Post-operative radiochemotherapy in patients with gastric cancer: one department's experience of 56 patients

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Objectives: Prognosis in patients with locally advanced stomach cancer undergoing surgery alone is poor. High local failure rates in gastric cancer have been reported of up to 70%. When a relapse occurs, attempts at curative treatment are generally unsuccessful. A retrospective analysis was performed in order to determine whether post-operative radiochemotherapy improves treatment results in patients with locally advanced gastric cancer.

Methods: Between November 2004 and July 2008, 56 patients with clinical Stage IB–IV cancer of the stomach underwent curative gastrectomy and adjuvant radiochemotherapy. Patients with distant metastases were excluded from the analysis. The total radiation dose was 45.0 Gy. The chemotherapy regimen comprised a 5 day cycle of 5-fluorouracil at 425 mg m⁻² and leucovorin at 20 mg m⁻². Overall survival and disease-free survival, as well as toxicity, were estimated for all patients.

Results: Within the study group there were 7 (13%) local recurrences, 4 (7%) distant metastases and 8 (14%) local and distant relapses. The 2 year overall survival was 48%. A total of 19 (34%) patients developed Grade 3 gastrointestinal toxicity. There were no treatment-related deaths.

Conclusion: Post-operative radiochemotherapy is an effective and safe regimen in patients with curatively resected locally advanced gastric cancer.

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Surgery remains the main treatment for stomach cancer; however, prognosis in patients with locally advanced stomach cancer who undergo surgery alone is poor. The 5 year survival rates in resected-only gastric cancer patients are 90% for clinical Stage I, 60% for Stage II, 33% for Stage III and <5% for Stage IV [1]. Clinical stage, age, histological differentiation, depth of invasion, lymph node metastases and proximal third site of origin have been identified as the independent prognostic factors [1, 2]. Local relapse in the tumour bed and regional lymph node or distant metastases are the cause of relapse after curative resection. Extension of surgical procedures, including splenectomy, omentectomy and radical lymph node dissection, have not been shown to improve survival or to decrease the rate of locoregional failure [3]. For patients with high risk, clinically advanced Stage IB–IV with M0 gastric cancer, there is undoubtedly a need for effective adjuvant treatment following surgery. The results of Phase III randomised trials of adjuvant chemotherapy after resection in gastric cancer are inconsistent; most studies of post-operative chemotherapy did not show a significant improvement in overall survival [4–8]. The results of three published meta-analyses suggest that adjuvant chemotherapy after curative resection for gastric cancer might produce a small or borderline statistically significant improvement in overall survival [9–11]. Moreover, the results of randomised trials with

radiotherapy as the sole treatment with curative gastric cancer resection also differ. In a British trial, adjuvant radiotherapy following surgery reduced locoregional failures, but no survival benefits were found [12]. By contrast, the results of a Chinese study showed a survival benefit for patients treated with pre-operative radiotherapy compared with surgery alone. In addition, locoregional failures were reduced in the arm of the study with pre-operative irradiation. The above-noted differences from the Chinese study were statistically significant [13]. Finally, an intergroup trial (INT-0116) on patients with gastric cancer treated with a combination of post-operative radiochemotherapy and surgery showed a distinct survival advantage for adjuvant radiochemotherapy, as well as higher rates of locoregional control in this treatment arm [14]. An update of the results of the intergroup study, which was presented in 2004 at the American Society for Clinical Oncology (ASCO) conference in San Francisco, confirmed existing survival benefits in long-term follow-up [15]. In the present study, we report our own experiences and results of post-operative radiochemotherapy in patients treated for gastric cancer. We also attempt to evaluate the possible benefits and toxicity risks of this treatment schedule.

Methods and materials

A total of 56 patients with cancer of the stomach who underwent surgery and adjuvant radiochemotherapy were enrolled in this retrospective study. Patients were

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treated from November 2004 to July 2008 in the radiotherapy department of the Medical University of Lodz. Post-operative irradiation with concurrent and maintenance chemotherapy was recommended for patients with pT_1-T_2 N1-N3 or pT_3-T_4 N0-3 disease extension and R0, R1 resection (clinical Stage IB-IV with M0 gastric cancer). The study included 43 (77%) males and 13 (23%) females: the male to female ratio was 3.3:1. The age of the patients ranged between 43 and 73 years (mean 58.3 years; median 58.0 years; 95% confidence interval (CI) 56.3-60.2; standard deviation (SD) 7.2). Of the patients who qualified for post-operative radio-chemotherapy, 25 (45%) were classified as clinical Stage IIIA, 8 (14%) as Stage I, 17 (30%) as Stage II and 6 (11%) as Stage IV. Patients with metastatic disease were excluded from the analysis. Clinical stage distribution according to TNM (tumour, node, metastases) classification is presented in Table 1. The haemoglobin concentration before treatment fluctuated between 5.4 g dl^{-1} and 16.2 g dl^{-1} (mean $11.67 \pm 1.9 \text{ g dl}^{-1}$; median 11.4 g dl^{-1} ; 95% CI 11.17-12.17). In the group of patients analysed, performance status was evaluated using the Karnofsky performance scale (KPS): 10 (18%) patients were classified as 100% KPS, 15 (27%) as 90% KPS, 25 (45%) as 80% KPS and 6 (10%) as 70% KPS. Weight loss $>10\%$ was detected in 26 (46%) patients. A total gastrectomy was performed in 36 (64%) patients; 20 (36%) patients underwent a subtotal gastrectomy. D1 and D2 lymph node dissection was performed in 43 (77%) and 13 (23%) patients, respectively. Tumour size (the largest diameter defined in millimetres, measured in a pathological specimen) ranged from 10 to 150 mm (mean $51.3 \pm 28 \text{ mm}$; median 42.5 mm; 95% CI 43.7-58.9). Negative (R0) surgical margins were present in 48 (86%) patients. The duration of hospital stay after surgery ranged from 9 to 31 days (mean duration of hospitalisation 16.63 ± 5.0 days; median 16.0 days; 95% CI 15.28-17.97). According to the Lauren classification, there were 14 (27%) intestinal-type, 24 (46%) diffuse and 14 (27%) mixed-type tumours. According to tumour histology, there was 1 (2%) well-differentiated tumour, 18 (32%) moderately differentiated tumours and 37 (67%) poorly differentiated tumours. The mean number of resected lymph nodes was 12.2 ± 7.9 (range 3-36; median 9.5; 95% CI 10.07-14.35). The mean nodal ratio (*i.e.* the number of dissected metastatic lymph nodes divided by the total number of removed nodes) was 0.37:25 (45%) patients exhibited a nodal ratio ≥ 0.4 . All patients received adjuvant radiochemotherapy. The chemotherapy regimen comprised a 5 day cycle of 5-fluorouracil (5-FU) at 425 mg m^{-2} and leucovorin at 20 mg m^{-2} . The mean number of chemotherapy cycles was 4.29 ± 1.6 (range 1-7; median 5.0; 95% CI 3.87-4.71). The intended chemotherapy regimen was to deliver five cycles

of systemic treatment: the first cycle before radiotherapy, the second at the time of initiating radiotherapy, the third during the last week of radiotherapy and then two additional cycles following radiotherapy. In the group of patients analysed, 38 (68%) patients received four or more cycles of chemotherapy. The remaining patients received less than four chemotherapy cycles owing to treatment toxicity. All except one of these patients received the first three cycles of chemotherapy. One patient received only one cycle of chemotherapy owing to treatment toxicity. External beam radiotherapy was delivered using a linear accelerator (6-15 MV photons). Patient and tumour characteristics are presented in Tables 2 and 3, respectively. All patients were treated according to an homogeneous radiotherapy department in-house protocol. The treatment volumes, as well as critical organs and radiation dose, were defined using the "Eclipse Varian" computer planning system (Varian Medical system Inc., Palo Alto, CA). Every case was planned individually using a three-dimensional conformal technique. Treatment volumes were defined according to the 50 and 62 ICRU (The International Commission on Radiation Units and

Table 1. Clinical stage according to TNM classification

T/N	N0	N1	N2	N3	n
T_1	0	1	0	0	1
T_2	6	12	5	2	25
T_3	6	12	8	2	28
T_4	0	0	2	0	2
n	12	25	15	4	56

TNM, tumour, node, metastases.

Table 2. Patient characteristics

Characteristic	n (%)
Age	
<58 years	23 (41%)
≥ 58 years	33 (59%)
Weight loss	
<10%	30 (54%)
$\geq 10\%$	26 (46%)
Duration of disease symptoms	
<3 months	24 (43%)
3-6 months	25 (45%)
>6 months	7 (12%)
Tumour site	
Cardia and fundus of stomach	8 (14%)
Body of stomach	21 (38%)
Pylorus	9 (16%)
Entire stomach	18 (32%)
Lauren classification	
Intestinal type	16 (29%)
Diffuse type	25 (45%)
Mixed type	15 (26%)
Haemoglobin concentration	
< 10.5 g dl^{-1}	14 (24%)
$10.5-12.0 \text{ g dl}^{-1}$	21 (38%)
$>12.0 \text{ g dl}^{-1}$	21 (38%)
Margin status	
R0	48 (86%)
R1	8 (14%)
Lymph node dissection	
D1	43 (77%)
D2	13 (23%)
No. cycles CHTH	
<4	18 (32%)
≥ 4	38 (68%)
Start of radiotherapy	
Before 2nd cycle of CHTH	39 (70%)
After 2nd cycle of CHTH	17 (30%)
Toxicity	
RTOG Grade 1-2	37 (66%)
RTOG Grade 3	19 (34%)

CHTH, chemoradiotherapy; RTOG, Radiation Therapy Oncology Group classification.

Table 3. Tumour characteristics

Characteristic	n (%)
Tumour size	
<5 cm	30 (54%)
≥5 cm	26 (46%)
Stage T	
T ₁	1 (2%)
T ₂	25 (45%)
T ₃	28 (50%)
T ₄	2 (3%)
Stage pN	
N0	12 (21%)
N1	25 (45%)
N2	15 (27%)
N3	4 (7%)
Nodal ratio	
<0.4	30 (54%)
≥0.4	26 (46%)
Stage	
I	8 (14%)
II	17 (30%)
III	25 (45%)
IV	6 (11%)
Grade	
1	1 (2%)
2	18 (32%)
3	37 (66%)

Measurements) reports. The tumour bed, the anastomosis, the stump and the locoregional lymph nodes were treated. The locoregional lymph nodes were defined as lymph nodes along the lesser and greater curvature, left and right cardia lymph nodes, supra and infra pyloric lymph nodes along the left gastric artery, common hepatic artery, coeliac artery, and splenic artery and the splenic hilum lymph nodes, as well as pancreatoduodenal lymph nodes and lymph nodes of the hepatoduodenal ligament. In the case of the gastro-oesophageal junction or cardia tumours, the periesophageal and mediastinal lymph nodes were also included in the clinical target volume. A team of five radiotherapists from our department who specialise in the treatment of gastrointestinal tumours was involved in treatment planning according to homogeneous in-house protocols. The target volume was covered by the 95% isodose curve. A total of 39 (70%) patients started radiotherapy before or on the first day of the second cycle of chemotherapy. The intended radiotherapy regimen was to deliver the total dose of 45.0 Gy with a daily fractional dose of 1.8 Gy over a 5 week period. All patients included in the study completed radiotherapy without interruption. In 19 (34%) patients, Grade 3 diarrhoea according to the RTOG/EORTC (Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer) toxicity scale was noted; however, intensive symptomatic treatment induced relatively rapid amelioration without the need to interrupt or terminate treatment. Correctness of treatment plan realisation was checked on a simulator, where treatment fields were transmitted to the patient's skin and saved in the computer system simultaneously. The reproducibility of the treatment field setup was evaluated through the fusion of simulator and accelerator images and through geometric error measure.

All patients were followed up after the end of radiotherapy. A chest radiograph and CT scans of the pelvis and abdomen were evaluated during follow-up visits. Patients were evaluated for treatment-related toxicity, local recurrences and distant metastases. Treatment-related toxicity was evaluated according to the RTOG/EORTC classification.

Statistical analysis

The overall survival and disease-free survival were estimated for all patients using a Kaplan–Meier analysis. The end point was death as a result of any cause. The univariate and multivariate analysis were carried through to single out prognostic factors in patients treated for gastric cancer with post-operative radiochemotherapy. The χ^2 test was used to determine whether the distribution of prognostic variables was significantly different. Comparisons of survival curves were made using the log-rank test. Clinical prognostic factors including age, weight loss, duration of disease symptoms, tumour site, Lauren classification, haemoglobin serum concentration, post-operative margin status, tumour size, T and N stage, clinical stage, nodal ratio, histological grade, number of cycles of chemotherapy, start of radiotherapy and toxicity grade were included in the statistical analysis. A *p*-value <0.05 was considered significant.

Results

Within a median follow-up of 17.4 months (range 3.5–47 months), disease progression was reported in 19 (34%) patients: 7 (13%) patients exhibited local recurrences, 4 (7%) distant metastases and 8 (14%) local and distant relapses. The most common site of metastases was the liver: 6 (11%) patients had liver metastases. The other sites of metastases occurrence were regional lymph nodes, lungs and bones. The 2 year overall survival was 48%. Mean survival was 15.4 months (range 3.9–46 months; median 22.8; 95% CI 12.9–18.1; SD 9.3; Figure 1). In the univariate analysis we observed a statistically significant lower overall survival rate in patients over 58 years of age (*p*=0.003). The pN stage and nodal ratio were also associated with decreased overall survival (*p*=0.03 and *p*=0.026, respectively). We noted that weight loss correlated with the lower overall survival factors, including tumour site, surgical margin status, extent of lymph node dissection, Lauren classification, the duration of disease symptoms and haemoglobin concentration; however, weight loss did not have any effect on progression-free and overall survival in the univariate analysis (*p*≥0.13). The number of chemotherapy cycles did not have a significant effect on overall survival, but we noted a trend towards statistical significance (*p*=0.057). The multivariate analysis showed that only positive surgical margin status was correlated with a lower overall survival (*p*=0.001). The results of the univariate and multivariate analyses are presented in Tables 4 and 5, respectively. There were no treatment-related deaths in the group of patients in the study. The most

Figure 1. Overall survival of patients treated with post-operative radiochemotherapy.

common haematological toxicity was Grade 1 and 2 leucopenia reported in 46 (82%) cases. Grade 3 and Grade 4 haematological toxicity, according to the RTOG/EORTC scale, was reported in 8 (14%) and 2 (4%) patients, respectively. Acute gastrointestinal toxicity was generally mild and manageable. The most common Grade 1/2 gastrointestinal toxicities were nausea, vomiting and diarrhoea; 19 (34%) patients developed Grade 3 diarrhoea. In the univariate analysis there was no difference in the overall survival of patients with Grade 3 acute gastrointestinal toxicity, as compared with patients with Grade 1 or 2 toxicity ($p=0.89$).

Table 4. Univariate analysis

Factor	n (%)	2 Year survival	p Value
Age			
<58 years	23 (41%)	83%	0.003
≥58 years	33 (59%)	27%	
Weight loss			
≥10%	30 (54%)	70%	0.02
>10%	26 (46%)	33%	
Stage pN			
N0	12 (21%)	68%	0.03
N1	25 (45%)	76%	
N2	15 (27%)	13%	
N3	4 (7%)	0	
Nodal ratio			
≥0.4	30 (54%)	63%	0.026
<0.4	26 (46%)	21%	
No. cycles chemotherapy			
<4	18 (32%)	34%	0.057
≥4	38 (68%)	54%	

Discussion

The prognosis in patients with locally advanced stomach cancer who undergo surgery alone is poor: the 5 year overall survival is 20–30% for patients with T_3 – T_4 N+ stomach cancer. Over the past decade, however, treatment schedules for patients with stomach cancer have changed. The development of radiotherapy techniques has made it possible to escalate the dose, while simultaneously sparing healthy tissues and structures. The effective use of chemotherapy, in particular in association with radiation therapy, has led to an increase in the number of patients who undergo surgery being cured from stomach cancer. Despite a large number of published studies, no uniform adjuvant treatment regimen has been widely accepted. In 2001, the results of the INT-0116 study were published [14]. Since then, post-operative radiochemotherapy has become the standard of care in the USA. In the trial by McDonald et al [14], 556 patients were randomised to either adjuvant chemoradiotherapy or surgery alone. Most of the patients in both arms had T_3 or T_4 tumours and had nodal metastases. For those patients receiving adjuvant chemoradiotherapy *vs* surgery alone, the authors noted at 3 years a median disease-free survival of 30 months *vs* 19 months and a median overall survival of 36 months *vs* 27 months. Both differences reached statistical significance. The 3 year disease-free survival and overall survival were 48% and 50%, respectively, in the treatment arm. These rates were significantly higher than in the group of patients treated with surgery alone. These results were confirmed by other authors reporting the overall survival benefit of post-operative radiochemotherapy in patients with gastric cancer [16–18]. The present analysis showed that post-operative radiochemotherapy is an effective and safe regimen in patients

Table 5. Multivariate analysis

	β Coefficient	SD	Hazard ratio	Wald statistic	p Value
Age	2.37603	1.232934	10.76208	3.713845	0.053972
Weight loss	1.36225	0.828412	3.90498	2.704098	0.100101
Tumour site	-0.58956	0.488156	0.55457	1.458624	0.227158
Lauren classification	-0.72749	0.757502	0.48312	0.922336	0.336870
Hb concentration	-0.09701	0.481762	0.90755	0.040545	0.840421
R1 margins	0.07125	0.023029	1.07385	9.572429	0.001977
Tumour size	-0.90706	0.850911	0.40371	1.136341	0.286435
N stage	1.74671	1.047507	5.73569	2.780524	0.095427
Clinical stage	-1.97879	1.399333	0.13824	1.999663	0.157344
Nodal ratio	0.80172	0.986961	2.22936	0.659842	0.416622
No. CT cycles	-1.06609	0.998487	0.34435	1.139995	0.285662
Radiotherapy start	0.48449	0.923848	1.62334	0.275019	0.599988

CT, chemotherapy; Hb, haemoglobin; SD, standard deviation.

with operable, locally advanced gastric cancer. In our study, the 2 year overall survival was 48% (mean survival 15.4 months). Wydmanski [19] reported a 2 year overall survival rate of 50%. In another study, the authors reported that 32 year overall survival was 25% in 31 patients who underwent surgery and adjuvant radiochemotherapy [20].

In the INT-0116 study, of the 281 patients randomised to receive the combined adjuvant treatment regimen, 181 (64%) completed the intended therapy. Most patients that stopped adjuvant therapy did so owing to toxicity. Grade 3 and 4 toxicity occurred in 41% and 32% of the chemoradiotherapy arm, respectively. Three patients (1%) died from treatment-related toxic effects [14]. In the study from Gliwice, an adjuvant radiotherapy was well tolerated in most cases. Leucopenia of Grade 3 or higher was reported in 1% of patients. Gastrointestinal acute toxicity of Grade 3–4 was reported in 2% of patients [19]. Lim et al [17] reported Grade 3 acute nausea and diarrhoea in 12% and 10% of patients, respectively, according to the Southwest Oncology Group (SWOG) toxicity criteria. Leucopenia Grade 3 or higher was reported in 31% of patients. In the present study, Grade 3 and 4 haematological toxicity (according to the RTOG/EORTC scale) was reported in 14% and 4% of patients, respectively. Acute gastrointestinal toxicity was generally mild and manageable; 34% of patients developed Grade 3 diarrhoea. Dose distribution in the radiotherapy of gastric cancer covers the stomach with the primary tumour bed, as well as the locoregional lymph nodes. At the time of post-operative radiotherapy, the treatment volume is filled by the small intestine and this might be related to the clinical manifestation of gastrointestinal toxicity. In the study by McDonald [14], the high percentage of gastrointestinal toxicity was probably due to the use of two-dimensional anteroposterior–posteroanterior opposite fields. The use of three-dimensional conformal techniques is a significant factor that has an effect on the decreased toxicity of post-operative radiotherapy in patients with gastric cancer [21]. Most patients with gastric cancer who undergo surgery and adjuvant treatment present with advanced-stage disease. Long-term survival is limited owing to local recurrences and distant metastases. When a relapse occurs, attempts at curative treatment are generally unsuccessful. In the present study, 34% of patients developed locoregional recurrence and/or distant metastasis.

In other studies rates of relapse were reported to be in the range 29–50%, which are in agreement with our own experience [14, 17–19].

With regards to surgery, D2 lymph node dissection is recommended in most centres. In the INT-0116 study, the recommended D2 lymph node dissection was performed in only 10% of cases and 54% of patients did not even undergo a D1 resection [15]. However, there is much controversy with regards to the benefit of more aggressive surgical procedures, owing to post-operative complications. In British (Medical Research Council; MRC) and Dutch (Dutch Gastric Cancer Group; DGCG) trials, the post-operative morbidity and mortality were significantly greater in those patients undergoing D2 resection. In the MRC and DGCG trials, 711 and 400 patients were randomised to D1 *vs* D2 resection, respectively. Overall survival and recurrence-free survival were equivalent. In the MRC study, the 5 year overall survival was 35% in the D1 arm *vs* 33% in the D2 arm ($p=0.43$). Likewise, in the Dutch trial the 5 year survival remained equivalent for both groups: 47% in the D2 arm and 45% in the D1 arm [22, 23]. In the current study, D1 and D2 lymph node dissection was performed in 77% and 23% of patients, respectively. In the statistical analysis no significant difference in overall survival was noted in the group of patients with D1 and D2 lymph node dissection, which is in agreement with the MRC and DGCG results. In the present analysis, pN was associated with a decrease in overall survival ($p=0.03$). The pathological stage of lymph nodes according to the American Joint Committee on Cancer (AJCC) was defined as an independent prognostic factor in a number of published studies. In addition, the lack of metastases in resected lymph nodes improved survival in patients with gastric cancer [1, 2, 18, 19, 24]. Some authors postulate that not only the pN stage but also the number of resected lymph nodes inversely correlate with lower survival rates [1, 24, 25]. Marchet et al [24] reported a correlation between the resection of 16 or less lymph nodes and the lower 5 year overall survival rate in comparison with patients where 16 or more lymph nodes were resected. In the present study, not only the pN stage but also the number of dissected metastatic lymph nodes divided by the total number of removed nodes (defined as a nodal ratio) was correlated with a decrease in overall survival. It appears that the nodal ratio is a more precise prognostic factor than the absolute number

of dissected metastatic lymph nodes. The nodal ratio might eliminate a shortage of pN stage data resulting from inadequate nodal dissection. Wydmanski [19] reported that a nodal ratio <0.6 correlated with a better prognosis; the 5 year overall survival in a group of patients with a nodal ratio <0.6 was 45% compared with 19% in cases where the nodal ratio was >0.6 . Another prognostic factor is tumour size. Together with growth of tumour volume, the risk of distant metastases and locoregional recurrence is increased. Tumour grade as well as the depth of gastric wall invasion are also recognised prognostic factors [16, 24, 25]. In the present study, tumour size, tumour grade and depth of gastric wall invasion were not found to be correlated with lower survival. This lack of correlation was probably a consequence of the relatively small number of patients in the study and, associated with this, the asymmetric distribution of variables inside individual prognostic factor subgroups. Results related to the prognostic value of patient age are inconsistent. The hypothesis exists that the prognosis is worse in younger patients owing to the rapid growth rate and diagnosis in most cases at an advanced clinical stage. The results of our study did not confirm this hypothesis: patients over 58 years of age had a worse prognosis than younger patients. Others confirm these results [24, 25].

In a recently published meta-analysis, radiotherapy was compared with the use of surgery alone or followed by chemotherapy in resectable gastric cancer [26]. From 20 randomised trials, 9 studies with 2025 patients were finally included in the statistical analysis. The meta-analysis examined the role of radiotherapy in improving survival in patients treated with different schedules of radiotherapy at 3 and 5 years follow-up. At 5 years follow-up the overall benefit result was $RR=1.26$ (95% CI 1.08–1.48; $p=0.004$; number needed to treat =17) with a relative benefit of 26%. In another meta-analysis published in 2007, the authors reported a significant reduction in the 5 year mortality rate for patients undergoing surgery followed by chemoradiotherapy (odds ratio 0.45; 95% CI 0.32–0.64) [27].

Other promising strategies for patients with resectable gastric cancer have been explored and showed that patients with operable gastric adenocarcinoma might benefit from perioperative chemotherapy. The Phase III MAGIC (MRC Adjuvant Gastric Infusional Chemotherapy) trial randomised 503 patients with gastric cancer (74%), oesophageal cancer (11%) or gastro-oesophageal junction adenocarcinoma (15%) to perioperative chemotherapy. Patients in the experimental arm received pre-operative epirubicin, cisplatin and 5-FU (ECF) for three cycles, followed by surgery and three post-operative cycles of ECF. In the control arm patients underwent surgery alone. The study results were reported at the 2005 annual ASCO meeting and finally published in 2006. With a median follow-up of 3 years, the authors demonstrated a statistically significant difference in the chemotherapy arm with respect to the curative resection rate (79% *vs* 69%; $p=0.018$). After 5 years, the overall survival rate was higher in the experimental arm over the surgery arm (hazard ratio 0.75; 95% CI 0.60–0.93; $p=0.009$). The 5 year survival rate was 36% in the chemotherapy arm *vs* 23% in the surgery alone arm. Statistically significant differences were observed in the

progression-free survival rate (hazard ratio 0.66; 95% CI 0.53–0.81; $p<0.001$) [28].

Our data showed that a positive surgical margin (R1) was the most significant independent prognostic factor associated with low survival rate. This is in agreement with most retrospective and prospective randomised studies; therefore, in most centres, patients with R1 or R2 resection are not recommended for adjuvant treatment [14, 16]. In general, R2 resection is considered as a palliative operation; however, the value of R1 resection is controversial. In the European Society for Medical Oncology (ESMO) recommendations published in 2009, R1 resection was regarded as palliative treatment [29]. Admittedly, it seems that R1 resection is an unfavourable prognostic factor; however, this should not disqualify patients from post-operative radiochemotherapy, as median survival after R1 resection without adjuvant treatment is quite short and 5 year overall survival does not exceed 15%. The optimal sequencing of surgery, radiotherapy and chemotherapy remains unclear. This is an important topic for future trials.

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