



Chemoradiotherapy or chemotherapy as adjuvant treatment for resected gastric cancer: should we use selection criteria?

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ABSTRACT

Background: The management of gastric adenocarcinoma is essentially based on surgery followed by adjuvant treatment. Adjuvant chemotherapy (CT) as well as chemoradiotherapy (CRT) have proven their effectiveness in survival outcomes compared to surgery alone. However, there is little data comparing the two adjuvant approaches. This study aimed to compare the prognosis and survival outcomes of patients with gastric adenocarcinoma operated and treated by adjuvant radiochemotherapy or chemotherapy

Materials and methods: We retrospectively evaluated 80 patients with locally advanced gastric cancer (LGC) who received adjuvant treatment. We compared survival outcomes and patterns of recurrence of 53 patients treated by CRT and those of 27 patients treated by CT.

Results: After a median follow-up of 38.48 months, CRT resulted in a significant improvement of the 5-year PFS (60.9% vs. 36%, $p = 0.03$) and the 5-year OS (55.9% vs. 33%, $p = 0.015$) compared to adjuvant CT. The 5-year OS was significantly increased by adjuvant CRT ($p = 0.046$) in patients with lymph node metastasis, and particularly those with advanced pN stage ($p = 0.0078$) and high lymph node ratio (LNR) exceeding 25% ($p = 0.012$). Also, there was a significant improvement of the PFS of patients classified pN2-N3 ($p = 0.022$) with a high LNR ($p = 0.018$). CRT was also associated with improved OS and PFS in patients with lymphovascular and perineural invasion (LVI and PNI) compared to chemotherapy.

Conclusion: There is a particular survival benefit of adding radiotherapy to chemotherapy in patients with selected criteria such as lymph node involvement, high LNR LVI, and PNI.

Key words: gastric cancer; chemoradiotherapy; chemotherapy; survival

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Introduction

Gastric cancer is the fifth most commonly diagnosed cancer in the world and the third leading cause of death related to cancer, representing a real health problem worldwide [1]. The overall survival rate of patients who have undergone only

surgery is around 45% at 5 years and has undergone little change over the past decade. Local recurrences on the tumor bed, on the anastomosis, and in the locoregional lymph nodes occur in 40 to 65% of patients after resection for curative purposes. To compensate for this, an extension of the surgical procedure was recommended without reaching the

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goal of improving survival or reducing the rate of locoregional recurrence [2, 3]. Thus, for patients with stage > IB, who are at high risk of recurrence, it is undoubtedly necessary that an adjuvant treatment is offered after surgery [2, 4]. The gastrointestinal cancer intergroup (INT-0116) was the first phase III trial to demonstrate that adjuvant concomitant radio-chemotherapy improves recurrence-free survival and overall survival [5]. On the other hand, several meta-analyses have demonstrated the survival benefit of adjuvant chemotherapy in gastric cancer [6–8]. Furthermore, two randomized controlled phase III clinical trials showed that adjuvant therapy prolonged survival and decreased recurrence [5, 9]. Clinical trials have also directly compared postoperative CT alone with CRT for patients with locally advanced gastric cancer and the meta-analysis of three randomized clinical trials showed that CRT reduced the risk of locoregional relapses, but without significant improvement in distant relapse and overall survival [10]. Results of the ARTIST phase III randomized controlled trial showed that both adjuvant CT and CTRT are tolerated and equally beneficial in preventing relapse and suggested that CTRT had significantly improved the DFS in patients with node-positive disease and with intestinal-type [11]. Given these results, the choice of the optimal adjuvant therapeutic attitude remains a subject of controversy.

This study aimed to compare retrospectively the prognosis and survival outcomes of patients with gastric adenocarcinoma operated and treated by adjuvant radio-chemotherapy or chemotherapy alone and to assess the toxicity and safety of the two treatment modalities to identify suitable patients for an intensified adjuvant treatment.

Materials and methods

Patients

We retrospectively evaluated 80 patients with LGC who received adjuvant treatment from January 2005 to December 2015. Patients were eligible for analysis if they had histological confirmation of gastric cancer, had curative gastrectomy with nodal dissection. Exclusion criteria included the use of neoadjuvant treatment, metastatic disease at diagnosis, and patients with coexisting malignancies or those who could not tolerate the adjuvant treatment because of other systemic diseases.

We started identifying medical files, clinic (age, gender, reason of counseling, WHO status), endoscopic data (tumors site, size, aspect), tumor markers (CA 19-9 and CEA level), histological data (histological type, tumors size, differentiation grade, number of removed nodes, parietal infiltration depth, lymphovascular invasion (LVI), perineural tumor invasion (PNI), lymph node status and the lymph node ratio (LNR) that corresponded to the ratio between metastatic and dissected lymph nodes. The lymph nodes metastasis (N stage) and the depth of invasion (T stage) were classified according to the TNM staging system 8th edition elaborated by the American Joint Committee on Cancer/International Union Against Cancer (AJCC/UICC) TNM staging system (AJCC/UICC). In this study, Histological classification was based on the WHO classification and Lauren classification with 3 subgroups: intestinal type, diffuse type, and mixed type [12]. Poorly differentiated tumors included moderately differentiated tubular adenocarcinoma, independent signet ring cells adenocarcinoma, and mucinous adenocarcinoma.

Surgical procedure

The surgical variables included the type of procedure (total versus partial gastrectomy), the extent of lymph node dissection (D0, D1.5, and D2) based on the different updated versions of the Japanese Gastric Cancer Treatment Guidelines [13–15]. Lymphadenectomy was classified into three types according to the site of the tumor and the type of gastrectomy: D1 dissection, D1.5 dissection, and D2 dissection. A D1.5 lymphadenectomy corresponds to a D2 lymphadenectomy with no dissection of the hilar and the splenic artery (relay 10 and 11). Splenectomy was performed in cases of metastatic lymph nodes at the hilum of the spleen or because of iatrogenic injury. The extent of stomach resection was related to the primary tumor site: total gastrectomy was performed in all proximal tumor locations and total gastric tumors, and subtotal gastrectomy was performed for distal tumor locations, provided that a 5- to 6-cm safety margin was present. After undergoing gastrectomy, patients were assigned to either adjuvant chemo radiotherapy or adjuvant chemotherapy.

Adjuvant chemotherapy

We used 4 regimens of adjuvant chemotherapy: The LV5FU2 regimen consisted of Leucovo-

rin 100 mg/m² in 2 hours infusion days 1–2 and 5-FU 400 mg/m² as a bolus followed by daily 22 h infusion of 600 mg/m² every 14 days for nine cycles. The ELF regimen consisted of Folinic acid at a dose of 300 mg/m² given as a 10-minute IV infusion, followed immediately by Etoposide 120 mg/m² given as a 50-minute IV infusion, followed by bolus 5-FU 500 mg/m² for 3 consecutive days. The cycles were repeated every 22 days. Patient treated with the FOLFOX4 regimen received an intravenous infusion of oxaliplatin (85 mg/m² 2 hours) at day 1, a bolus injection of Leucovorin (200 mg/m²) at days 1–2, bolus injection of 5-FU (400 mg/m²) at days 1–2, and continuous intravenous infusion of 5-FU (600 mg/m²) for 22 hours at days 1–2.

Adjuvant chemo radiotherapy

In the CRT group, a contrast-enhanced computed tomography scan with 3 mm-thick slices was conducted from the top of the diaphragm to the bottom of L4. The target volumes were defined as per INT 0116 protocol [16] and included the residual stomach, tumor bed, anastomosis, and the regional lymph nodes. Most radiotherapy plans were 3-dimensional conformal radiotherapy (3D-CRT). Photon beams from linear accelerators with the energy of 6/10 or 6/23 MV were used for radiotherapy planning. The planning target (PTV) volume for each patient was generated from the clinical target volume (CTV) plus 1 cm margins. The prescription dose was 45–50.4 Gy, with 1.8 Gy daily fractions administered over 5–5.6 weeks. Associated chemotherapy regimen was based either on the INT 0116 trial using 5 cycles of intravenous bolus 5-fluorouracil and leucovorin (FUFOL regimen) before, during, and after radiotherapy, or 9 cycles of simplified LV5FU2 regimen (two to four cycles before radiotherapy, then three cycles during radiotherapy and, finally, four cycles after radiotherapy) delivered as follows: 2-hour infusion of leucovorin 200 mg/m² on day 1 followed by a 400 mg/m² bolus of 5FU on day 1, then a continuous infusion of 5FU 2400 mg/m² over 46 hours. Some patients received 6 cycles of modified FOLFOX (three cycles during radiotherapy and three cycles after radiotherapy) administered as follows: oxaliplatin 85 mg/m², leucovorin 200 mg/m², bolus fluorouracil 400 mg/m², and infusional fluorouracil 1600 mg/m²).

Data regarding treatment toxicity were recorded according to the National Cancer Institute — Common Toxicity Criteria (NCI-CTC, version 4.0) (17).

Statistical methods

The categorical variables were presented as numbers and percentages. Continuous variables were expressed as the mean ± standard deviation (SD) with ranges. Moreover, some continuous variables were converted to dichotomous variables for convenience, including the age (< 70 years vs. ≥ 70 years), the weight loss (< 10% vs. ≥ 10%), the tumor size (< 50 mm vs. ≥ 50 mm) and the NRLN (≤ 15 LN vs. > 15 LN). To compare the continuous variables with normal distribution we used the T-test. To compare the categorical variables we used the χ^2 or Fisher test if the assumption for the first has not complied.

OS was defined as the time from surgery to death, or the end of follow-up and PFS was defined as the time from surgery to disease recurrence, as confirmed by using imaging. The rate and types of recurrence were compared between the two groups. Loco-regional recurrences correspond to recurrences occurring in the tumor bed, to anastomotic and lymph node recurrences. Metastatic relapses corresponded to hepatic, peritoneal, bone, pulmonary, and ovarian sites. The Progression-free survival (DFS) and overall survival (OS) rates were obtained using the Kaplan Meier methods. In the case of comparing subgroups, the log-rank test was used. We used the Statistical Package for Social Science (SPSS), version 20.0 for Windows, and a p-value less than 0.05 was considered significant.

Results

Patients' characteristics

From January 2005 to December 2015, a total of 80 patients were eligible for the study, 53 in the CRT group and 27 in the CT group. Baseline characteristics are summarized in Table 1. Age, gender, performance status, and tumor location as well as surgical procedures were similar between groups. However, the proportion of patients with stage III/IV disease was significantly higher in the CT cohort than in the CRT group (85.2% vs. 54.7%, $p = 0.007$). Groups were not balanced regarding the lymph node status: lymph node metastasis was more frequent in the CT group than in the CRT

Table 1. Patient characteristics

Variables		All patients n (%)	CT ADJ n (%)	CTRT n (%)	p
Gender	Men	48 (60%)	13(48.1%)	35 (66%)	0.122
	Women	32 (40%)	14 (51.9%)	18 (34%)	
Age (years)	Mean ± SD [mm]	59.21± 12.89	62.66±11.43	57.45±13.33	0.087
	≤ 65	55(68.8%)	17 (63%)	38 (71.7%)	0.425
	> 65	25 (31.2%)	10 (37%)	15 (28.3%)	
ASA score	ASA1–2	69 (86.2%)	24 (88.9%)	45 (84.9%)	0.625
	ASA3	11 (13.8%)	3 (11.1%)	8 (15.1%)	
Weight loss	< 10%	31 (43.1%)	11(42.3%)	20 (45.5%)	0.923
	≥ 10%	41 (56.9%)	15 (57.7%)	26 (56.5%)	
Tumor location	Proximal	10 (12.5%)	3 (11.1%)	7 (13.2%)	0.833
	Middle 1/3	29 (36.2%)	11 (40.7%)	18 (34%)	
	Distal	41 (51.2%)	13 (48.1%)	28 (52.8%)	
UICC stage	I–II	28 (35%)	4 (14.8%)	24 (45.3%)	0.007
	III–IV	52 (65%)	23 (85.2%)	29 (54.7%)	
UICC stage	I	2 (2.5%)	0 (0%)	2 (3.8%)	0.014
	II	26 (32.5%)	4(14.8%)	22 (41.5%)	
	III	47 (58.8%)	19(70.4%)	28 (52.8%)	
	IV	5 (6.2%)	4 (14.8%)	1 (1.9%)	
pT stage	pT1	2(2.5%)	0	2(3,8%)	0.162
	pT2	18(22.5%)	4(14,8%)	14(26,4%)	
	pT3	31(38.8%)	9 (33,3%)	22 (41,5%)	
	pT4	29 (36.2%)	14 (51,9%)	15(28,3%)	
pN stage	N0	7 (8.8%)	0	7 (13.2%)	0.120
	N1	20(25%)	8 (29.6%)	12 (22.6%)	
	N2	26 (32.5%)	7 (25.9%)	19 (35.8%)	
	N3	27 (33.8%)	12 (44.4%)	15 (28.3%)	
LN status	N–	7 (8.8%)	0	7 (13.2%)	0.048
	N+	73 (91.2%)	27 (100%)	46 (86.8%)	
LNR	≤ 25%	39 (48.8%)	12 (44.4%)	27 (50.9%)	0.582
	> 25%	41 (51.2%)	15 (55.6%)	26 (49.1%)	
NRLN	< 15 LN	16 (20%)	7 (25.9%)	9 (17%)	0.344
	≥ 15 LN	64 (80%)	20 (74.1%)	44 (83%)	
Resection	TG	41 (51.2%)	13 (48.1%)	28 (52.8%)	0.692
	PG	39 (48.8%)	14 (51.9%)	25 (47.2%)	
LND	D1	7 (8.8%)	4 (14.8%)	3 (5.7%)	0.423
	D1.5	20 (25%)	6 (22.2%)	14 (26.4%)	
	D2	53 (66.2%)	17 (63%)	36 (67.9%)	
Tumor size [mm]	< 50 mm	32 (40%)	12 (44.4%)	20 (37.7%)	0.592
	≥ 50 mm	48 (60%)	15 (55.6%)	33 (62.3%)	
Differentiation	Well	40 (50%)	11 (40.7%)	29 (54.7%)	0.358
	Moderly	23 (28.8%)	8 (29.6%)	15 (28.3%)	
	Poorly	17 (21.2%)	8 (29.6%)	9 (17%)	



Table 1. Patient characteristics

Variables		All patients n (%)	CT ADJ n (%)	CTRT n (%)	p
Lauren type	Intestinal	59 (73.8%)	19 (70.4%)	40 (75.5%)	0.624
	Mixed/diffuse	21 (26.2%)	8 (29.6%)	13 (24.5%)	
LVI	No	43 (53.8%)	11 (40.7%)	32 (60.4%)	0.096
	Yes	37 (46.2%)	16 (59.3%)	31 (39.6%)	
PNI	No	44 (55%)	11 (40.7%)	33 (62.3%)	0.067
	Yes	36 (45%)	16 (59.3%)	20 (37.7%)	

CT ADJ — adjuvant chemotherapy; CTRT — adjuvant radiochemotherapy; NRLN — number of retrieved lymph nodes; N- — no lymph node metastasis, N+ — lymph node metastasis; LVI — lymphovascular invasion; PNI — perineural invasion

group (100% vs. 86.8%, $p = 0.048$) with more advanced N stage, (stage N3 accounted for 44.4% in the CT group vs. 28.3% in the CTRT group) and more patients with a LNR exceeding 25% (55.6% vs. 49.1%). The two groups were comparable regarding the histological subtype, the grade of differentiation, and tumor size. However, lymphovascular space invasion lymphovascular (LVI) were more frequent in the CT group than in the CRT group (59.3% vs. 39.6%) and more perineural invasion (PNI) was observed in the CT group (59.3 vs. 37.7%). However, these differences were not statistically significant ($p = 0.096$ and $p = 0.067$, respectively).

Adjuvant treatment

Patients assigned to adjuvant chemotherapy received variable regimens. From all, twelve patients received the LV5FU2 regimen (44.4%), 7 patients received the FOLFOX regimen (25.9%), 8 patients received the ELF regimen (29.6%), and two patients received ELF regimen (7.4%).

In the CTRT group, the most frequent associated chemotherapy was the LV5FU2 regimen in 41

patients (77.4%), followed by the FUFOL regimen in 8 patients (15.1%) and the FOLFOX regimen in 4 patients (7.5%).

Toxicity

The toxicity of each treatment is summarized in Table 2. The most frequent toxicity in the CTRT group were gastrointestinal in 37.7% of cases and hematologic toxicity in the CT group 66.66% of cases. The most common grade 3 and 4 adverse events in the CT group were asthenia/anorexia (33.3%), hematologic (29.6%), and infectious (14.8%); while, the most common grade 3–4 adverse event in the CTRT was gastrointestinal toxicity (13.2%). No death during treatment was recorded in the two groups. Treatment discontinuity was recorded in 26.4% of patients in the CTRT group (14 patients) and 29.6% in the CT group (8 patients). The most common cause of treatment discontinuity in the CTRT group was toxicity in 50% of cases followed by disease progression in 28.57% and loss of follow up in 21.42% of cases. For the CT group, treatment discontinuity was secondary to toxicity in 50% of

Table 2. Adverse events

Toxicity	Chemoradiation group (n = 53)					Chemotherapy group (n = 27)				
	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Hematologic	4 (7.5%)	1 (1.88%)	3 (5.6%)	2 (3.7%)	–	3 (11.1%)	7 (25.9%)	8 (29.6%)	–	–
Gastrointestinal	8 (15%)	5 (9.4%)	7 (13.2%)	–	–	2 (7.4%)	8 (29.2%)	2 (7.4%)	3 (11.1%)	–
Mucositis	4 (7.5%)	2 (3.7%)	1 (1.88%)	–	–	5 (18.5%)	7 (25.9%)	4 (14.8%)	4 (14.8%)	–
Asthenia/ /anorexia	–	2 (3.7%)	–	–	–	5 (18.5%)	6 (22.2%)	9 (33.3%)	–	–
Neuropathy	1 (1.88%)	1 (1.88%)	–	–	–	1 (3.7%)	3 (11.1%)	1 (3.7%)	–	–
Infectious	–	1 (1.88%)	–	–	–	1 (3.7%)	5 (18.5%)	4 (14.8%)	–	–
Renal	–	–	–	–	–	–	4 (14.8%)	–	–	–

Table 3. Comparative study of pattern of relapse*

Site	All patients n (%)	CT group (n = 27)	CTR group (n = 53)	p
Overall recurrence	34 (42.5%)	15 (55.6%)	19 (35.8%)	0.092
Locoregional recurrence	16 (20%)	6 (22.2%)	10 (18.9%)	0.723
Distant recurrence	29 (36.3%)	12 (44.4%)	17 (32.1%)	0.277
Peritoneal	15 (18.8%)	10 (37%)	5 (9.4%)	0.003
Liver	13 (16.3%)	6 (22.2%)	7 (13.2%)	0.301
Lung	8 (10%)	1 (3.7%)	7 (13.2%)	0.255
Ovary	2 (2.5%)	1 (3.7%)	1 (1.9%)	1
Bone	1 (1.3%)	0%	1 (1.9%)	1

*Patients relapsed at multiple sites. The total number of recurrence sites was greater than the number of relapsed patients; CT — chemotherapy; CTRT — radio chemotherapy

cases followed by disease progression in 37.5% and lost of follow up in 12.8% of cases.

Relapses and progression free survival

The median follow-up was 38.48 ± 28.67 months (range, 4–139 months). Data of the first relapse only were recorded and categorized as loco-regional or distant (Tab. 3). After a mean follow-up of 18.85 ± 15.60 (3–75 months), recurrence occurred in 42.5% of patients within 22.5 months in the CTRT group and 14 months in the CT group ($p = 0.182$). The overall rate of recurrence was higher in the CT group (55.6%) compared to the CTRT group (35.8%) without significant difference ($p = 0.092$). The frequency of locoregional and distant relapses was higher in the CT group (22.2% and 44.4%, respectively) compared to the CTRT group (18.9% and 32.1%, respectively) without significant difference. Additionally, peritoneal recurrence was significantly higher in the CT group compared to the CTRT group (37% vs. 9.4%, $p = 0.003$).

The 5-year PFS was 60.9% in the CTRT group and 36% in the CT group ($p = 0.03$) (Fig. 1). Subgroup analyses were performed to identify patient populations who may benefit from CTRT (Tab. 4) showing that significant benefit from the addition of radiotherapy to adjuvant chemotherapy could not be excluded in women ($p = 0.008$), patients under 70 years old ($p = 0.035$), intestinal-type GC ($p = 0.032$), moderately/poorly differentiated tumors ($p = 0.022$) and positive LVI tumor ($p = 0.03$) (Fig. 3). There also was a trend toward improved PFS with adjuvant CTRT in patients with advanced-stage III and IV (29.5% vs. 53.8%, $p = 0.213$) with increased outcomes especially in patients with pT3–T4 tumors (64% vs. 35.6%, $p = 0.051$). In the

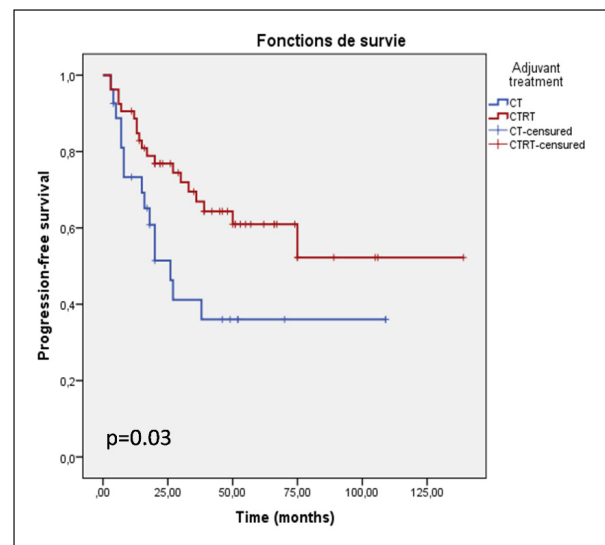


Figure 1. Kaplan-Meier survival curves of progression-free survival in all patients. There was a significant difference between adjuvant chemotherapy (CT) group and adjuvant radiochemotherapy (CTR) ($p = 0.03$)

73 patients with node-positive disease, 5-year PFS was slightly different (59.9% in CTRT group vs. 36% in CT group, $p = 0.057$) (Fig. 2). Furthermore, the subgroup analysis demonstrated the superiority of adjuvant CTRT compared to CT in terms of PFS in patients classified pN2–N3 (57.8% vs. 16.5%, $p = 0.022$) with a lymph node ratio greater than 25% (58.6% vs. 11.7%, $p = 0.018$). Moreover, we found that the benefit of adjuvant CTRT was statistically evident mainly for patients who had a D2 lymphadenectomy (56% vs. 28.4%, $p = 0.01$). Nevertheless, it seems that in patients who did not have extended lymphadenectomy, the CTRT brings a gain of 19.5% on PFS at 5 years but also an obvious increase in PFS in patients whose number of

Table 4. Univariate analysis of the 5 years progression-free survival (PFS)

Variables		5 years PFS		P
		CT ADJ	CTRTR	
All patients (n = 80)		36%	60.9%	0.03
Gender	Men	51.4%	59.3%	0.671
	Women	23.8%	64.8%	0.008
Age (years)	< 70	32.1%	59.8%	0.035
	≥ 70	47.6%	65.5%	0.440
ASA score	ASA1–2	36.1%	66.1%	0.014
	ASA3	33.3%	33.3%	0.918
Weight Loss	< 10%	56.1%	72.2%	0.613
	≥ 10%	24.4%	51.9%	0.054
UICC stage	I–II	75%	70.7%	0.801
	III–IV	29.5%	53.8%	0.213
pT stage	pT1–T2	37.5%	57.4%	0.416
	pT3–T4	35.6%	64%	0.051
pN stage	N0–N1	72.8%	16.5%	0.919
	N2–N3	16.5%	57.8%	0.022
LN status	N–	–	66.7%	NA
	N+	36%	59.9%	0.057
LNR	≤ 25%	61.4%	64.1%	0.708
	> 25%	11.7%	58.6%	0.018
NRLN	< 15 LN	21.4%	77.8%	0.056
	≥ 15 LN	41.3%	56.9%	0.182
Resection	TG	38.1%	70.2%	0.077
	PG	35.4%	50.9%	0.226
LND	D1/D1.5	50.6%	70.1%	0.581
	D2	28.4%	56.3%	0.01
Tumor size [mm]	< 50 mm	37.4%	84.4%	0.016
	≥ 50 mm	33.3%	45.1%	0.324
Differentiation	Well differentiated	78.8%	83%	0.661
	Others	0%	30.1%	0.022
Lauren type	Intestinal	37.8%	68.8%	0.032
	Mixed/diffuse	30%	33.8%	0.568
LVI	No	88.9%	86.7%	0.828
	Yes	0%	20.6%	0.03
PNI	No	88.9%	90.1%	0.930
	Yes	0%	13.5%	0.076

CT ADJ — adjuvant chemotherapy; CTRTR — adjuvant radiochemotherapy; NRLN — number of retrieved lymph nodes; N– — no lymph node metastasis; N+ — lymph node metastasis; LVI — lymphovascular invasion; PNI — perineural invasion

removed lymph nodes was less than 15 (77.8% vs. 21.4%, $p = 0.056$).

Overall survival

The 5-year overall survival was significantly higher in the CTRTR group compared to the CT

group (55.9% vs. 33%, $p = 0.015$) (Fig. 5, Tab. 5). The subgroup analysis revealed that adjuvant CTRTR resulted in an improved overall survival compared with adjuvant CT, especially in women ($p = 0.014$), patients with ASA score under 3 ($p = 0.007$), stage pT3–pT4 tumors (58.5% vs. 34.4%, $p = 0.048$), pa-

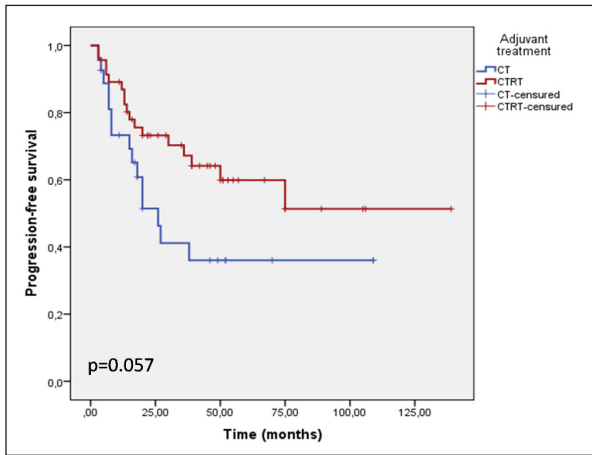


Figure 2. Kaplan-Meier survival curves of progression-free survival in lymph node-positive patients. There was a tendency to significant difference between adjuvant chemotherapy (CT) group and adjuvant radiochemotherapy (CRTT) ($p = 0.057$)

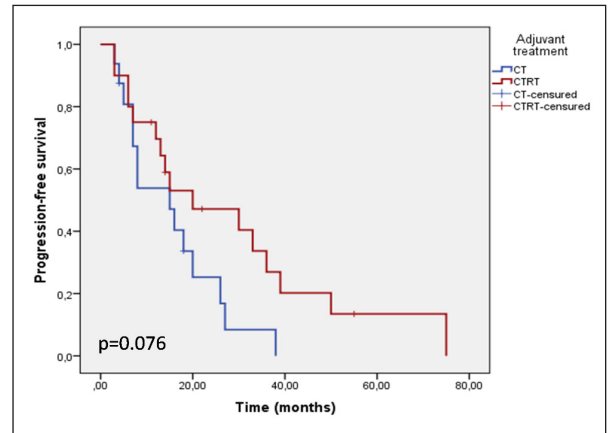


Figure 4. Kaplan-Meier survival curves of progression-free survival in PNI-positive patients. There was a significant difference between adjuvant chemotherapy (CT) group and adjuvant radiochemotherapy (CRTT) ($p = 0.076$)

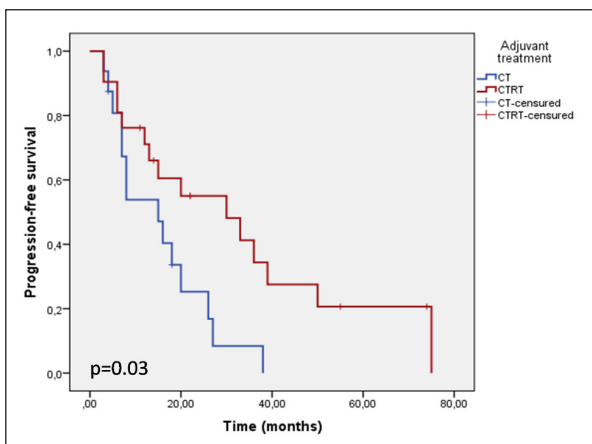


Figure 3. Kaplan-Meier survival curves of progression-free survival in LVI-positive patients. There was a significant difference between adjuvant chemotherapy (CT) group and adjuvant radiochemotherapy (CRTT) ($p = 0.03$)

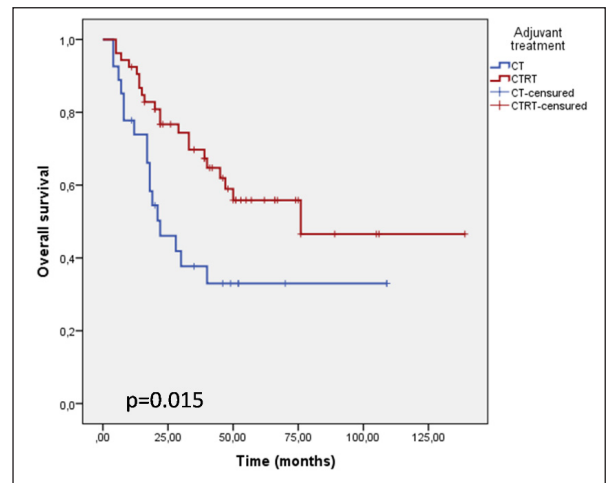


Figure 5. Kaplan-Meier survival curves of overall survival in all patients. There was a significant difference between adjuvant chemotherapy (CT) group and adjuvant radiochemotherapy (CRTT) ($p = 0.015$)

tients with lymph node metastasis (51.5% vs. 33%, $p = 0.046$) (Fig. 6) and particularly those with advanced pN stage ($p = 0.0078$) and high lymph node ratio exceeding 25% (49% vs. 8.8%, $p = 0.012$). Moreover, some histological criteria were associated with an improved overall survival with CRTT compared to adjuvant CT notably intestinal subtype ($p = 0.017$), LVI positive tumors ($p = 0.006$) (Fig. 7), PNI positive tumors ($p = 0.027$) (Fig. 8). In the case of D2 lymphadenectomy, the benefit in terms of overall survival was higher in the adjuvant CRTT group compared to the adjuvant CT group (51.5% vs. 29.4%, $p = 0.008$) on the other hand,

there was no significant difference between the two groups in the event of D1–D1.5 lymphadenectomy with a gain of 20.9% in terms of OS at 5 years in the CRTT group. Also, the adjuvant CRTT allowed a 47.7% increase in the overall survival of patients whose number of lymph nodes removed was less than 15 compared to the adjuvant CT ($p = 0.07$).

Discussion

Despite the advancement in adjuvant and neoadjuvant therapy, the 5-year survival rate for patients with positive lymph node gastric cancer is as low

Table 5. Univariate analysis of the 5 years overall survival (OS)

Variables		5 years OS		p
		CT ADJ	CTRT	
All patient (n = 80)		33%	55.9%	0.015
Gender	Men	43.1%	54.7%	0.300
	Women	23.6%	58.9%	0.014
Age (years)	< 70	31%	59.2%	0.033
	≥ 70	37.5%	40.4%	0.304
ASA score	ASA1–2	32.9%	60.7%	0.007
	ASA3	33.3%	25%	0.976
Weight Loss	< 10%	42.4%	64.4%	0.230
	≥ 10%	29.6%	43.9%	0.131
UICC stage	I–II	50%	70.9%	0.176
	III–IV	29.3%	42.8%	0.260
pT stage	pT1–T2	25%	51.4%	0.112
	pT3–T4	34.4%	58.5%	0.048
pN stage	N0–N1	75%	69.1%	0.948
	N2–N3	13%	48.8%	0.007
LN status	N–	-	83.3%	NA
	N+	33%	51.5%	0.046
LNR	≤ 25%	57.1%	62.7%	0.437
	> 25%	8.8%	49%	0.012
NRLN	< 15 LN	19%	66.7%	0.07
	≥ 15 LN	36.6%	53.1%	0.08
Resection	TG	28%	64.5%	0.016
	PG	39%	47.4%	0.277
LND	D1/D1.5	42.2%	63.1%	0.472
	D2	29.4%	51.5%	0.008
Tumor size [mm]	< 50 mm	33.3%	84.7%	0.002
	≥ 50 mm	33.3%	36.9%	0.471
Differentiation	Well differentiated	79.5%	77.2%	0.858
	Others	0%	29%	0.007
Lauren type	Intestinal	33.8%	62.2%	0.017
	Mixed/diffuse	30%	32.6%	0.483
LVI	No	90 %	76.9%	0.507
	Yes	0%	23.7%	0.006
PNI	No	90%	8.3%	0.659
	Yes	0%	16.3%	0.027

CT ADJ — adjuvant chemotherapy; CTRT — adjuvant radiochemotherapy; NRLN — number of retrieved lymph nodes; N– — no lymph node metastasis; N+ — lymph node metastasis; LVI — lymphovascular invasion; PNI — perineural invasion

as 15–20%, and even node-negative patients have a 5-year survival rate of 45–55% in the case of advanced T stage (T3–T4N0) [18] with recurrence rates ranging from 20% to 40% within 2 years after complete resections depending on specific factors such as the initial stage of the disease, proximal

location and Lauren's histological type [19]. These data justify the need for an adapted or even intensified adjuvant therapeutic strategy to reduce the relapse rate depending on these prognostic factors. Although the role of adjuvant chemotherapy (CT) has been established and adjuvant CT is routinely

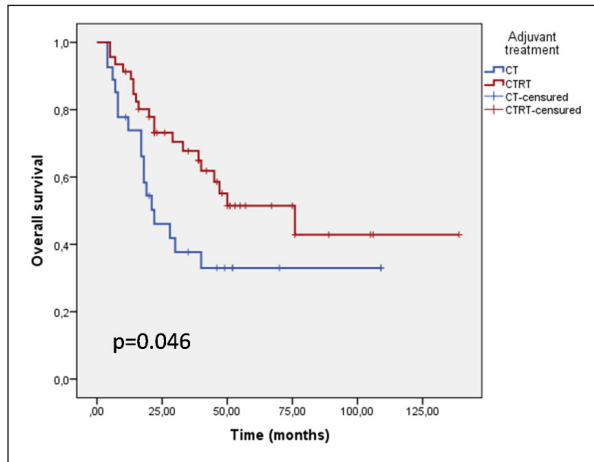


Figure 6. Kaplan-Meier survival curves of overall survival in lymph node-positive patients. There was a significant difference between adjuvant chemotherapy (CT) group and adjuvant radiochemotherapy (CTR) ($p = 0.046$)

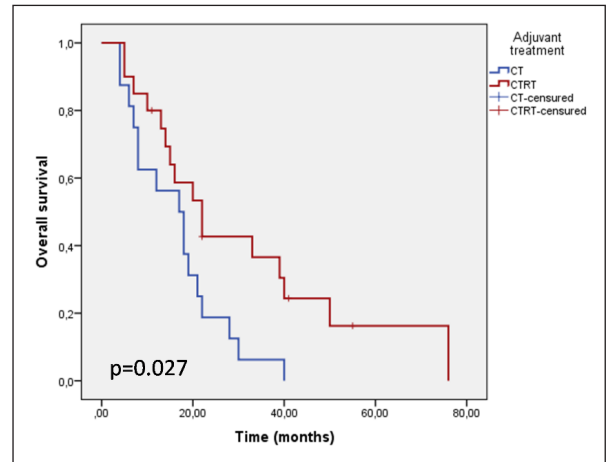


Figure 8. Kaplan-Meier survival curves of overall survival in patient with PNI positive tumors. There was a significant difference between adjuvant chemotherapy (CT) group and adjuvant radiochemotherapy (CTR) ($p = 0.027$)

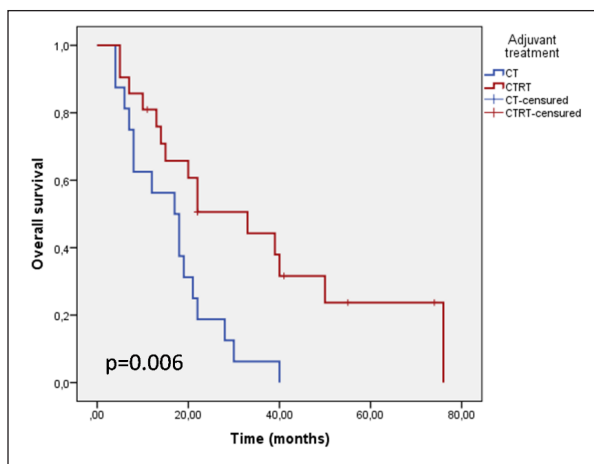


Figure 7. Kaplan-Meier survival curves of overall survival in patient with LVI positive tumors. There was a significant difference between adjuvant chemotherapy (CT) group and adjuvant radiochemotherapy (CTR) ($p = 0.006$)

used for D2-dissected gastric cancer, the value of combining postoperative RT with CT is still largely debated. Our study suggested the superiority of adjuvant CTRT to adjuvant CT not only in terms of reducing the risk of overall recurrence but also in improving the 5-year OS, especially in patients with lymph node metastasis, high LNR and lymphovascular and perineural invasion which is the most interesting feature. Moreover, based on the literature data, we aimed to identify selection criteria to propose intensive adjuvant treatment for a subgroup of patients presenting conventional pejorative prognostic factors of survival. These results

were consistent with data from the literature regarding the prognostic impact of CTRT on recurrence. However, it seems that our study is distinguished by encouraging results in favor of CTRT in improving overall survival (55.9% vs. 33%; $p = 0.015$).

Very few studies have compared adjuvant CT with adjuvant CTRT and most of them did not show a significant improvement of overall survival by associating RT to CT despite the gain in terms of recurrence survival. The ARTIST trial was the first phase III study that compared the adjuvant treatment with chemotherapy (6 cycles of XP — capecitabine and cisplatin) in 172 patients vs. the association of chemotherapy and radiotherapy (2 cycles of XP + XP and radiotherapy + 2 more cycles of XP) in 188 patients after D2-lymphadenectomy [20]. The addition of XRT to XP chemotherapy did not significantly prolong the 3-year disease-free survival (DFS) (78.2% vs. 74.2%; $p = 0.862$). Moreover, in the updating of their results after 7 years of follow-up, DFS remained similar between treatment arms (HR = 0.740; 95% CI = 0.520–1.050; $p = 0.0922$), OS was also similar (HR = 1.130; 95% CI = 0.775–1.647; $p = 0.5272$) but the addition of radiotherapy provided an improvement in disease-free survival for node-positive patients [11]. In a South Korean phase III study of Kim et al, 90 patients having had R0 surgery with D2 dissection were randomized between two arms: an adjuvant CT arm (44 patients) and an adjuvant CTRT arm (46 patients) [21]. In this study, although five-year

disease-free survival (DFS), which was the primary endpoint of this trial, was not significantly improved in the combined modality, locoregional recurrence-free survival (LRRFS) (93.2% vs. 66.8%, $p = 0.014$) and metastatic recurrence-free survival (73.5% vs. 54.6%, $p = 0.056$) were improved. In contrast to these two trials, a significant benefit in 5-year RFS (45.2% vs. 35.8; $p = 0.012$), but not in OS, was shown in a Chinese multicenter randomized trial in which patients with D2-dissection were randomly assigned to chemotherapy alone (165 patients) or intensity-modulated RT plus concurrent chemotherapy (IMRT-C) (186 patients) [22]. In this study, the IMRT-C was associated with an increase in the median duration of RFS compared to chemotherapy (50 months vs. 32 months) and the hazard ratio for recurrence was 1.35 (95% CI: 1.03–1.78; $p = 0.029$). These data support our results as we found significant improvement in PFS at 5 years (60.9% vs. 36%, $p = 0.03$) with adjuvant radiochemotherapy compared to adjuvant CT.

The analysis of the patterns of recurrence of our patients revealed that locoregional and distant relapses were more frequent in the adjuvant CT group than in the CTRT group without a significant statistical difference, which is in line with the results of the ARTIST trial where locoregional relapse was more frequent in the XP arm (13%) than in the XPRT arm (7%; $p = 0.033$) and distant metastases were observed in 27% and 24% of patients in the XP and XPRT arms, respectively ($p = 0.5568$) [11]. Moreover, in the randomized study of Zhu et al. the rate of distant metastasis was slightly higher in the chemotherapy group (26.7% vs. 24.2%, $p = 0.595$) [22].

The meta analysis of the results of the two randomized controlled trials from South Korea [20, 21] and the study of China [22] comparing adjuvant chemotherapy and CRT, which included a total of 895 patients, showed that postoperative CTRT significantly improved locoregional recurrence-free survival (HR = 0.53, 95% CI = 0.32–0.87, $p = 0.01$) and disease-free survival (HR = 0.72, 95% CI = 0.59–0.89, $p = 0.002$); without a significant improvement of distant metastasis recurrence-free survival (HR = 0.86; 95% CI = 0.66–1.11; $p = 0.25$) and overall survival (HR = 0.79, 95% CI = 0.61–1.03, $p = 0.08$) [10].

In our study, the analysis of subgroups according to the extent of lymphadenectomy had demonstrat-

ed the superiority of CTRT to CT as an adjuvant treatment to D2 lymphadenectomy both in terms of OS and PFS. In the group of patients with less extensive lymphadenectomy, CTRT offered a better OS (19% vs. 66.7%) and PFS (21.4% vs. 77.8%) without significant difference. This last observation agrees with the data from the SWOG/INT-0116 trial where the CTRT improved the oncological results of all patients who had mostly had D0–D1 dissection [23]. Paradoxically, Dikken et al. had retrospectively compared survival and recurrence patterns of 91 patients in phase I and II studies evaluating more intensified postoperative CRT with 694 patients from the Dutch Gastric Cancer Group Trial (DGCT) that randomly assigned patients between D1 and D2 lymphadenectomy and suggested that the addition of CTRT seemed to be beneficial in preventing local recurrence after D1-dissection, but not after D2-dissection [24].

Consequently, the role of adjuvant RT remains unclear after an adequate lymphadenectomy but it seems that the identification of a high-risk subgroup for loco-regional recurrence among D2-dissected patients is essential and of higher priority than assessing the efficacy of a regular application of adjuvant CRT in all D2-dissected gastric cancer patients [25].

Regardless of the type of lymphadenectomy, the lymph node status remains largely involved in the therapeutic indications since it represents a prognostic factor determining survival and recurrence [26, 27]. In fact, in our study, the adjuvant CTRT allowed a significant improvement in the overall 5-year survival of patients with lymph node involvement ($p = 0.046$), with a tendency to better progression-free survival ($p = 0.057$). These data appear to be consistent with those of the ARTIST trial where the subgroup analysis of 396 patients with node-positive disease revealed that the 3-year DFS was significantly improved in the XPRT arm compared to the XP arm (76% vs. 72% in XPRT arm; $p = 0.04$) and found that in patients without lymph node involvement, chemotherapy would be more beneficial than CTRT in terms of DFS (HR = 1.359, 95% CI = 0.477–3.876) with no significant difference [11]. Moreover, we have found that the benefit provided by the adjuvant CTRT in terms of OS (13% vs. 48.8%, $p = 0.0078$), but especially in terms of PFS (16.5% vs. 57.8%, $p = 0.022$), was significantly higher than the adjuvant CT, es-

pecially in patients with more advanced pN stages (pN2–pN3). This is consistent with the Korean report of Chang et al. which revealed that N3 patients are at substantial risk of regional recurrence as well as peritoneal and distant spread despite D2 dissection and adjuvant chemotherapy suggesting that an intensified treatment by chemoradiotherapy would improve survival outcomes [28].

As lymph node ratio (LNR) was previously identified as an independent prognostic factor after D1 and D2 lymph node dissections [29, 30], we compared the prognostic impact of adjuvant CTRT to that of adjuvant CT according to the lymph node ratio. This subgroup analysis had demonstrated that, unlike patients whose LNR was less than 25%, those whose lymph node ratio was greater than 25% and treated with adjuvant CTRT had a significant gain of 40.2% in terms of OS at 5 years and 46.9% in terms of PFS at 5 years compared to patients who received adjuvant CT. These findings are consistent with the results of the subgroup analysis of the ARTIST trial where the effect of radiotherapy in patients with a high lymph node ratio (≥ 0.083) was different from the effect in patients with a low lymph node ratio in both DFS (HR = 2.03; 95% CI = 1.44–2.87; $p < 0.01$) and overall survival (HR = 1.98; 95% CI = 1.38–2.83; $p < 0.01$) suggesting that the lymph node ratio might represent an absolute, reproducible factor that could help select patients for CTRT [11]. On the other hand, the integration of the notion of the lymph node ratio during the evaluation of the prognostic contribution of adjuvant CTRT was mentioned in the retrospective study by Costa et al. [31]. Indeed, this study included 142 patients (90 patients treated with surgery only and 52 patients treated with resection followed by adjuvant CTRT) classified according to the LNR (NR0 = 0%, NR1 = 1–9%, NR2 = 10–25%, NR3 > 25%) and concluded that the individuals with a lower LNR had no benefit with adjuvant CTRT both in OS (78.8% vs. 76.9%) and DFS (81.8% vs. 76.9%), whereas those with a higher LNR treated by CTRT had a significant improvement in OS (71.4% vs. 30.9%; $p = 0.038$) and superior but not statistically significant gain regarding DFS (48.9% vs. 30.3%; $p = 0.145$). In view of these data, it seems that lymph node involvement represents a decisive element in favor of the intensification of the adjuvant treatment of locally advanced gastric cancers by associating radiotherapy

with chemotherapy, which represents the rationale of the ongoing ARTIST II trial aiming to evaluate the benefit of adjuvant combined therapy only in pN+ patients.

Depth of parietal invasion has long been considered an independent factor for survival and recurrence in gastric cancer [32–34] and authors consider this parameter as a determining factor of the delay of relapses. In fact, in the study by Otsuji [35], the depth of parietal infiltration represents an independent factor determining the time to recurrence with a median time of 11.7 months in the T4 stages, and 15.5 months in the pT3 stages, 22.2 months in pT2 stages, and 39.5 months in pT1 stages without forgetting that lymph node involvement is significantly correlated with the depth of parietal invasion. Based on these data, we suggest a combined strategy for T3–T4 tumors as we found that in this group of patients the benefit provided by CTRT compared to CT both in terms of OS (34.4% vs. 58.5%; $p = 0.048$) and PFS (35.6% vs. 64%; $p = 0.051$) is superior. Whereas in the case of earlier tumors the two strategies remain comparable.

Moreover, as PNI and LVI have been investigated as prognostic factors of recurrence and overall survival in resected gastric cancer [36, 37], we found that CTRT provided better overall survival rates and lower recurrence in the subgroup of patients with PNI and LVI compared to adjuvant chemotherapy and this significant difference was not reported in cases of PNI and LVI negative tumors. Our findings are similar to those reported by Yu et al. who evaluated the influence of adjuvant RT on recurrence at each locoregional subsite, and investigated which subgroups received the most benefit by comparing failure patterns between CCRT and chemotherapy groups of the ARTIST trial [38]. In this study, the authors used Forest plots to represent locoregional recurrence-free survival (LRRFS) HRs and 95% CIs and demonstrated that patients with lymphovascular invasion (HR = 0.45, 95% CI = 0.22–0.90, $p = 0.02$) showed greater LRRFS benefit from XPRT than XP. It is therefore wise to consider that these two histological data would be helpful to select patients for an intensified treatment with radiotherapy as suggested by the review of Agolli et al. [39].

In addition, the results of our study agree with those of the Mac Donald trial suggesting that post-

operative CRTT would be more effective in the intestinal type [16]. The ARTIST trial also demonstrated that the effect of the addition of radiotherapy on DFS and OS differed by Lauren classification (interaction $p = 0.04$ for PFS; interaction $p = 0.03$ for OS). The Forest plot of HRs and 95% CIs for disease-free survival revealed that the effect of radiotherapy in patients with intestinal-type GC (HR = 0.442, 95% CI = 0.231–0.845) was different from the effect in patients with diffuse GC (HR = 0.826, 95% CI = 0.543–1.255) [11].

And, finally, in 2016, in the CRITICS study, 788 patients were randomized after preoperative chemotherapy with ECX or EOX and surgery between a group of postoperative chemotherapy (393 patients) and a group of postoperative radiochemotherapy (395 patients) [40]. This international study showed the absence of difference in terms of OS between the two groups (41.3% in the CT adj arm and 40.9% in the CRTT adj arm, $p = 0.99$) with different profiles of toxicity: higher grade III hematological toxicity in the adj CT arm (44% vs. 34%; $p = 0.01$) and higher grade III gastrointestinal toxicity in the CRTT arm (37% vs. 42%; $p = 0.14$), which is in line with our results where the rate of grade 3–4 gastrointestinal toxicity was 22.6% in the CRTT group and 18.5% in the CT group and the rate of grade 3–4 hematological toxicity was higher in the CT group (29.6%) than in the CRTT group (9.3%). Moreover, most comparative studies have shown no increase in grade 3–4 treatment-related toxicity in the CRTT group with modern RT techniques (IMRT or CT-based 3D-CRT) compared with the chemotherapy alone group [10].

However, our study has certain limitations. Indeed, this is a retrospective monocentric study including a small number of patients with variable CT regimens, which leads to a higher risk of selection bias. Furthermore, there was a different stage distribution between the two groups, with more stage III patients in the CT group than in the CRT group (70.4% vs. 52.8%; $p = 0.014$), which reflects the attitude adopted in our institution favoring an aggressive systemic treatment strategy for locally advanced tumors likely to present a higher risk of metastatic recurrence rather than locoregional recurrence. This high rate of stage III in the CT group did not translate into a statistically significant difference in terms of survival and CRTT was still superior to adjuvant CT. In addition, our study

included patients whose lymphadenectomy was not extensive with a rate of D1-lymphadenectomy of 8.8% and a number of LN lower than 15 in 20% of the cases. However, our results remain interpretable since the interest of an extended lymphadenectomy remains a subject of controversy in the area of adjuvant therapies and new techniques of irradiation taking into account the morbidity associated with lymph node surgery reported in the majority of randomized studies.

Conclusion

Even if there are no strict recommendations concerning the intensification of the adjuvant treatment of locally advanced gastric cancers by associating radiotherapy with chemotherapy, the indication of this combined approach should take into account the prognostic factors that have a significant impact on recurrence and survival outcomes to select patients who can benefit from this approach, especially those with lymph node involvement, high LNR LVI, and PNI.

Conflicts of interest

The authors declare no conflicts of interest.

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Ethics approval

The ethics review board approved this study and did not require informed consent from study participants since this was a strictly registry-based study.

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