rate low, but also the rate of PD was unacceptably high. The most important finding, however, was that for the curative resectability an opposite effect was found to that expected: the curative resectability rate in the multimodality treatment arm was lower than in the surgery only arm.

Among the reasons for the very low accrual rate, disbelief in the concept of pre-operative chemotherapy for some clinicians was noted: scepticism about the efficacy of FAMTX made many clinicians hesitate about the trial, which implied delay of surgery. Moreover the extra costs to the participating hospitals, because chemotherapy would otherwise not be administered to this group of patients, was also a reason for not participating in this trial. This disappointing accrual rate was finally the argument for the DGCG to close the trial prematurely. Nevertheless, despite a limited number of 56 eligible patients, we can still learn from the available data. The analysis demonstrated that a 15% higher curative resection rate with pre-operative administration of FAMTX with operable gastric cancer is very unlikely according to our study. After 56 eligible patients over 2.5 years' intake, the difference (pre-operative FAMTX + surgery minus surgery only) in curative resectability rate was − 6% (95% confidence interval − 32%– + 19%). Downstaging for stages I + II did not occur.

Forty-four per cent of the patients could not complete the planned four courses due to PD and/or toxicity, while 7 patients (26%) in the multimodality treatment arm could not have a resection at all; 5 of these patients had completed all four planned courses. A total of 11 patients received haemopoietic growth factors.

FAMTX was recommended in 1992 to be a promising regimen to improve resectability in randomised trials [10, 14, 18, 20]. Our data suggest that FAMTX is not suitable for this purpose. After a follow-up of at least 12 months, there was also no difference in survival rates in both treatment arms.

However, the rationale of this first randomised trial studying the effect of pre-operative chemotherapy in operable gastric cancer is still relevant: surgical results are not satisfying, despite some hopeful reports of increased early detection [23] and increasing survival rates during the last decades [24]. There is also a possible survival advantage (albeit small, but statistically significant) with adjuvant chemotherapy with inferior chemotherapy regimens according to present knowledge [6, 7]. Recently, optimistic results were reported in locally advanced cancer using pre-operative chemotherapy with the combination of continuous i.v. 5-FU and bolus cisplatin [25], with FLEP therapy (5-FU, leucovorin, etoposide and cisplatinum [26], a modified FAMTX regimen [27], the combination of cisplatin, 5-FU and VP16 [16] and with PMUE (cisplatin, mitomycin, uracil and etoposide) [28]. Also, no effective regimens have been reported in locally advanced gastric cancer [15]. However, all of these studies stress the importance of pre-operative chemotherapy with a more effective regimen.

In this study, we could not demonstrate that the FAMTX regimen is suitable as neoadjuvant chemotherapy in operable gastric cancer. For future randomised trials, more active regimens such as ECF [15, 29] may be better. Therefore, the DGCG has decided to participate in the MRC trial using ECF.

1. Akoh JA, Sedgwick DM, Macintyre IM. Improving results in the treatment of gastric cancer: an 11 year audit. *Br J Surg* 1991, **78**, 349–351.
2. Breaux JR, Bringaze WL, Chappuis CW, *et al.* Adenocarcinoma of the stomach: a review of 35 years and 1710 cases. *World J Surg* 1990, **14**, 580–586.
3. Cady B, Rossi RL, Silverman ML, *et al.* Gastric adenocarcinoma. A disease in transition. *Arch Surg* 1989, **124**, 303–308.
4. Bonenkamp JJ, Songun I, Hermans J, *et al.* Randomized comparison of morbidity after D1 and D2 dissection for gastric cancer in 996 Dutch patients. *Lancet* 1995, **345**, 745–748.
5. Cuschieri A, Fayers P, Fielding J, *et al.* Postoperative morbidity and mortality after D1 and D2 resections for gastric cancer:

preliminary results of the MRC randomised controlled surgical trial. *Lancet* 1996, **347**, 995–999.
6. Hermans J, Bonenkamp JJ, Boon MC, *et al*. Adjuvant therapy after curative resection for gastric cancer: meta-analysis of randomized trials. *J Clin Oncol* 1993, **11**, 1441–1447.
7. Hermans J, Bonenkamp JJ. In reply. *J Clin Oncol* 1994, **12**, 879–880.
8. Ajani JA, Ota DM, Jessup M, *et al*. Resectable gastric carcinoma: an evaluation of preoperative and postoperative chemotherapy. *Cancer* 1991, **68**, 1501–1506.
9. Wilke H, Preusser P, Fink U, *et al*. Pre-operative chemotherapy in locally advanced and non-resectable gastric cancer. A phase II study with etoposide, doxorubicin and cisplatin. *J Clin Oncol* 1989, **7**, 1318–1326.
10. Kelsen D, Karpeh M, Schwartz G, *et al*. Neoadjuvant therapy of high-risk gastric cancer: a phase II trial of preoperative FAMTX and postoperative intraperitoneal fluorouracil-cisplatin plus intravenous fluorouracil. *J Clin Oncol* 1996, **14**(6), 1818–1828.
11. Kiyabu M, Leichman L, Chandrasoma P. Effects of preoperative chemotherapy on gastric adenocarcinomas: a morphologic study of 25 cases. *Cancer* 1992, **70**, 2239–2245.
12. Leichman L, Silberman H, Leichman CG, *et al*. Preoperative systemic chemotherapy followed by adjuvant postoperative intraperitoneal therapy for gastric cancer: a University of Southern California pilot program. *J Clin Oncol* 1993, **10**, 1933–1942.
13. Klein HO. Long-term results with FAMTX in advanced gastric cancer. *Anticancer Res* 1989, **9**, 1025–1026.
14. Wils JA, Klein HO, Wagener DJTh, *et al*. Sequential high-dose methotrexate and fluorouracil combined with doxorubicin—a step ahead in the treatment of advanced gastric cancer: a trial of the EORTC Group. *J Clin Oncol* 1991, **5**, 827–831.
15. Findlay M, Cunningham D, Norman A, *et al*. A phase II study in advanced gastro-esophageal cancer using epirubicin and cisplatin in combination with continuous infusion 5-fluorouracil (ECF). *Ann Oncol* 1994, **5**, 609–616.
16. Kang YK, Choi DW, Im YH. A phase III randomized comparison of neoadjuvant chemotherapy followed by surgery versus surgery for locally advanced stomach cancer. *Proc Am Soc Clin Oncol* 1997, **154** (abstr. 66).
17. Roelofs EJM, Wagener DJTh, Conroy Th, *et al*. Phase II study of sequential high-dose methotrexate (MTX) and 5-fluorouracil (F) alternated with epirubicin (E) and cisplatin (P) [FEMTX-P] in advanced gastric cancer. *Ann Oncol* 1993, **4**, 426–428.
18. Kelsen D, Atiq OT, Saltz L, *et al*. FAMTX versus etoposide, doxorubicin and cisplatin: a random assignment trial in gastric cancer. *J Clin Oncol* 1992, **10**, 541–548.
19. Preusser P, Wilke H, Achterrath W, *et al*. Phase II study with the combination etoposide, doxorubicin and cisplatin in advanced measurable gastric cancer. *J Clin Oncol* 1989, **7**, 1310–1317.
20. Muggia F. How to improve survival after diagnosis of gastric cancer? It's back to the drawing board. *J Clin Oncol* 1993, **11**, 1437–1438.
21. Sparano JA, Schwartz EL, Salva KM, *et al*. Phase II trial of etoposide, doxorubicin (adriamycin) and cisplatin (EAP regimen) in advanced gastric cancer. *Am J Clin Oncol* 1990, **13**, 374–378.
22. Leichman L, Berry B. Cisplatin therapy for adenocarcinoma of the stomach. *Semin Oncol* 1991, **18**(Suppl. 3), 25–33.
23. Sue-Ling HM, Johnston D, Martin IG, *et al*. Gastric cancer: a curable disease in Britain. *Br Med J* 1993, **307**, 591–596.
24. Hallissey MT, Allum WH, Jewkes AJ, *et al*. Early detection of gastric cancer. *Br Med J* 1990, **301**, 513–515.
25. Rougier Ph, Mahjoubi M, Lasser Ph, *et al*. Neoadjuvant chemotherapy in locally advanced gastric carcinoma—a phase II trial with combined continuous intravenous 5-fluorouracil and bolus cisplatinum. *Eur J Cancer* 1994, **30**, 1269–1275.
26. Nakajima T, Ota K, Ishihara S, *et al*. Combined intensive chemotherapy and radical surgery for incurable gastric cancer. *Ann Surg Oncol* 1997, **4**(3), 203–208.
27. Facchini G, Tortoriello A, Caponigro F, *et al*. Neoadjuvant chemotherapy in locally advanced gastric cancer: preliminary results of a phase III trial with a modified FAMTX combination. *Oncol Reports* 1995, **2**, 727–730.
28. Yonemura Y, Sawa T, Kinoshita K, *et al*. Neoadjuvant chemotherapy for high-grade advanced gastric cancer. *World J Surg* 1993, **17**, 256–262.
29. Webb A, Cunningham D, Scarffe JH, *et al*. Randomized trial comparing epirubicin, cisplatin, and fluorouracil versus fluorouracil, doxorubicin, and methotrexate in advanced esophagogastric cancer. *J Clin Oncol* 1997, **15**(1), 261–267.

APPENDIX
PARTICIPATING HOSPITALS AND ELIGIBLE PATIENTS (*n*) ENTERED

Zwolle, 15 patients (P. Klementschitsch, M. Oudkerk-Pool, M.A. Alleman, J.E. de Vries, M. van Marwijk Kooy); Roermond, 7 patients (R.J.A. Estourgie, J.A. Wils); Brunssum, 6 patients (J. van der Bijl, J. Wals); Leiden, 5 patients (K. Welvaart, H.J. Keizer); Harderwijk, 5 patients (R.B. Beck, P.J.C. Zoon); Den Haag, 3 patients (B. Knippenberg, H.P. Sleeboom); Zaandam, 2 patients (J.L.T. Oomen, A. van Bochove); Nijmegen, 2 patients (E.D.M. Bruggink, H.R. Oosten); Amsterdam, 3 patients (F. van coevorden, B.G. Taal, H.F.W. Hoitsma, K.J. Roozendaal); Roosendaal, 2 patients (H.W.P.M. Kemperman, D.J. de Gooyer); Arnhem, 2 patients (W.F. Eggink, J.J. Mol); Veldhoven, 2 patients (R. Roumen, W.M.M. Driessen); Rotterdam, 1 patient (H.J. Mud, W.F. Stiegelis) and Vlissingen, 1 patient (J.H. ten Thije, M. Beudeker).