Adjuvant Chemoradiotherapy in Patients With Stage III or IV Radically Resected Gastric Cancer

A Pilot Study

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Background: Adjuvant chemoradiotherapy does not represent the standard of care in patients with resected high-risk gastric cancer; however, results from phase 2 and randomized trials suggest improvement in overall survival. We assessed the feasibility and toxic effects of chemoradiotherapy as adjuvant treatment in locally advanced gastric cancer.

Design: Pilot study.

Setting: University hospital.

Patients: Twenty-nine patients with T4N+ or any TN23 gastric cancer previously treated with potentially curative surgery were enrolled. All of the patients received combined adjuvant chemotherapy with FOLFOX-4 (ie, a combination of folinic acid [leucovorin], fluorouracil, and oxaliplatin [Eloxatin]) for 8 cycles and concomitant radiotherapy (45 Gy in 25 daily fractions over 5 weeks). Radiotherapy was begun after the first 2 cycles of FOLFOX-4, which was reduced by 25% during the period of concomitant radiotherapy.

Main Outcome Measures: Treatment toxic effects according to the National Cancer Institute–Common Toxicity Criteria classification, overall and disease-free survival rates, and identification of prognostic indicators.

Results: All of the patients completed treatment. Severe hematologic and gastrointestinal toxic effects occurred in 10% and 33%, respectively. No acute hepatic or renal toxic effects were observed; 1 patient experienced severe neurotoxicity. Disease-free and overall survival rates at 1, 2, and 3 years were 79%, 35%, and 35% and 85%, 62.6%, and 50.1%, respectively, and were shown to be substantially better than those observed in untreated patients. Long-term outcome was related to TNM stage, basal serum tumor marker level, and, particularly, lymph node ratio.

Conclusion: A multimodal approach with FOLFOX-4 and radiotherapy is feasible and effective for the treatment of patients with resected high-risk gastric cancer.

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WORLDWIDE, GASTRIC cancer is the fifth most common malignancy and the second leading cause of cancer death, with significant geographic variation.[1,2] Complete removal of macroscopic and microscopic tumor masses with regional lymph nodes (LNs) (so-called R0 surgical resection) represents the treatment of choice in localized, nonmetastatic gastric cancer.[3]

See Invited Critique at end of article

More than 50% of patients will experience locoregional recurrence after receiving potentially curative resection. This evidence supports the need for optimal surgery and evaluation of complementary strategies aimed at decreasing local relapse and distant metastases. Although a recent meta-analysis[4] including 14 randomized controlled trials did not demonstrate that extended lymphadenectomy offered specific advantages for gastric cancer, D2 lymphadenectomy seemed to improve overall (OS) and disease-free (DFS) survival rates, and it is the standard of care in Eastern and high-volume Western medical centers.[5,6] However, even after adequate surgery, recurrence and metastatic spread frequently occur, warranting the need for integrated treatments.[7]

The role of chemotherapy (CT) and radiotherapy (RT) as adjuvant treatments is controversial. Based on the results of the MAGIC (Medical Research Council Adjuvant Gastric Infusional Chemotherapy) trial,[8] perioperative chemotherapy is the more frequently used approach for resectable gastric cancer in Europe. On the contrary, postoperative fluorouracil-based CT-RT is the recommended standard of care for pT3 and N+ gastric cancers in the United States,[9] and several phase 2 studies exploring substitution of bolus fluorouracil with the better-

Table 1. Univariate Analysis Related to Overall Survival in 29 Patients With Gastric Cancer Treated With Curative Surgery and Postoperative Adjuvant Chemoradiotherapy

	Patients, No.	Patients Who Died, No.	3-y Survival, %	Hazard Ratio (95% CI)	*P* Value
Age, ≤51 y/>51 y[a]	16/13	6/4	62/47	1.17 (0.32-4.35)	.80
Sex, M/F	18/11	8/2	45/80	1.73 (0.40-7.53)	.45
Performance Status, 0/1	27/2	9/1	50/50	0.45 (0.01-5.93)	.44
Pathologic grading				NA	.32
G1	1	0	100		
G2	10	5	38		
G3	18	5	38		
Serum CEA level, ≤3.5/>3.5 ng/mL[b]	20/9	4/6	60/15	0.15 (0.01-0.29)	<.001
Serum CA19-9 level, ≤40/>40 ng/mL[b]	19/10	3/7	67/13	0.13 (0.0001-0.29)	.0003
Site				NA	.58
Antrum	17	5	65		
Fundus	2		100		
Corpus	5	3			
Cardias	5	2	60		
Size, ≤4/>4 cm[a]	17/12	5/5	67/29	0.75 (0.20-2.66)	.65
Tumor				NA	.53
T2	1	0	100		
T3	26	10	44		
T4	2	0	100		
Nodes					.46
N1	5	1	80	NA	
N2	19	7	39		
N3	5	2	50		
UICC stage				NA	.17
IIIA	6	0	100		
IIIB	17	8	53		
IV (M0)	6	2	40		
Bormann classification				NA	.0002
I	1	1	0		
II	6	0	100		
III	16	5	32		
IV	6	4	20		
Lauren classification, intestinal/diffuse	10/19	3/7	67/30	0.76 (0.20-2.86)	.68
Ming classification, expansive/infiltrative	9/20	3/7	63/42	1.02 (0.25-4-09)	.97
Vascular-lymphatic invasion, no/yes	22/7	7/3	58/44	0.97 (0.23-4.01)	.96
Resected nodes, ≤26/>26[a]	17/12	7/3	37/73	1.68 (0.46-5.95)	.44
Metastatic nodes, ≤9/>9[a]	18/11	5/5	55/38	0.35 (0.06-1.17)	.08
LNR,≤0.4211/>0.4211[a]	15/14	4/6	66/0	0.47 (0.12-1.62)	.22

Abbreviations: CEA, carcinoembryonic antigen; CI, confidence interval; LNR, lymph node ratio; NA, not applicable; UICC, International Union Against Cancer.
SI conversion factors: To convert CEA to micrograms per liter, multiply by 1.0.
[a] Based on the median value.
[b] Reference range.

tolerated continuous infusion of fluorouracil and the addition of cisplatin or paclitaxel as a second drug were recently published.[10-12] Overall, all of these studies were characterized by difficulty in completing the planned treatment in more than 80% of patients. However, CT-RT is not considered the standard of care in Europe for patients with radically resected gastric cancer. In this scenario, we performed a pilot study to assess the toxic effects and the efficacy of postoperative CT-RT with a FOLFOX-4 regimen (ie, a combination of folinic acid [leucovorin calcium], fluorouracil, and oxaliplatin) in selected patients with high-risk (stages III and IV, M0) gastric cancer previously treated with potentially curative surgery.

METHODS

ELIGIBILITY

This study was approved by the Department of Clinical and Experimental Medicine and Surgery of the Second University of Naples. All patients with stage III and IV (M0), according to the American Joint Committee on Cancer,[13] gastric cancer undergoing R0 surgical resection (defined as complete removal of all macroscopic tumor masses, the absence of microscopic residual tumor, histology-negative resection margins, and lymphadenectomy extended beyond the involved nodes at postoperative pathologic examination with negative more-distant LNs) were eligible for the study provided that they met all of the following criteria: a histologically confirmed diagnosis of adenocarcinoma and the complete absence of residual tumor (disease-free patients); age older than 18 years and younger than 75 years; Eastern Cooperative Oncology Group Performance Status of 1 or less; adequate bone marrow, hepatic, and renal function; no previous CT or RT; and written informed consent provided before recruitment.

Twenty-nine patients were enrolled between January 1, 2006, and December 31, 2007. Baseline characteristics of the intention-to-treat population are depicted in **Table 1**. Median patient age was 51 years (age range, 36-75 years), 18 patients were men and 11 were women, and most patients had a Performance Status of 0 according to the Eastern Cooperative Oncology Group scale. Seventy-nine percent of the patients had stage III cancer and 21% had stage IV cancer. Overall, 781 LNs were removed (mean [SD], 26 [10]; range, 15-59; median, 26), and 305 turned out to be metastatic (LN+). The LN ratio (LNR) (defined as the ratio be-

tween the number of metastatic nodes to the number of harvested nodes)[14] ranged from 0.0698 to 0.9310 (mean [SD], 0.4075 [0.2190]; median, 0.4211).

CT, CT-RT SCHEDULE, AND TOXIC EFFECT ASSESSMENT

Chemotherapy was started within 6 weeks of surgery and consisted of oxaliplatin, 85 mg/m^2 on day 1; folinic acid, 200 mg/m^2 as a 2-hour infusion, followed by bolus fluorouracil, 400 mg/m^2; and a 22-hour infusion of fluorouracil, 600 mg/m^2 on days 1 and 2 every 2 weeks (FOLFOX-4). Use of central venous catheters and disposable pumps allowed CT administration on an outpatient basis. The FOLFOX-4 was administered at full dose for 2 cycles and at reduced dose (by 25%) during concurrent RT. Two more cycles of full-dose CT were delivered after CT-RT for a total of 8 courses. The CT-RT was started 2 weeks after the second cycle of FOLFOX-4 and consisted of 1.8 Gy daily for 5 weeks up to 45 Gy for a total of 25 fractions. The FOLFOX-4 at a 25% dose reduction was concomitantly applied biweekly, and chemointerruption was planned in cases of gastrointestinal toxic effects of grade 3 or 4. Computed tomography–based 3-dimensional RT planning and RT with 18-MV photons was performed in all the patients, and RT was delivered by means of a 3-field technique. The clinical target volume was defined using preoperative computed tomographs, endoscopic findings, surgical clips, and all other available information. The clinical target volume included the gastric bed, the draining LNs as described in the Intergroup 0116 study,[9] the anastomosis region, and a safety margin around the former tumor involving all mucosal cavity walls for at least 3 cm.

Toxic effects were assessed before starting and at each 2-week cycle using the National Cancer Institute Common Toxicity Criteria.[15] Treatment delays and dose modifications were based on the results of a complete hematologic evaluation performed on the day of the planned treatment. When thrombocytopenia or neutropenia grade (G)>2 or other significant nonhematologic toxic effects developed, CT recycle was delayed for up to 2 weeks. The fluorouracil dose was reduced in cases of G>3 diarrhea, stomatitis, and dermatitis. Peripheral-sensitive neuropathy was graded according to the following oxaliplatin-specific scale: G1, paresthesia or hypoesthesia of short duration with complete recovery before the next cycle; G2, paresthesia or hypoesthesia persisting between 2 cycles without functional impairment; and G3, permanent paresthesia or hypoesthesia resulting in functional impairment.[16] The oxaliplatin dose was reduced for G3/4 neutropenia or thrombocytopenia and in cases of persistent (>14 days) paresthesia or temporary (7-14 days) painful paresthesia or functional impairment. In cases of persistent (>14 days) painful paresthesia or functional impairment, oxaliplatin was omitted from the treatment until recovery. All the patients ate well, and enteral or parenteral nutrition was added when inadequate intake of energy caused weight loss or body mass index modification.

STUDY END POINTS AND STATISTICS

The primary study end points were determination of toxic effects and the safety profile of the treatment. Secondary end points included DFS and OS rates, calculated from the time of surgery to evidence of relapse or the date of the last evaluation and death, respectively. No patient was lost to follow-up, and the study was complete by December 31, 2008. Statistical analysis was performed using a statistical software package (SPSS; SPSS Inc, Chicago, Illinois), integrated using a software program (MedCalc version 9.4.2.0; MedCalc Software bvba, Mariakerke, Belgium). In all the analyses, the significance level was specified as $P<.05$. For continuous variables, such as number of LNs harvested and LNR, patients were unequivocally categorized into 2 groups according to the median value, thus avoiding pluristratification. Univariate statistical analysis related to OS and DFS rates was determined using the Mantel-Cox log-rank test. Curves were plotted using the Kaplan-Meier method; *P* values and hazard ratios (HRs) with 95% confidence intervals (CIs) were provided. The independent significance of prognostic variables was determined by means of multivariate analysis using the Cox proportional hazards model. A stepwise multivariate analysis was performed to generate a model of the best linear combination of variables able to predict long-term outcome.

Table 2. Main Toxic Effects Registered in the Study

Toxic Effect	Grades 1-2, No. (%)	Grades 3-4, No. (%)
Hematologic		
Neutropenia	14 (48)	5 (7)
Thrombocytopenia	13 (45)	1 (3)
Anemia	6 (21)	0
Febrile neutropenia	0	0
Gastrointestinal		
Nausea	15 (52)	7 (24)
Vomiting	9 (31)	2 (7)
Diarrhea	6 (21)	1 (3)
Stomatitis	5 (17)	0
Hepatic	0	0
Neurologic	10 (34)	1 (3)
Others		
Asthenia	7 (24)	4 (14)
Allergic	0	0

RESULTS

TREATMENT TOXIC EFFECTS

The occurrence and incidence of the main toxic effects are reported in **Table 2**. Overall, the treatment was well tolerated; a mean of 7 cycles per patient of FOLFOX-4 were administered, and the most common adverse effects were gastrointestinal. The National Cancer Institute Common Toxicity Criteria (all grades) of nausea, vomiting, diarrhea, and stomatitis were recorded in 22 patients (76%), 11 (38%), 7 (24%), and 5 (17%), respectively. No G4 gastrointestinal toxic effects were registered.

Grades 1 and 2 hematologic toxic effects were the main adverse effects registered; no patients experienced febrile neutropenia. Neurologic toxic effects were moderate; they were recorded in 37% of patients (G1-2 in 34% and G3 in 3%). In a patient experiencing G3 neurotoxicity, administration of oxaliplatin was stopped after 3 cycles of CT. All the patients received the planned adjuvant therapy, and no treatment-related deaths were reported. No patient required nutritional supplementation.

SURVIVAL AND RELAPSE

All 29 patients were included in the survival analysis on an intention-to-treat basis. Mean (SD) follow-up was 19 (8) months (range, 5-36 months; median, 19 months).

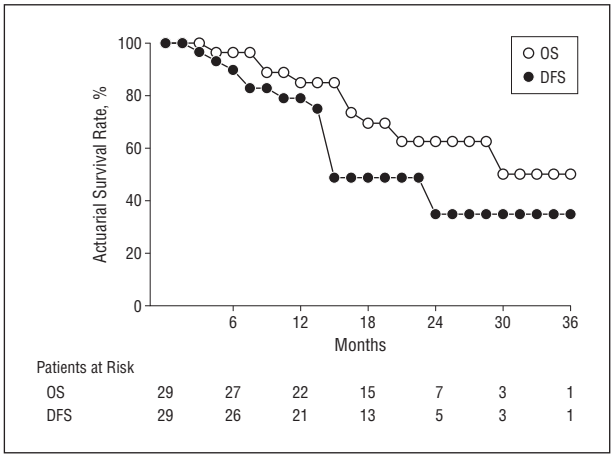

Figure 1. Three-year overall (OS) and disease-free (DFS) survival rates in 29 patients with gastric cancer undergoing potentially curative surgery and adjuvant chemoradiotherapy.

During this period, 10 patients (34%) died of disease. One- to 3-year OS was 85.0%, 62.6%, and 50.1%, respectively (**Figure 1**). Mean (SD) survival time was 27 (2) months (95% CI, 22-31 months). On univariate analysis, elevated basal serum tumor marker levels and Bormann classification were the only variables significantly related to OS rate. However, note that significance was affected by the few patients in this series. Important differences in long-term outcome were observed when stratifying for some prognostic factors. Particularly, the survival rate was shown to decrease in the case of male sex and worsening TNM stage, reduction in the number of resected nodes, and increase in LNs+ and LNR (Table 1). On multivariate analysis, TNM stage (HR, 10.17; 95% CI, 0.91-13.2; $P=.06$) and LNR (HR, 67.82; 95% CI, 1.12-192.1; $P=.04$) were demonstrated to be independent prognostic variables related to OS rate.

Cancer recurrence was observed in 16 patients (55%). Eighty percent of cancer recurrences presented in the first 18 months, and no cancer relapse was observed after 2 years. One- to 3-year DFS was 79%, 35%, and 35%, respectively (Figure 1). Mean (SD) and median (SD) DFS times were 21 (2) months (95% CI, 17-26 months) and 15 (4) months (95% CI, 6-24 months), respectively. The presence of elevated preoperative carcinoembryonic antigen and CA19-9 levels, advanced Bormann grade, and high LNR were the only covariates that were significantly associated with a worse DFS rate on univariate analysis. To these 4 variables, Cox analysis added TNM stage and number of resected nodes as independent variables correlated with the DFS rate (**Table 3**). After backward elimination, stepwise regression selected LNR (HR, 3.10; 95% CI, 1.06-9.03; $P=.04$) as the only covariate able to predict long-term DFS rates. The 3-year DFS rate was significantly better in patients with a low LNR (≤ 0.4211) than in patients with a high LNR (>0.4211) ($P=.03$). According to this LNR cutoff value, the HR for DFS rate was 0.34 (95% CI, 0.10-0.88), corresponding to a 46% increase in the 3-year DFS rate (from 11.8% to 57.8%) in patients showing a low LNR. A 66% reduction in the estimated relative risk of cancer recurrence was recorded in this group (**Figure 2**).

The peritoneum was the main site of relapse. As a single site of progression, it was shown to be involved in 6 patients (21%), and 1 patient had simultaneous dissemination to lumboaortic LNs. Ovarian metastases were discovered in 3 women, 1 of whom underwent radical resection. One patient developed a single-site metastasis in supraclavicular nodes that was treated with RT. One patient developed multiple liver metastases and anastomotic recurrence. Other single sites of disease progression were bone (2 patients), pleura (1 patient), and lumboaortic LNs (1 patient). Seven of the progressed patients were treated with CT for advanced disease.

COMMENT

Gastric cancer still represents a leading cause of death worldwide. Several cytotoxic and biological agents have demonstrated activity, and combination regimens have been shown to improve progression-free survival, OS, and quality of life in patients with advanced gastric cancer.[17]

In the adjuvant setting, 3 randomized trials[18-20] and a meta-analysis[21] concluded that postoperative CT did not add a survival benefit to surgery. Accordingly, in the present trial, in which the ELF (etoposide, leucovorin, and fluorouracil) regimen was compared with surgery alone, a relevant advantage in terms of OS was not shown for the CT-treated arm.[22] Furthermore, the results of 6 meta-analyses[23-28] suggest a modest but statistically significant improvement in relapse-free survival and OS for adjuvant CT. Finally, perioperative CT is under investigation, and the excellent Japanese results with S-1, to our knowledge, have not been reproduced in the West.[8,29]

The role of RT alone as adjuvant treatment was reported in a randomized trial[30] in which 145 patients received surgery alone, 138 were administered postoperative CT, and 153 were given postoperative RT. No survival differences were reported, but RT offered an advantage in terms of reduction in local recurrence (27% with surgery alone vs 10% with surgery and RT). Forty percent of patients had gross or microscopic residual disease after surgery, and 24% in the RT arm did not receive any RT.[30]

The importance of CT-RT in the adjuvant setting was first evaluated in a Mayo Clinic study. Although local control favored the CT-RT arm, it did not reach a statistically significant difference.[31] The largest trial evaluating the role of CT-RT as adjuvant treatment was the US Intergroup 0116.[9] In this study, 556 patients with resected adenocarcinoma of the stomach or gastroesophageal junction were randomized to receive surgery alone or surgery plus postoperative CT-RT. Survival at 3 years was 50% vs 40% in favor of postoperatively treated patients. After 5 years of follow-up, OS was shown to improve by 11.6% (28.4% vs 40%; $P<.001$) and relapse-free survival to increase from 25% to 31%, both in favor of patients treated with postoperative CT-RT as opposed to surgery alone. Locoregional relapse was shown to decrease from 29% to 19%, CT-RT arm vs surgery alone. However, toxic effects were significantly higher with CT-RT, whereas treatment-related mortality was acceptable (1% in the CT-RT arm vs 0% in the surgery alone arm).[9]

Table 3. Multivariate Analysis Related to Disease-Free Survival in 29 Patients With Gastric Cancer Treated With Curative Surgery and Postoperative Adjuvant Chemoradiotherapy

	Coefficient	Standard Error	Hazard Ratio (95% CI)[a]	*P* Value
Serum CEA level	2.9538	1.4188	19.1 (1.18-309.39)	.04
Serum CA19-9 level	1.6839	0.8022	5.38 (1.11-25.95)	.04
Bormann classification	2.3535	1.0222	10.52 (1.41-78.02)	.02
Resected nodes	–0.4525	0.1954	0.63 (0.43-0.93)	.02
TNM stage	2.4370	0.9547	11.43 (1.76-74.30)	.01
LNR	3.2923	1.1633	26.90 (2.75-263.01)	.005

Abbreviations: CEA, carcinoembryonic antigen; CI, confidence interval; LNR, lymph node ratio.
[a] Of disease progression.

This study is the only trial, to our knowledge, in which an advantage for CT-RT treatment after surgery emerged. The CT regimen used in this study is not considered the more active in gastric cancer; therefore, benefit is mainly evident only after adequate surgery.

Four phase 2 studies by the Arbeitsgemeinschaft Internistische Onkologie/Arbeitsgemeinschaft Radiologischer Onkologie/Chirurgische Arbeitsgemeinschaft fur Onkologie (AIO/ARO/ACO) were recently conducted with the aim of developing novel regimens for adjuvant CT-RT in patients with cancer undergoing potentially curative resection. In the German experience, CT-RT with a variety of fluorouracil-based CT regimens (cisplatin plus paclitaxel; fluorouracil, leucovorin, and cisplatin; fluorouracil and leucovorin plus irinotecan; fluorouracil, cisplatin, and docetaxel) seemed safe and effective in this setting.[10-12]

In the present study, we sought to establish an intensified CT-RT regimen using one of the most active and recently investigated CT combinations for the treatment of advanced gastric cancer,[32-34] including continuous fluorouracil infusion and oxaliplatin, with the same drugs at reduced doses during concomitant RT.

Long-term outcome in patients with stage III and IV (M0) gastric cancer undergoing potentially curative surgery differs substantially throughout the world, with the best results obtained by Eastern researchers. In Western countries, 3-year survival was reported to be approximately 27% in stage IIIA, 14% in stage IIIB, and 10% in stage IV.[35] In the present series, patients with stage IIIA, IIIB, and IV (M0) disease were shown to have 3-year OS of 100%, 53%, and 40%, respectively, which were substantially better than the percentages recorded in untreated patients. In the 29 patients enrolled, a good safety profile with a low rate of toxic effects was observed. The main toxic effects were gastrointestinal (nausea, vomiting, diarrhea, and stomatitis of any grade except grade 4). These toxic effects were more intense during CT-RT but did not interfere with general nutritional status. Hematologic toxic effects were grades 1 and 2; peripheral-sensitive neurotoxicity was moderate. No treatment-related death, toxic effect–related therapy discontinuation, or febrile neutropenia was recorded. Thus, treatment seemed to be feasible in terms of toxic effects, although during RT it is recommended to reduce the dose of the drugs to avoid cumulative toxic effects. Although limited by the small number of patients in this series, these findings suggest that adjuvant CT-RT could significantly improve long-term outcome in these patients.

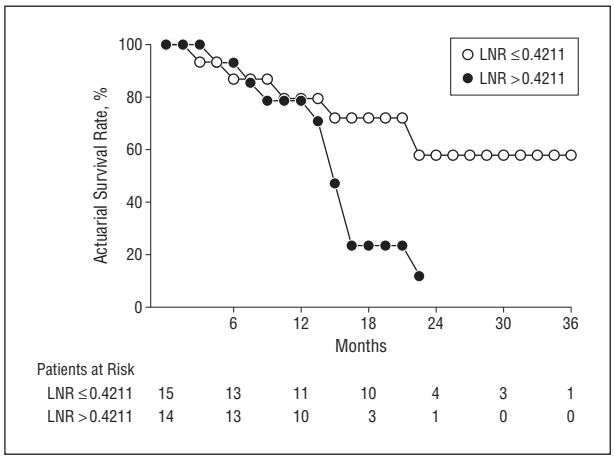

Figure 2. Three-year disease-free survival rates in 29 patients with gastric cancer (15 with a low lymph node ratio [LNR] and 14 with a high LNR) undergoing potentially curative surgery and adjuvant chemoradiotherapy.

The LNR is a relatively newly investigated prognostic factor in many human tumors, including gastric cancer. The LNR was demonstrated to be an important predictor of long-term outcome and to reduce the stage migration phenomenon in patients with gastric cancer.[36] Recently, this ratio-based staging was validated by a large, multicenter study[14] that suggested its inclusion in the current TNM staging system. In the present study, the LNR was shown to be an independent prognostic factor for OS and DFS rates and the only covariate selected for the best model predicting disease progression. The LNR statistical performance was more powerful than were number of resected and metastatic nodes and TNM staging system. Thus, these results add further evidence to the prognostic significance of LNR because it was demonstrated to hold its importance also in the present study, consisting of a homogeneous series of patients with advanced gastric cancer treated with radical surgery and adjuvant CT-RT.

In conclusion, CT and CT-RT with FOLFOX-4 and 25 daily fractions of 1.8 Gy were shown to be well tolerated and safe in fit patients with locally advanced gastric cancer after potentially curative surgery. The intriguing results in terms of DFS and OS warrant further studies.

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