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ORIGINAL REPORT

Neoadjuvant Chemotherapy Compared With Surgery Alone for Locally Advanced Cancer of the Stomach and Cardia: European Organisation for Research and Treatment of Cancer Randomized Trial 40954

Christoph Schuhmacher, Stephan Gretschel, Florian Lordick, Peter Reichardt, Werner Hohenberger, Claus F. Eisenberger, Cornelie Haag, Murielle E. Mauer, Baktiar Hasan, John Welch, Katja Ott, Arnulf Hoelscher, Paul M. Schneider, Wolf Bechstein, Hans Wilke, Manfred P. Lutz, Bernard Nordlinger, Eric Van Cutsem, Jörg R. Siewert, and Peter M. Schlag

From the Klinikum rechts der Isar, Chirurgische Klinik der TU München, München; Charite, Universitätsmedizin Berlin, Berlin; Klinikum Braunschweig, Hannover Medical School; Klinik für Innere Medizin III, HELIOS Klinikum Bad Saarow, Bad Saarow; Universitätsklinik Erlangen, Erlangen; Heinrich-Heine Universitätsklinik Düsseldorf, Düsseldorf; Universitätsklinikum Carl Gustav Carus, Dresden; Universitätsklinikum Heidelberg, Chirurgische Klinik; Universitätskliniken zu Köln, Köln; Johann Wolfgang Goethe University, Frankfurt; Kliniken Essen-Mitte, Essen; Caritasklinik St Theresia, Saarbrücken, Germany; European Organisation for Research and Treatment of Cancer (EORTC), EORTC Headquarters, Brussels; University Hospital Gasthuisberg, Leuven, Belgium; and the Centre Hospitalier Universitaire Ambroise Paré, Boulogne, France.

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Corresponding author: Christoph Schuhmacher, MD, Klinikum rechts der Isar, Chirurgische Klinik der TU München, Ismaningerstr. 22, D-81675 München, Germany; e-mail: schuhmacher@chir.med.tu-muenchen.de.

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ABSTRACT

Purpose
Patients with locally advanced gastric cancer benefit from combined pre- and postoperative chemotherapy, although fewer than 50% could receive postoperative chemotherapy. We examined the value of purely preoperative chemotherapy in a phase III trial with strict preoperative staging and surgical resection guidelines.

Patients and Methods
Patients with locally advanced adenocarcinoma of the stomach or esophagogastric junction (AEG II and III) were randomly assigned to preoperative chemotherapy followed by surgery or to surgery alone. To detect with 80% power an improvement in median survival from 17 months with surgery alone to 24 months with neoadjuvant, 282 events were required.

Results
This trial was stopped for poor accrual after 144 patients were randomly assigned (72:72); 52.8% patients had tumors located in the proximal third of the stomach, including AEG type II and III. The International Union Against Cancer R0 resection rate was 81.9% after neoadjuvant chemotherapy as compared with 66.7% with surgery alone ($P = .036$). The surgery-only group had more lymph node metastases than the neoadjuvant group (76.5% *v* 61.4%; $P = .018$). Postoperative complications were more frequent in the neoadjuvant arm (27.1% *v* 16.2%; $P = .09$). After a median follow-up of 4.4 years and 67 deaths, a survival benefit could not be shown (hazard ratio, 0.84; 95% CI, 0.52 to 1.35; $P = .466$).

Conclusion
This trial showed a significantly increased R0 resection rate but failed to demonstrate a survival benefit. Possible explanations are low statistical power, a high rate of proximal gastric cancer including AEG and/or a better outcome than expected after radical surgery alone due to the high quality of surgery with resections of regional lymph nodes outside the perigastric area (celiac trunc, hepatic ligament, lymph node at a. lienalis; D2).

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INTRODUCTION

Gastric cancer is an aggressive disease with poor prognosis,[1,2] even if it is completely resectable without distant metastasis. About two thirds of patients with gastric cancer have locally advanced disease at diagnosis.[3] In Western countries, the R0 resection (macroscopic and microscopic complete resection according to the International Union Against Cancer [UICC]) rate with surgery alone in this patient population is unfavorable (41.1%) and the median overall survival barely reaches 16.4 months.[4]

Numerous randomized clinical trials have compared surgery alone with adjuvant chemotherapy, but definitive evidence was lacking. A recently published meta-analysis of 17 randomized controlled trials of adjuvant chemotherapy in gastric cancer demonstrated a statistically significant overall (hazard ratio [HR], 0.82; 95% CI, 0.76 to 0.90; $P < .001$) and disease-free survival (HR, 0.82; 95% CI, 0.75 to 0.90; $P < .001$) benefit for patients treated with fluorouracil-based adjuvant chemotherapy versus surgery alone.[5] The 503-patient Medical Research Council Adjuvant Gastric Infusional Chemotherapy

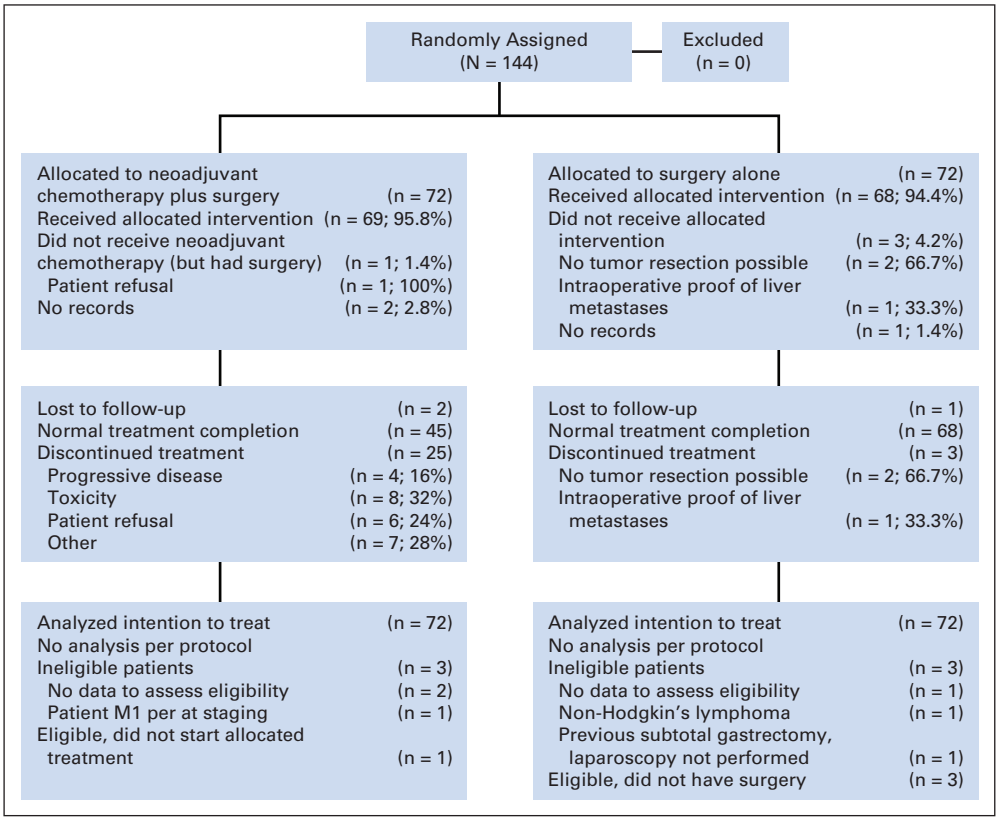

Fig 1. CONSORT diagram. M, Metastatic stage of TNM.

(MAGIC) trial evaluated the effect of a combination of pre- and postoperative chemotherapy compared with surgery alone in patients with resectable adenocarcinoma of the stomach or lower esophagus. Both the overall (HR, 0.75; 95% CI, 0.60 to 0.93; $P = .009$) and progression-free survival (HR, 0.66; 95% CI, 0.53 to 0.81; $P < .0019$) were significantly improved in the chemotherapy-containing arm. Similarly, 5-year survival favored that arm (36% *v* 23%).[6] Likewise, the French Action Clinique Coordonnées en Cancérologie Digestive (ACCORD-07) study seems to confirm these results but has not yet been fully published.[7]

However, it is difficult to assess the relative contribution of the pre- versus postoperative component with respect to survival benefit for both the MAGIC and ACCORD-07 trials. Given the modest efficacy of adjuvant chemotherapy in randomized controlled trials performed in the Western hemisphere, and the infrequency with which chemotherapy can be administered postoperatively, a purely preoperative chemotherapy regimen is an attractive option. We therefore designed this trial parallel to the MAGIC and ACCORD-07 trial using the combination of cisplatinum, folinic acid, and infusional fluorouracil previously tested in a prospective, randomized European Organisation for Research and Treatment of Cancer phase II study of patients with advanced gastric cancer.[8]

In another phase II trial in the same patient population, staging by endoscopic ultrasonography (EUS) and extended diagnostic laparoscopy before neoadjuvant therapy resulted in the exclusion of up to 30% of patients due to the detection of peritoneal carcinosis or occult visceral metastases.[9] We therefore used this approach to better select truly resectable patients.

PATIENTS AND METHODS

Study Design and Inclusion Criteria

Patients with locally advanced (UICC stages III and IV [cM0]) adenocarcinoma of the stomach including Siewert I and II tumors of the esophagogastric junction[10] were randomly assigned between preoperative chemotherapy followed by surgery or surgery alone (Fig 1).

Study inclusion criteria were: age 18 to 70 years (amended to 75 years in 2003); WHO performance status 0 to 1; histologically proven adenocarcinoma of the stomach or the esophagogastric junction (AEG II and III); T3 or T4 tumor based on endoscopic ultrasound; no evidence of distant metastases or disease considered nonresectable by EUS, computed tomography (CT) and extended diagnostic laparoscopy; no prior gastric surgery; no previous chemotherapy or radiotherapy; no uncontrolled infectious or cardiac disease; adequate renal function; and no previous or other current cancer except for curatively treated nonmelanoma skin cancer or carcinoma in situ of the cervix. The protocol was reviewed by the European Organisation for Research and Treatment of Cancer protocol review committee and approved by the ethics committees of participating institutions. All patients provided written informed consent.

Staging

In addition to staging by CT and chest x-ray, a general laparoscopic survey of the abdominal cavity and lesser sac with laparoscopic ultrasound of the liver was performed through three abdominal port sites before study inclusion.[11] No histologic confirmation of an infiltration of the serosa was performed during the diagnostic laparoscopy to avoid dissemination from the primary tumor, although suspect distant visceral or parietal peritoneal lesions were excised and histologically examined.

Treatment

Chemotherapy started within 7 days of random assignment and consisted of two 48-day cycles of cisplatin 50 mg/m^2 intravenous (IV) over 1 hour with hydration on days 1, 15, and 29, followed by d-L-folinic acid 500 mg/m^2 IV over 2 hours and fluorouracil 2,000 mg/m^2 continuous IV infusion over 24 hours on days 1, 8, 15, 22, 29, and 36.[12]

Restaging by endoscopy and CT scan was performed in the last 3 days of the first cycle. In the absence of progression, deterioration of performance status above WHO grade 1, unacceptable toxicity, or patient refusal, a second cycle of chemotherapy was administered. Dose modifications were defined for patients with toxicities (other than alopecia and vomiting) higher than grade 2.

Resection of the gastric tumor was performed within 14 days after random assignment in patients randomly assigned to surgery alone and within 4 weeks after the last day of chemotherapy in patients receiving chemotherapy. Resection consisted of a subtotal or gastrectomy with extension depending on the location of the primary tumor with either a D1 lymphadenectomy (for perigastric nodes at lesser and greater curvature; seven patients) or, preferably, a D2 lymphadenctomy (for regional lymph nodes outside the perigastric area; 130 patients).[13] The resection could be extended to other organs or locations to achieve complete removal of the primary tumor or suspicious lymph nodes. Reconstruction of the gastrointestinal passage was performed according to local standards. The extent of resection was documented (subtotal-, total-, or extended gastrectomy with D1 or D2 lymphadenectomy, extension to neighboring organs) including estimation of the dissection margins, which were later cross-checked with histopathology.

Table 1. Baseline Demographic and Patient Characteristics

Demographic and Characteristic	Treatment: Chemotherapy and Surgery (n = 72) No.	%	Treatment: Surgery Alone (n = 72) No.	%	Total (N = 144) No.	%
Age, years						
Median	56		58		57	
Range	38-70		26-69		26-70	
Sex						
Male	50	69.4	50	69.4	100	69.4
Female	22	30.6	22	30.6	44	30.6
WHO performance status						
0	48	66.7	55	76.4	103	71.5
1	24	33.3	17	23.6	41	28.5
Clinical T stage						
T3	68	94.4	67	93.1	135	93.8
T4	4	5.6	5	6.9	9	6.3
Histologic subtype						
Intestinal	33	45.8	33	45.8	66	45.8
Nonintestinal	39	54.2	39	54.2	78	54.2
Tumor localization						
Upper third + cardia II, III	37	51.4	39	54.2	76	52.8
Middle third	20	27.8	18	25.0	38	26.4
Lower third	15	20.8	15	20.8	30	20.8
Laparoscopy						
Complete	61	84.7	60	83.3	121	84.0
Incomplete	8	11.1	10	13.9	18	12.5
Not done	0	0.0	1	1.4	1	0.7
Missing	3*	4.2	1	1.4	4	2.8
T category across different staging methods						
T3	62	86.1	64	88.9	126	87.5
T4	8	11.1	7	9.7	15	10.4
Missing	2	2.8	1	1.4	3	2.1
N category across different staging methods						
N0	4	5.6	6	8.3	10	6.9
N1	48	66.7	44	61.1	92	63.9
N2	6	8.3	5	6.9	11	7.6
N3	1	1.4	1	1.4	2	1.4
N positive*†	11	15.3	15	20.8	26	18.1
Missing	2	2.8	1	1.4	3	2.1
M category across different staging methods						
M0	66	91.7	69	95.8	135	93.8
M1	1	1.4	1	1.4	2‡	1.4
Mx	3	4.2	1	1.4	4	2.8
Missing	2	2.8	1	1.4	3	2.1

*Laparoscopy done for one patient but no specification if complete or incomplete.
†N positives are patients for whom the number of positive nodes is unknown (the classification may be either N1 or N2 or N3).
‡One patient was ineligible as a result of metastases; one patient had lymph node metastases.

Assessment and Follow-Up

Specimens were classified according to the fifth edition UICC TNM system[14] with documentation of tumor size, number of dissected and metastatic lymph nodes, and presence of lymphangiosis carcinomatosa.

Assessment of response to neoadjuvant therapy was based on reduction of primary tumor size measured by endoscopy (EUS was not mandatory due to the known difficulties in assessing response using this method) and CT scan. Complete disappearance of lesions, as a subjective visual finding at endoscopy, and measurement of organ wall thickening in CT scans was considered as complete clinical response. A greater than 50% tumor size reduction compared with initial findings was defined as a partial response. New lesions or more than a 25% increase in primary tumor size were considered progressive disease.

Toxicity and adverse events were reported using the National Cancer Institute Common Toxicity Criteria grading version 2.0.[15] Intraoperative and postoperative complications and corresponding interventions (eg, reoperation, conservative treatment) were documented.

Patients were followed by CT scans at 3, 6, 9, 12, 18, and 24 months after operation and yearly thereafter. Other investigations at each visit included a medical history, toxicity assessment, physical examination, endoscopy, blood count, blood chemistry, chest x-ray, optional abdominal ultrasound, and, if indicated, bone scan. In the event of unclear radiology findings, a biopsy was recommended.

End Points and Sample Size

The primary end point of this trial was overall survival. It was designed to detect an improvement in median overall survival from 17 months in the surgery alone arm to 24 months in the neoadjuvant arm (HR, 0.708) with a power of 80% at the two-sided significance level of 4%. To observe the required 282 events in the projected 4 years of accrual and 2 years of follow-up, it was estimated that 180 patients would be required per arm. Secondary end points were the R0 resection rate (according to the UICC), progression-free survival, toxicity during preoperative chemotherapy, postoperative morbidity, and effect of chemotherapy on the primary tumor and lymph node metastasis.

Statistical Analysis

Statistical analysis was performed on all randomly assigned patients on an intent-to-treat basis. Overall survival and progression-free survival were calculated from random assignment. Survival curves were estimated by the Kaplan-Meier technique. Durations of survival were compared between the arms using a two-sided log-rank test. To adjust for confounding factors, the Cox proportional hazard model with retrospective stratification was used. Stratification factors included institution, primary tumor extension (cT3 or cT4), tumor location (upper third of the stomach including the cardia *v* middle and lower third), sex, and histologic subtype (intestinal *v* nonintestinal). All data analyses were performed using Statistical Analysis Software version 9 (SAS Institute, Cary, NC).

Table 2. Type of Surgery

	Treatment					
	Chemotherapy and Surgery (n = 70)		Surgery Alone (n = 68)		Total (N = 138)	
Surgery	No.	%	No.	%	No.	%
Gastrectomy						
With D2 lymphadenectomy	67	95.7	63	92.6	130	94.2
With limited lymphadenectomy D1	2	2.9	5	7.4	7	5.1
Missing	1	1.4	0	0.0	1	0.7
Additional transhiatal resection						
No	38	54.3	33	48.5	71	51.4
Yes	31	44.3	35	51.5	66	47.8
Missing	1	1.4	0	0.0	1	0.7
Additional hepatoduodenal						
No	49	70.0	46	67.6	95	68.8
Yes	20	28.6	22	32.4	42	30.4
Missing	1	1.4	0	0.0	1	0.7
Subtotal distal resection						
No	68	97.1	66	97.1	134	97.1
Yes	1	1.4	2	2.9	3	2.2
Missing	1	1.4	0	0.0	1	0.7
Multivisceral resection						
No	63	90.0	56	82.4	119	86.2
Yes	6	8.6	12	17.6	18	13.0
Missing	1	1.4	0	0.0	1	0.7
Metastasis resection						
No	68	97.1	61	89.7	129	93.5
Yes	1	1.4	7	10.3	8	5.8
Missing	1	1.4	0	0.0	1	0.7
Type of reconstruction						
Roux-en-Y	48	68.6	50	73.5	98	71.0
Pouch	17	24.3	12	17.6	29	21.0
Billroth-II	0	0.0	2	2.9	2	1.4
Other*	4	5.7	3	4.4	7	5.1
Not performed	0	0.0	1	1.5	1	0.7
Missing	1	1.4	0	0.0	1	0.7

*Other method or combination of methods.

RESULTS

Patients

Between July 1999 and February 2004, 144 patients were recruited. The study was prematurely closed for poor accrual after reaching 40% of its goal. At the time of analysis in June 2007, 67 patients had died. Due to this low number of deaths as compared with the 282 needed, the power for the formal statistical analysis was limited.

Apart from a slight imbalance in WHO performance status (66.7% performance status 0 in the chemotherapy plus surgery arm *v* 76.4% in the surgery alone arm), baseline characteristics were evenly distributed (Table 1). Respectively, two and one patients were lost to follow-up immediately after random assignment in the neoadjuvant arm and in the surgery alone arm. In addition, one and two patients were found not to meet eligibility criteria. Overall, three patients per arm were considered ineligible.

Treatment

In the neoadjuvant arm, 69 (95.8%) of 72 patients received both modalities. One patient refused chemotherapy but underwent surgery. Among the 69 patients who received chemotherapy, 19 discontinued protocol treatment in the first cycle and five more during the second cycle. Thus, 45 patients received two cycles of chemotherapy. Major reasons for protocol discontinuation were toxicity (n = 8; 11.6%), patient refusal (n = 5; 7.2%), progressive disease (n = 4; 5.8%), and other (n = 7; 10.1%) including worsening of symptoms without evidence of progression (n = 2), noncompliance due distance to treatment center (n = 1), local investigator judgment (n = 3), and an infarction of the pons cerebri assumed to be unrelated to chemotherapy. Eight patients were withdrawn from the study due to toxicity: n = 2 for renal toxicity (maximum grade 2), n = 1 for cardiac toxicity grade 3, n = 4 for nausea (maximum grade 3) and vomiting (maximum grade 3) and n = 1 for neutropenia grade 2. In addition, dose was reduced for toxicity but did not lead to protocol discontinuation for n = 6 patients (8.7%).

In the surgery alone arm, 68 (94.4%) of 72 patients were resected. Two did not undergo resection because of irresectable tumors. Liver metastasis was discovered intraoperatively in one patient, and data are missing for the other patient.

In the neoadjuvant arm, data are missing for two patients, but the remainder (70 of 72) underwent resection. Sixty-seven patients (95.7%) underwent gastrectomy versus 63 patients (92.6%) in the surgery alone arm (Table 2). Based on the proximal localization of the primary tumor, surgery was extended to the distal esophagus in 39 patients (55.7%) in the neoadjuvant arm compared with 41 patients (60.3%) in the surgery alone arm.

The total number of postoperative complications was higher in the neoadjuvant (n = 19; 27.1%) than surgery alone arm (n = 11; 16.2%, $P = .09$; Table 3). There were no fatal complications documented during surgery. Injury of a major blood vessel occurred in three patients (4.3%) in the neoadjuvant arm versus one (1.5%) in the surgery alone arm. In the surgery alone arm, one splenectomy was required to achieve hemostasis. The most common other complications were pneumothorax (n = 3), pleural effusion (n = 2), and pancreatitis (n = 2). Three deaths were due to postoperative complications in the neoadjuvant treatment arm (sepsis in two patients and one cardiac arrest after pulmonary embolism) and one in the surgery alone arm (sepsis).

Outcome

Of 69 patients who received neoadjuvant chemotherapy, a complete clinical response was seen in four (5.8%) and a partial response in 21 (30.4%) yielding an overall response rate of 36.2% (95% CI, 25.0% to 48.7%). Postoperative tumor size tended to be smaller in the neoadjuvant arm (Table 4). In that arm, 65.7% of tumors were categorized as pT0/1/2 compared with 50% in the surgery alone group. Five

Table 3. Postoperative Complications

Postoperative Complication	Treatment				Total (N = 138)	
	Chemotherapy and Surgery (n = 70)		Surgery Alone (n = 68)			
	No.	%	No.	%	No.	%
Bleeding	3	4.3	1	1.5	4	2.9
Transfusion	10	14.3	4	5.9	14	10.1
Anastomotic insufficiency	3	4.3	2	2.9	5	3.6
Duodenal stump leakage	1	1.4	0	0.0	1	0.7
Peritonitis	2	2.9	1	1.5	3	2.2
Fistula	3	4.3	5	7.4	8	5.8
Septicemia	5	7.1	2	2.9	7	5.1
Retention	0	0.0	1	1.5	1	0.7
Wound infection	2	2.9	1	1.5	3	2.2
Abscess	4	5.7	4	5.9	8	5.8
Intestinal occlusion	1	1.4	1	1.5	2	1.4
Other postoperative complication	11	15.7	4	5.9	15	10.9
Death resulting from postoperative complications	3	4.3	1	1.5	4	2.9
Any postoperative complication*	19	27.1	11	16.2	30†	21.7

*No. of patients with at least one postoperative complication.
†Some patients experienced more than one postoperative complication.

Table 4. Pathology Report

Pathology Report	Treatment: Chemotherapy and Surgery (n = 70) No.	%	Treatment: Surgery Alone (n = 68) No.	%	Total (N = 138) No.	%
Resection margin*						
R0	59	84.3	49†	72.1	108	78.3
R1	10	14.3	17	25.0	27	19.6
R2	1	1.4	0	0.0	1	0.7
Unknown	0	0.0	1	1.5	1	0.7
Missing	0	0.0	1	1.5	1	0.7
Tumor localization: upper third						
No	28	40.0	25	36.8	53	38.4
Yes	42	60.0	42	61.8	84	60.9
Missing	0	0.0	1	1.5	1	0.7
Tumor thickness, mm						
Median	11.0		13.0		12.0	
Range	0.0-100.0		1.0-130.0		0.0-130.0	
No. observed	51		55		106	
Tumor length, mm						
Median	50.0		57.5		55.0	
Range	0.0-160.0		10.0-170.0		0.0-170.0	
No. observed	66		64		130	
Tumor width, mm						
Median	40.0		45.0		45.0	
Range	0.0-150.0		10.0-170.0		0.0-170.0	
No. observed	65		62		127	
Primary tumor classification						
T0	5	7.1	0	0.0	5	3.6
T1	5	7.1	4	5.9	9	6.5
T2	36	51.4	30	44.1	66	47.8
T3	20	28.6	24	35.3	44	31.9
T4	4	5.7	7	10.3	11	8.0
Unknown	0	0.0	2	2.9	2	1.4
Missing	0	0.0	1	1.5	1	0.7
Lymph node classification						
N0	27	38.6	13	19.1	40	29.0
N1	29	41.4	22	32.4	51	37.0
N2	9	12.9	13	19.1	22	15.9
N3	5	7.1	17	25.0	22	15.9
Unknown	0	0.0	2	2.9	2	1.4
Missing	0	0.0	1	1.5	1	0.7
Distant mets classification						
M0	45	64.3	36	52.9	81	58.7
M1	9	12.9	11	16.2	20	14.5
Mx	16	22.9	19	27.9	35	25.4
Unknown	0	0.0	1	1.5	1	0.7
Missing	0	0.0	1	1.5	1	0.7

Abbreviation: mets, metastasis.
*Seven patients were assessed R2 by the surgeon; specimens for five of these patients were submitted to the pathologist; among these five patients, one was assessed R2 by the pathologist, three R1, and one R0.
†Only 48 patients in the surgery-alone arm were R0 as assessed by the surgeon and confirmed by the pathologist.

patients (7.1%) had a complete pathologic response after neoadjuvant therapy.

By intraoperative assessment, complete resection was achieved in 87.5% of all randomly assigned patients in each arm (63 of 72 per arm). The R0 resection rate as assessed by the pathologist was 81.9% in the neoadjuvant chemotherapy arm (n = 59) as compared with 66.7% in the surgery alone arm (n = 48; Table 5). This difference reached statistical significance (Z-test, $P = .036$). With a 95% CI, one can estimate the absolute benefit between +1.2% and +29.3%.

Even though the median number of dissected lymph nodes was similar in both arms, (31 with chemotherapy; range, 5 to 80, *v* 33 with surgery alone, range 10 to 88), lymph node metastases were more frequent in patients who had surgery alone, 52 patients (76.5%) versus 43 (61.4%; $P = .018$). The median number of positive lymph nodes was one (range, 0 to 32) in the chemotherapy group versus six (range, 0 to 38) in the surgery alone group. Lymphatic invasion was absent in 41 patients (58.6%) in the neoadjuvant versus 23 (33.8%) in the surgery alone group ($P = .01$).

Table 5. Resection Rate

Resection Rate	Treatment: Chemotherapy and Surgery (n = 72) No.	%	Surgery Alone (n = 72) No.	%	Total (N = 144) No.	%
Resection margin						
R0	59	81.9	48	66.7	107	74.3
R1	9	12.5	15	20.8	24	16.7
R2	2	2.8	5	6.9	7	4.9
No surgery	2	2.8	4	5.6	6	4.2

The median follow-up for all patients was 4.4 years: 4.7 years in the neoadjuvant arm and 4.1 year in the surgery only arm. This difference was not statistically significant ($P = .637$). There were 32 deaths in the neoadjuvant arm: 24 due to progressive disease, three due to postoperative complications, four due to other causes, and one due to unknown cause versus 35 deaths in the surgery alone arm: 33 due to progressive disease, one due to postoperative complications and one due to an unknown cause (Fig 2A). Because the Kaplan-Meier curves barely cross the 50th percentile, the median survival times in both arms could not be reliably estimated. The estimated median survival was 64.62 months (95% CI, 42.41 to not available [NA]) in the neoadjuvant arm versus 52.53 months (95% CI, 31.70 to NA) in the surgery alone arm. Based on the 67 observed events, the power for the primary analysis was 25%. The HR for comparing chemotherapy and surgery versus surgery alone for overall survival was 0.84 (95% CI, 0.52 to 1.35; $P = .466$). Results were similar when adjusted for the stratification factors: tumor location, sex, and histologic subtype (adjusted $P = .43$). The survival rates at 2 years were, respectively, 72.7% (95% CI, 60.7% to 81.7%) and 69.9% (95% CI, 57.7% to 79.2%) in the neoadjuvant and surgery-only arms.

Progression-free survival analysis was based on 44 events observed in the surgery alone arm versus 40 in the neoadjuvant arm (Fig 2B). The HR comparing chemotherapy and surgery versus surgery alone was 0.7 6 (95% CI, 0.49 to 1.16; $P = .20$).

DISCUSSION

While a number of important findings significantly favored the neoadjuvant approach: higher complete resection rate, smaller primary tumor size, less lymph node metastases, and less frequent lymphangiosis carcinomatosa as compared with surgery alone, this study did not demonstrate a statistically significant survival benefit for neoadjuvant therapy in locally advanced gastric cancer. The low number of events in both arms due to early termination of accrual and also attributable to better than expected surgical outcomes resulted in a very low power to demonstrate the targeted benefit of a HR of 0.708. This trial is hampered by the inadequate statistical power to detect a potential survival difference, and by the real possibility that preoperative chemotherapy does not have a beneficial impact on patients treated in this trial.

Besides the low power, several differences with the MAGIC trial may have contributed to this negative trial outcome. In the MAGIC trial, D2 lymphadenectomies were performed in only 43% of cases, versus more than 92% in both arms of this trial. More extensive lymphadenectomy may marginalize the contribution of neoadjuvant chemotherapy, as a more complete primary resection is performed. In addition, the rate of completion of neoadjuvant therapy was higher in MAGIC than this study (86% *v* 65%), and MAGIC included earlier tumor categories. The higher rates of postoperative complications may also have contributed to impaired overall survival in this study.

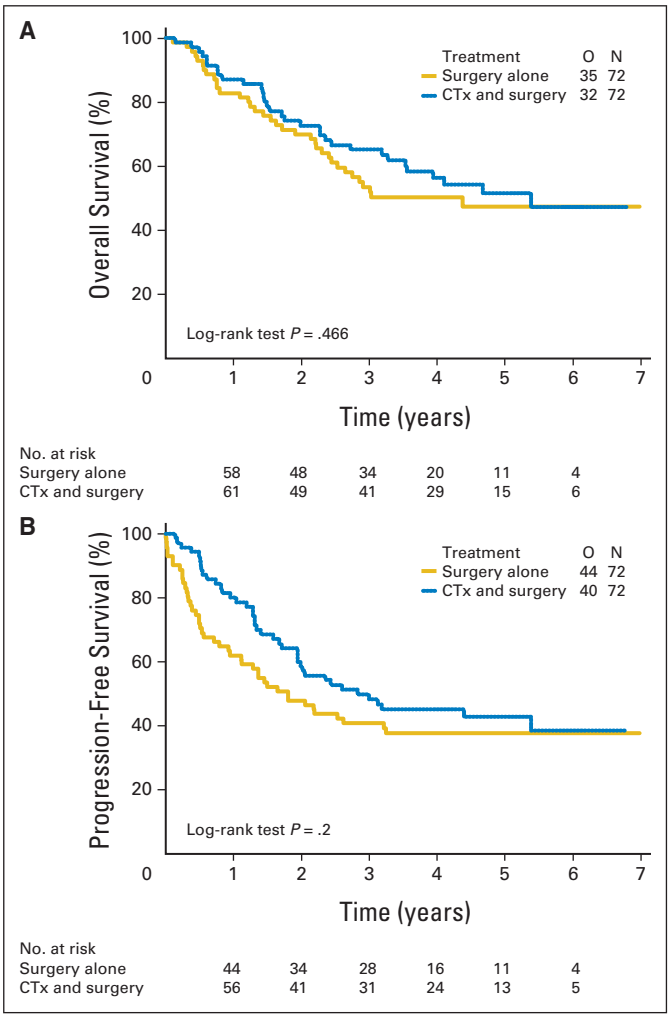

Fig 2. (A) Overall survival and (B) progression-free survival. CTx, chemotherapy; O, events (deaths) observed; N, overall number.

Importantly, the prognostic benefit of 43% postoperative adjuvant chemotherapy delivered in the MAGIC trial is unclear.

Another factor that could have contributed is the high percentage of patients with proximal tumors (52.8%) in this study. Even in the positive OE2 trial, the higher resection rate translated into a rather limited benefit of 6%, from 17.1% to 23.0% in the 5-year survival rate.[16]

The superior surgical outcome in our trial as compared with the other trials may be attributed at least in part to systematic preoperative overstaging. Despite the use of meticulous staging procedures including EUS, CT scan, and extended diagnostic laparoscopy intended to limit enrollment to cT3-4 tumors, a large proportion of patients in both arms were found to be pT2 without lymph node involvement at the time of surgery. This poor correlation might be attenuated by the high percentage of patients with proximal tumors (52.8%) in this study. In this location, fatty tissue rather than serosa covers the gastric muscle layer. Therefore, tumors located in the proximal third are classified as cT3 in EUS pretherapeutically, but are ultimately categorized as pT2. The prognosis of pT2 tumors in the proximal third is similar to pT3 tumors in the rest of the stomach.

The cisplatin, leucovorin, and fluorouracil regimen has been widely used in metastatic gastric cancer[12,17-18] and has shown promising activity in a multicenter randomized phase II study.[19] With 3 months of neoadjuvant therapy, the response rate to cisplatin, leucovorin, and fluorouracil was good (35.2% with 95% CI of 23.7% to 45.7%), but the rate of reduced or incomplete chemotherapy cycles was notable, most often due to patient wish, progression of disease, doctor's decision (24.1%), or measurable toxicity (11%). This contradicts our previous trial in metastatic gastric cancer, where 90% of the chemotherapy cycles were given without any dose reduction. We speculate that acceptance of chemotherapy may be reduced in the neoadjuvant setting. Other less toxic but similarly active oxaliplatin-based regimens might be better suited for this patient population.[20]

In designing a future trial, investigators may incorporate lessons learned in this trial: stage as accurately as possible including laparoscopy and adequate D2-lymph node dissection; and expect overstaging in the endosonographic evalution of proximal tumors. A solution is to include all categories more advanced than cT1 as previously reported by the MAGIC[6] and other trials.[21,22] This approach is pragmatic because the discrimination of early gastric cancer seems to be more reliable than the discrimination within the categories cT2 or cT3 by endoscopic ultrasound. In addition, pT2 tumors have already a high likelihood of lymphatic tumor dissemination, which justifies their inclusion into a worse prognostic risk group. Investigators should also anticipate better surgical outcome, particularly at high volume centers.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Christoph Schuhmacher, Stephan Gretschel, Katja Ott, Manfred P. Lutz, Bernard Nordlinger, Eric Van Cutsem, Peter M. Schlag
Administrative support: Stephan Gretschel, Bernard Nordlinger
Provision of study materials or patients: Christoph Schuhmacher, Stephan Gretschel, Florian Lordick, Peter Reichardt, Werner Hohenberger, Claus F. Eisenberger, Cornelie Haag, Baktiar Hasan, Katja Ott, Arnulf Hoelscher, Paul M. Schneider, Wolf Bechstein, Hans Wilke, Jörg R. Siewert, Peter M. Schlag
Collection and assembly of data: Stephan Gretschel, Florian Lordick, Peter Reichardt, Werner Hohenberger, Claus F. Eisenberger, Cornelie Haag, Baktiar Hasan, Katja Ott, Arnulf Hoelscher, Wolf Bechstein, Hans Wilke, Manfred P. Lutz, Jörg R. Siewert, Peter M. Schlag
Data analysis and interpretation: Christoph Schuhmacher, Stephan Gretschel, Florian Lordick, Peter Reichardt, Werner Hohenberger, Claus F. Eisenberger, Cornelie Haag, Murielle E. Mauer, Baktiar Hasan, John Welch, Katja Ott, Wolf Bechstein, Hans Wilke, Manfred P. Lutz, Eric Van Cutsem, Jörg R. Siewert, Peter M. Schlag
Manuscript writing: All authors
Final approval of manuscript: All authors

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