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ORIGINAL ARTICLE – GASTROINTESTINAL ONCOLOGY

Does Adjuvant Chemoradiotherapy Improve the Prognosis of Gastric Cancer After an R1 Resection? Results from a Dutch Cohort Study

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ABSTRACT

Objective. The aim of this study was to investigate the impact of adjuvant chemoradiotherapy (CRT) on survival of non-metastatic gastric cancer patients who had undergone an R1 resection.

Methods. We compared the survival of patients after an R1 gastric cancer resection from the population-based Netherlands Cancer Registry who did not receive adjuvant CRT (no-CRT group) with the survival of resected patients who had been treated with adjuvant CRT (CRT group) at our institute. Patients who had a resection between 2002 and 2011 were included. CRT consisted of radiotherapy (45 Gy) combined with concurrent cisplatin- or 5-fluorouracil-based chemotherapy. The impact of CRT treatment on overall survival was assessed using multivariable Cox regression and stratified propensity score analysis.

Results. A series of 409 gastric cancer patients who had undergone an R1 resection were studied (no-CRT, $N = 369$; CRT, $N = 40$). In the no-CRT group, median age was higher (70 vs. 57 years; $p < 0.001$) and the percentage of patients with diffuse-type tumors was lower (43 vs. 80 %; $p < 0.001$). There were no significant differences in pathological T- and N-classification. There was a significant difference in median overall survival between the no-CRT and CRT group (13 vs. 24 months; $p = 0.003$). In a multivariable analysis, adjuvant CRT was an independent prognostic factor for improved overall survival (hazard ratio 0.54; 95 % confidence interval 0.35–0.84). This effect of CRT was further supported by propensity score analysis.

Conclusions. Adjuvant CRT was associated with an improved survival in patients who had undergone an R1 resection for gastric cancer.

Surgical resection remains the cornerstone in potentially curative treatment of gastric cancer. However, performing a radical surgical resection with tumor-negative resection margins in locally advanced disease frequently poses a challenge. In current patient series, rates of microscopic tumor-positive margins, defined as an R1 resection, vary from 2 to 22 %.[1–3] Irrespective of its association with advanced tumor stage and aggressive tumor biology, an R1 resection has frequently been identified as an independent poor prognostic factor.[3–6] There are different opinions on the preferred strategy after an R1 gastric cancer resection. Some authors advocate considering a re-resection in every patient, while others believe this has little added value in patients with advanced nodal disease, given the high risk of peritoneal and distant metastases.[4–7] Another strategy could be the administration of adjuvant chemoradiotherapy (CRT). However, published randomized studies on adjuvant CRT have invariably included patients with a radical

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(R0) gastric cancer resection.[8,9] The recently published updated results of the INT-0116 study have shown that patients who had undergone an R0 gastric cancer resection followed by adjuvant CRT had a lower rate of locoregional recurrence and improved overall survival compared with patients treated with surgery only.[10] In several smaller studies, patients with an R1 resection have been included but these are mainly descriptive reports and feasibility studies, and the value of adjuvant CRT in R1 resected gastric cancer remains to be explored.[11–13] Albeit in a subgroup analysis of a retrospective cohort study, Dikken et al.[14] have suggested a benefit of adjuvant CRT after an R1 gastric cancer resection in terms of improved local control and overall survival compared with surgery only. Because of the scarcity of data on this subject, the aim of the current study was to compare the survival of patients who had undergone an R1 gastric cancer resection followed by adjuvant CRT at our institute with a cohort of patients from the Netherlands Cancer Registry (NCR) who had undergone an R1 gastric cancer resection without CRT.

PATIENTS AND METHODS

Adjuvant Chemoradiotherapy (CRT) Group (CRT Group)

All consecutive patients who had undergone adjuvant CRT after an R1 resection for non-metastatic gastric cancer between 1 January 2002 and 31 December 2011 were included. An R1 resection was defined as the presence of tumor cells in the resection margins on standard microscopic examination. We excluded patients in whom gross residual tumor was left behind after surgery (R2 resection). Patients were surgically treated in our hospital or referred for adjuvant CRT after surgical treatment elsewhere in The Netherlands. According to the national guidelines, gastric cancer resection was combined with, preferably, at least a D1 lymph node dissection without routine splenectomy or pancreatic tail resection. Between 2002 and July 2008, adjuvant CRT was given within clinical phase I and II trials.[15–17] Since 2009, this adjuvant treatment has been advised for patients at increased risk for locoregional recurrence, i.e. R1 resection and/or extensive lymph node involvement. The given CRT regimens were the same as used in the Intergroup 0116 trial or phase I/II studies.[8,15–17] In short, all patients received 45 Gy in 25 fractions in 5 weeks on the gastric bed, gastric remnant when present, the anastomosis and the surrounding lymph node basins. The clinical target volumes (CTVs) were constructed using a contouring atlas.[18] In addition, all patients received capecitabine twice daily on the days the patients received radiotherapy, with or without daily or weekly cisplatin, according to the study protocol in which the patient was entered. CRT had to be started within 4–12 weeks after surgery. This study was performed in accordance with institutional ethical guidelines based on good clinical practice.

No Adjuvant CRT Group (No-CRT Group)

A control group of patients who had undergone an R1 gastric cancer resection without adjuvant CRT was obtained from the population-based NCR. Data on all newly diagnosed patients with a malignancy in The Netherlands are entered in this nationwide registry. Patient, tumor and treatment characteristics are collected by trained registrars within 9 months after diagnosis. Topography and morphology are coded according to the International Classification of Disease for Oncology (ICD-O).[19] Patients who had undergone a gastric resection for non-metastatic (M0) gastric cancer (C16.1–16.9) between 1 January 2002 and 31 December 2011 were extracted from the NCR. For the current study, adenocarcinomas with ICD-O morphology codes 8140 (adenocarcinoma NAO), 8142 (linitis plastica), 8144–45 (intestinal and diffuse-type adenocarcinoma), 8211 (tubular carcinoma), 8480–81 (mucinous and mucin-producing adenocarcinoma), and 8490 (signet ring cell carcinoma) were selected. ICD-O codes were used to classify tumors as either diffuse or non-diffuse-type according to Lauren.[20] Patients with diffuse-type adenocarcinoma, linitis plastica, and signet ring cell carcinoma with a poor differentiation were classified as diffuse-type gastric cancer. All other patients were classified as non-diffuse-type gastric cancer. For the purpose of this study, all patients were staged according to the 7th edition of the International Union against Cancer (IUCC) TNM classification.[21] Follow-up was updated until 1 January 2012.

Statistical Analysis

Characteristics of patients with or without adjuvant CRT treatment were compared using the Pearson's Chi square or Fisher's exact test for nominal variables, the Chi square test of trend for ordinal variables, and the Mann–Whitney *U* test for continuous variables, as appropriate. Overall survival was defined as the period between surgery and the date of death from any cause. Patients lost to follow-up or alive at the end of the study were censored. Survival curves were plotted using the Kaplan–Meier method and compared using the log-rank test. The Cox proportional hazards model was used to perform univariable and multivariable analyses of prognostic factors for overall survival. The covariates studied were age, sex, total number of evaluated lymph nodes, tumor location, the extent of surgical resection, histological subtype, pathological T- and N- classification, the receipt of neoadjuvant chemotherapy,

TABLE 1 Clinicopathological characteristics of CRT and no-CRT groups

Characteristic	CRT		No-CRT		*p* value
All patients	*N* 40	% 100	*N* 369	% 100	
Sex					
Male	19	48	211	58	0.246[d]
Female	21	52	158	42	
Age (years)					
≤60	26	65	96	26	*<0.001*[e]
61–75	11	27	148	40	
≥75	3	8	125	34	
Tumor location					
Proximal	5	13	8	2	*0.005*[c]
Middle	7	18	64	17	
Distal	17	42	176	48	
Overlapping	11	27	121	33	
Extent of surgery					
Partial gastrectomy	20	50	197	53	*0.002*[c]
Total gastrectomy	12	30	152	42	
Multi-organ resection	8	20	20	5	
Number of evaluated lymph nodes					
<15	28	70	211	57	0.124[c]
≥15	12	30	132	36	
Unknown	0	0	26	7	
Histological subtype[a]					
Non-diffuse	8	20	210	57	*<0.001*[d]
Diffuse type	32	80	159	43	
pT classification[b]					
T1	0	0	6	2	0.746[e]
T2	0	0	24	7	
T3	16	40	95	26	
T4	24	60	244	66	
pN classification[b]					
N0	11	28	64	17	0.291[e]
N1/2	16	40	166	45	
N3	13	32	139	38	
Neoadjuvant chemotherapy					
No	30	75	283	77	0.845[d]
Yes	10	25	86	23	

Italic values indicate statistical significance ($p < 0.05$)

CRT chemoradiotherapy

[a] According to the classification of Lauren[20]

[b] Staging according to the pathological (pTNM) classification of the American Joint Committee on Cancer, 7th edition[21]

[c] Fisher's exact test

[d] Pearson's χ^2 test

[e] χ^2 test of trend

and the receipt of adjuvant treatment. Survival difference between the comparison groups was assessed using a multivariable Cox regression. Furthermore, to reduce the potential bias inherent with treatment assignment, analyses were stratified by propensity score. First, the propensity score (i.e. the conditional probability of receiving treatment given a set of observed covariates) was estimated using a logistic regression, with CRT treatment as the dependent variable and all other covariates, except the number of evaluated lymph nodes and pT classification, as independent variables. The two covariates were excluded from the propensity score model due to the lack of observations in one or more of their subcategories for the CRT group (Table 1). Second, the association between CRT and overall survival was assessed by Cox regression, with CRT, the number of evaluated lymph nodes, and pathological T classification as independent variables, and stratified by quartiles of the propensity score. All tests were two-sided and a p value < 0.05 was considered statistically significant. SPSS statistical software, version 20.0 (IBM Corporation, Armonk, NY, USA) was used for all statistical analyses.

RESULTS

Study Patients

All included patients were treated between 1 January 2002 and 31 December 2011. A detailed flow diagram of patient inclusion is shown in Fig. 1a (CRT group) and 1b (no-CRT group).

Patient Characteristics

Clinicopathological characteristics are summarized in Table 1. Patients in the CRT group were younger (median age 57 years, range 32–83 years) than in the no-CRT group (median age 70 years, range 21–89 years) and there was a significant difference in tumor location. Patients in the CRT group underwent more extended resections compared with patients in the no-CRT group (multi-organ resection in 20 % in the CRT group vs. 5 % in the no-CRT group). There were significantly more diffuse-type tumors in the CRT group (80 %) than in the no-CRT group (43 %). Tumor and nodal stage were not significantly different between both groups. In the no-CRT group, 35 of 369 patients (10 %) were treated with adjuvant chemotherapy.

Overall Survival, Prognostic Factors and CRT Treatment Effect

Median follow-up for all patients was 18 months in the CRT group and 11 months in the no-CRT group. Three-year overall survival in the CRT group was 40 % compared with 19 % in the no-CRT group (Fig. 2). There was a significant difference in median overall survival between

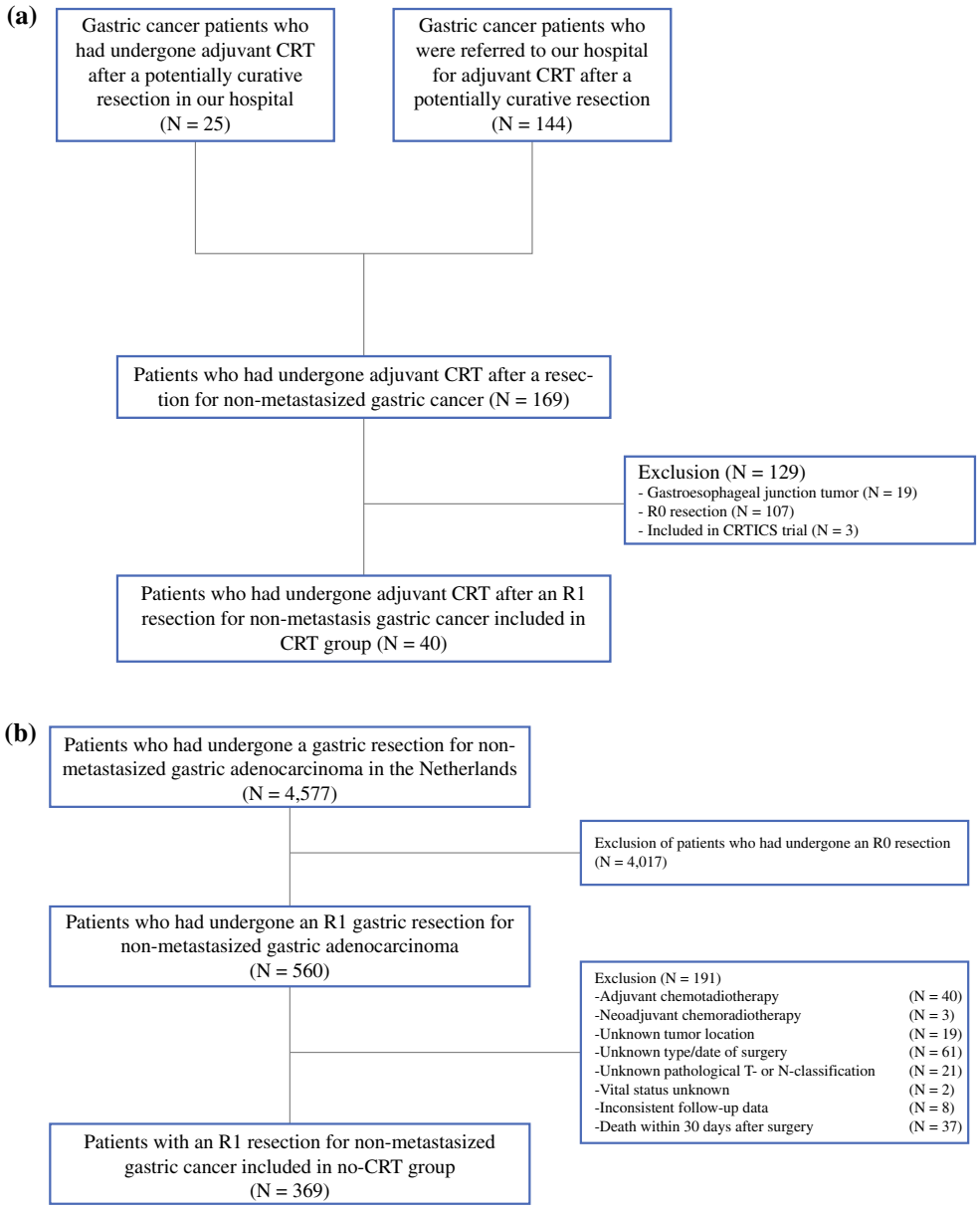

FIG. 1 Patient inclusion in the **a** CRT group ($N = 40$), and **b** no-CRT group ($N = 369$) (2002–2011). *CRT* chemoradiotherapy, *R0* microscopically radical, *R1* microscopically tumor-positive resection margin(s)

these two groups (24 months vs. 13 months; $p = 0.003$). In univariable analyses, tumor location, the extent of surgery, pathological T- and N- classification, and adjuvant therapy were significantly associated with survival (Table 2). Adjuvant CRT was a good prognostic factor for overall survival compared with no adjuvant treatment [univariate Cox hazard ratio (HR) 0.56; 95 % confidence interval (CI) 0.38–0.82]. In multivariable analysis, histological subtype, pathological T- and N-classification, and adjuvant therapy were independent significant prognostic factors. Adjuvant CRT remained an independent good prognostic factor (multivariate Cox HR 0.54; 95 % CI 0.35–0.84). The independent beneficial effect of CRT on overall survival was further confirmed by the propensity score analysis (propensity score-stratified HR 0.57; 95 % CI 0.38–0.88) (Table 2).

DISCUSSION

Microscopically tumor-positive margins remain a major problem in gastric cancer treatment, especially in Western countries where patients usually present with an advanced tumor stage, which can hinder radical resection. In the current study, the R1 resection rate was 12 % based on the

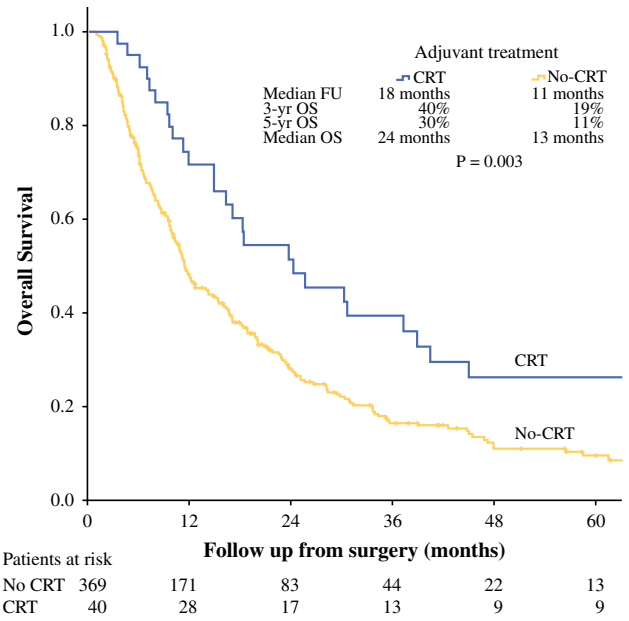

FIG. 2 Overall survival of patients who had undergone an R1 resection for non-metastasized gastric cancer with and without adjuvant chemoradiotherapy. *CRT* chemoradiotherapy, *FU* follow-up, *OS* overall survival

population-based NCR. Reported R1 resection rates differ considerably between patient series; in a recent systematic review on tumor-positive margins in gastric cancer surgery, R1 resection rates varied from 2 to 22 % in studies in which patients with an R2 resection were excluded.[22] The variation is likely caused by differences in tumor stage and histology, which are important predisposing factors for tumor-positive surgical margins.[3,4,6,7,23] The reported survival rates after an R1 gastric cancer resection are poor. In a large American study ($N = 18{,}365$), 5-year overall survival was 28 % after an R0 resection for gastric cancer and only 8 % in patients with an R1 resection.[24] In addition, in a Taiwanese study ($N = 1{,}565$), an R1 resection had a detrimental effect on survival (5-year overall survival 60 % after an R0 resection vs. 13 % after an R1 resection).[4] These results are in line with the 5-year overall survival of 11 % in the group of patients who did not receive CRT after an R1 resection in the current study.

In some studies on R0-resected gastric cancer, adjuvant CRT was associated with improved local control and overall survival. In the INT-0116 trial, patients were randomized for adjuvant CRT versus observation after an R0 gastric cancer resection.[8] In the updated analysis of this trial, the local recurrence rate was 24 % in the CRT group versus 47 % in the surgery-only group.[10] Overall survival was also significantly improved (median overall survival 27 vs. 19 months). In the recently published ARTIST trial, patients were randomized to adjuvant CRT versus chemotherapy after an R0 gastric cancer resection with a D2 lymph node dissection. Disease-free survival was not significantly different between these groups. One explanation for this result is that the majority of patients in both groups (60 %) had stage IB or II disease with a good prognosis (5-year disease-free survival 80–90 %), thereby increasing the difficulty to show additional benefit of further treatment. In a subgroup analysis of patients with positive nodal disease, disease-free survival in the CRT arm was statistically significantly improved to 77.5 versus 72.3 % in the chemotherapy arm.[9]

Given the improvement in locoregional control, and a benefit for patients with locally advanced disease, adjuvant CRT has also been suggested as a strategy after an R1 gastric cancer resection. However, both randomized trials on adjuvant CRT only included patients with an R0 gastric cancer resection,[8,9] thereby leaving uncertainty about the value of adjuvant CRT after an R1 resection. Studies including patients with an R1 resection are scarce and usually involve small retrospective patient series or phase I/II trials.[11–13,15,16,25] In the largest of these studies, 37 of 166 (22 %) patients had undergone an R1 resection.[12] Three-year overall survival was 33 % for patients with an R1 resection, which is in line with the results from the current study (3-year overall survival, 40 %). To our knowledge, there is only one study in which the effect of adjuvant CRT on outcome in gastric cancer patients treated with and without adjuvant CRT following an R1 resection is evaluated.[14] In that retrospective study, local recurrence and survival of patients treated with adjuvant CRT in our institute were compared with those treated with surgery alone in the previous Dutch D1/D2 trial (1989–1993).[26] In the subgroup of patients with an R1 resection, multivariable analysis showed that adjuvant CRT was associated with both less local recurrences and improved overall survival.[14] However, it should be noted that the number of patients who had undergone an R1 resection followed by adjuvant CRT was limited ($N = 22$) and the adjuvant CRT and surgery-only group did not match in time of accrual, and patients were treated approximately 10 years apart.

There are some limitations to the current study, including those related to the retrospective data analysis and the use of a large national database. A considerable number of patients from the NCR cohort had to be excluded due to missing data (Fig. 1b). Nevertheless, the no-CRT group in this study still contained a large number of unselected patients with an R1 resection for non-metastatic gastric cancer available for comparison. From the NCR, patients treated in the same time period were extracted to reduce bias caused by differences in diagnostic work-up and surgical treatment. However, referral bias is obviously present in this study as most patients (35 of 40) underwent surgery in another hospital and were referred for postoperative treatment in our center. These patients were

TABLE 2 Cox regression analysis of prognostic factors for overall survival

	No. of events	3-year OS (%)	Univariate		Multivariate	
			HR (95 % CI)	*p* value	HR (95 % CI)	*p* value
Sex						
Male	175	20	Ref.		Ref.	
Female	132	22	1.05 (0.84–1.32)	0.670	1.03 (0.81–1.29)	0.832
Age (years)				0.090[d]		0.132[d]
≤60	92	27	Ref.		Ref.	
61–75	122	15	1.18 (0.90–1.55)	0.239	1.07 (0.79–1.45)	0.650
≥75	93	21	1.28 (0.96–1.71)	0.092	1.29 (0.92–1.81)	0.136
Tumor location						
Overlapping[a]	109	10	Ref.		Ref.	
Proximal	10	25	0.70 (0.36–1.33)	0.276	0.90 (0.46–1.76)	0.751
Middle	56	17	0.74 (0.54–1.03)	0.072	0.74 (0.53–1.04)	0.085
Distal	132	30	0.59 (0.46–0.77)	*<0.001*	0.71 (0.52–0.95)	*0.023*
Extent of surgery						
Partial gastrectomy	152	29	Ref.		Ref.	
Total gastrectomy	130	12	1.52 (1.20–1.93)	*0.001*	1.15 (0.88–1.50)	0.319
Multi-organ resection	25	11	1.63 (1.07–2.50)	*0.024*	1.07 (0.66–1.73)	0.788
Number of evaluated lymph nodes						
<15	180	24	Ref.		Ref.	
≥15	103	18	1.22 (0.96–1.56)	0.110	0.92 (0.70–1.20)	0.533
Unknown	24	12	1.43 (0.93–2.19)	0.102	1.07 (0.68–1.66)	0.780
Histological subtype[b]						
Non-diffuse	155	24	Ref.		Ref.	
Diffuse	152	18	1.21 (0.97–1.51)	0.097	1.31 (1.03–1.68)	*0.030*
pT classification[c]				*<0.001*[d]		*0.001*[d]
T1/2	16	15	Ref.		Ref.	
T3	72	67	1.54 (0.89–2.65)	0.120	1.76 (1.01–3.07)	*0.047*
T4	219	31	2.28 (1.37–3.79)	*0.002*	2.30 (1.36–3.89)	0.002
pN classification[c]				*<0.001*[d]		*<0.001*[d]
N0	42	44	Ref.		Ref.	
N1/2	139	23	1.60 (1.13–2.26)	*0.008*	1.61 (1.13–2.29)	*0.009*
N3	126	7	2.63 (1.85–3.74)	*<0.001*	2.36 (1.61–3.45)	*<0.001*
Neoadjuvant chemotherapy						
No	250	21	Ref.		Ref.	
Yes	57	19	0.94 (0.70–1.25)	0.655	1.09 (0.79–1.50)	0.588
Adjuvant treatment (conventional adjustment)						
No chemoradiotherapy	278	19	Ref.		Ref.	
Chemoradiotherapy	29	40	0.56 (0.38–0.83)	*0.004*	0.54 (0.35–0.84)	*0.005*
Adjuvant treatment (propensity score stratification)						
No chemoradiotherapy	278	19	–		Ref.	
Chemoradiotherapy	29	40	–	–	0.57 (0.38–0.88)	*0.010*

Italic values indicate statistical significance ($p < 0.05$)

CI confidence interval, *HR* hazard ratio, *OS* overall survival

[a] Considering the number of events, this category was used as a reference

[b] According to the classification of Lauren[20]

[c] Staging according to the pathological (pTNM) classification of the American Joint Committee on Cancer, 7th edition[21]

[d] Test of trend based on significance of regression coefficient for continuous variable

required to have adequate postoperative recovery before starting CRT. Additional treatment is more often considered in younger patients, and the median age of our patients (57 vs. 70 years) is consistent with this phenomenon.

To correct for confounding by differences in clinicopathological characteristics (including age) between the CRT and no-CRT groups, we performed both a conventional multivariable analysis and propensity score analysis. The HR of CRT was virtually unchanged in the univariable, multivariable, and propensity score analysis, suggesting that this effect is not confounded by the observed variables. However, our findings could have been confounded by comorbidity measures, such as the American Society of Anesthesiologists (ASA) score or the Charlson Comorbidity Index, not available in the NCR dataset.

Obviously, a randomized phase III trial is the preferred method to evaluate the benefit of adjuvant treatment strategies. It is highly unlikely that such a trial will ever be completed in a group of gastric cancer patients who have undergone an R1 resection. Therefore, evidence for the optimal treatment strategy after an R1 gastric cancer resection will be limited to non-randomized cohort series and subgroup analyses from randomized trials. To our knowledge, the latter are currently not (yet) available. Prevention of an R1 resection would probably be the best treatment. Unfortunately, preoperative imaging, especially in diffuse-type carcinomas, frequently underestimates tumor extension and leads to surgical and/or pathological irradicality. Whether preoperative CRT can have a beneficial role is being explored in the TOPGEAR trial (clinicaltrials.gov NCT 01924819). Another unanswered question is the prognostic significance of an R1 resection in patients who received preoperative chemotherapy. It may well be that in these circumstances the prognostic significance is even worse compared with non-pre-treated patients. Also, the improvement of locoregional control and improved survival with postoperative CRT is unknown in these circumstances. The currently running CRITICS study will provide data, as the by randomization assigned postoperative treatment modality (chemotherapy vs. CRT) will not be changed due to pathological finding of an R1 resection.[27] Finally, as is frequently seen in Western patient series, the current study is also limited by an inadequate lymph node yield (<15 lymph nodes) in the majority of patients. This could have led to an inaccurate N classification.

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REFERENCES

1. Cunningham SC, Kamangar F, Kim MP, et al. Survival after gastric adenocarcinoma resection: eighteen-year experience at a single institution. *J Gastrointest Surg*. 2005;9:718–25.
2. Songun I, Bonenkamp JJ, Hermans J, van Krieken JH, van de Velde CJ. Prognostic value of resection-line involvement in patients undergoing curative resections for gastric cancer. *Eur J Cancer*. 1996;32A:433–7.
3. Stiekema J, Cats A, Kuijpers A, et al. Surgical treatment results of intestinal and diffuse type gastric cancer. Implications for a differentiated therapeutic approach? *Eur J Surg Oncol*. 2013;39:686–93.
4. Wang SY, Yeh CN, Lee HL, et al. Clinical impact of positive surgical margin status on gastric cancer patients undergoing gastrectomy. *Ann Surg Oncol*. 2009;16:2738–43.
5. Kim SH, Karpeh MS, Klimstra DS, Leung D, Brennan MF. Effect of microscopic resection line disease on gastric cancer survival. *J Gastrointest Surg*. 1999;3:24–33.
6. Morgagni P, Garcea D, Marrelli D, et al. Resection line involvement after gastric cancer surgery: clinical outcome in nonsurgically retreated patients. *World J Surg*. 2008;32:2661–7.
7. Sun Z, Li DM, Wang ZN, et al. Prognostic significance of microscopic positive margins for gastric cancer patients with potentially curative resection. *Ann Surg Oncol*. 2009;16:3028–37.
8. Macdonald JS, Smalley SR, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med*. 2001;345:725–30.
9. Lee J, Lim do H, Kim S, et al. Phase III trial comparing capecitabine plus cisplatin versus capecitabine plus cisplatin with concurrent capecitabine radiotherapy in completely resected gastric cancer with D2 lymph node dissection: the ARTIST trial. *J Clin Oncol*. 2012;30:268–73.
10. Smalley SR, Benedetti JK, Haller DG, et al. Updated analysis of SWOG-directed intergroup study 0116: a phase III trial of adjuvant radiochemotherapy versus observation after curative gastric cancer resection. *J Clin Oncol*. 2012;30:2327–33.
11. Tsang WK, Leung SF, Chiu SK, et al. Adjuvant chemoradiation for gastric cancer: experience in the Chinese population. *Clin Oncol (R Coll Radiol)*. 2007;19:333–40.
12. Kundel Y, Purim O, Idelevich E, et al. Postoperative chemoradiation for resected gastric cancer: is the Macdonald regimen tolerable? A retrospective multi-institutional study. *Radiat Oncol*. 2011;6:127.
13. Chang AT, Ng WT, Law AL, Ku KM, Lee MC, Lee AW. Adjuvant chemoradiation for resected gastric cancer: a 10-year experience. *Gastric Cancer*. 2011;14:63–71.
14. Dikken JL, Jansen EP, Cats A, et al. Impact of the extent of surgery and postoperative chemoradiotherapy on recurrence patterns in gastric cancer. *J Clin Oncol*. 2010;28:2430–6.
15. Jansen EP, Boot H, Dubbelman R, Bartelink H, Cats A, Verheij M. Postoperative chemoradiotherapy in gastric cancer: a phase I/II dose-finding study of radiotherapy with dose escalation of cisplatin and capecitabine chemotherapy. *Br J Cancer*. 2007;97:712–6.
16. Jansen EP, Boot H, Dubbelman R, Verheij M, Cats A. Postoperative chemoradiotherapy in gastric cancer: a phase I–II study of radiotherapy with dose escalation of weekly cisplatin and daily capecitabine chemotherapy. *Ann Oncol*. 2010;21:530–4.
17. Jansen EP, Boot H, Saunders MP, et al. A phase I-II study of postoperative capecitabine-based chemoradiotherapy in gastric cancer. *Int J Radiat Oncol Biol Phys*. 2007;69:1424–8.

18. Jansen EP, Nijkamp J, Gubanski M, Lind PA, Verheij M. Inter-observer variation of clinical target volume delineation in gastric cancer. *Int J Radiat Oncol Biol Phys*. 2010;77:1166–70.
19. WHO. International classification of diseases for oncology (ICD-O-3). 3rd ed. WHO; 2000.
20. Lauren P. The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma. An attempt at a histo-clinical classification. *Acta Pathol Microbiol Scand*. 1965;64:31–49.
21. Sobin L, Gospodarowicz M, Wittekind C (eds) International Union Against Cancer (UICC) TNM classification of malignant tumors. 7th ed. Oxford: Wiley-Blackwell; 2009.
22. Raziee HR, Cardoso R, Seevaratnam R, et al. Systematic review of the predictors of positive margins in gastric cancer surgery and the effect on survival. *Gastric Cancer*. 2011;15:116–24.
23. Lee JH, Ahn SH, Park do J, Kim HH, Lee HJ, Yang HK. Clinical impact of tumor infiltration at the transected surgical margin during gastric cancer surgery. *J Surg Oncol*. 2012;106:772–6.
24. Wanebo HJ, Kennedy BJ, Chmiel J, Steele G Jr, Winchester D, Osteen R. Cancer of the stomach. A patient care study by the American College of Surgeons. *Ann Surg*. 1993;218:583–92.
25. Hughes BG, Yip D, Chao M, et al. Audit of postoperative chemoradiotherapy as adjuvant therapy for resected gastroesophageal adenocarcinoma: an Australian multicentre experience. *ANZ J Surg*. 2004;74:951–6.
26. Bonenkamp JJ, Songun I, Hermans J, et al. Randomised comparison of morbidity after D1 and D2 dissection for gastric cancer in 996 Dutch patients. *Lancet*. 1995;345:745–8.
27. Dikken JL, van Sandick JW, Maurits Swellengrebel HA, et al. Neo-adjuvant chemotherapy followed by surgery and chemotherapy or by surgery and chemoradiotherapy for patients with resectable gastric cancer (CRITICS). *BMC Cancer*. 2011;11:329.