

research article

## Postoperative radiochemotherapy for gastric adenocarcinoma: long term results

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**Background.** To analyze the efficacy of postoperative radiochemotherapy with 5-fluorouracil (5-FU) and leucovorin (LV) applied in the patients with gastric carcinoma treated in a single institution.

**Patients and methods.** Between 2001 and 2004, 123 patients with resected gastric adenocarcinoma were treated with postoperative concomitant radiochemotherapy with 5-FU and LV. The adjuvant treatment consisted of five cycles of chemotherapy with 5-FU (425mg/m<sup>2</sup> IV) and LV (20 mg/m<sup>2</sup> IV) and concomitant radiotherapy with the total dose of 45 Gy.

**Results.** The treatment was completed according to the protocol in 82% of patients. The frequency and severity of early toxic effects induced by radiochemotherapy were manageable. Median follow-up time of 56 survivors was 64.5 months (range: 51.7-96.4 months). The 5-year locoregional control (LRC), disease-free survival (DFS), disease-specific survival (DSS) and overall survival (OS) were 81%, 48.3%, 50.4%, and 48.4%, respectively. The multivariate analysis showed that the tumor involvement of cardia and low intensity of chemotherapy were independent adverse prognostic factors for DSS and OS. More advanced pT-stage and tumors with diffuse growth type according to Lauren were identified as negative independent prognostic factor for OS. They were also on the threshold of statistical significance for DSS.

**Conclusions.** Postoperative radiochemotherapy for gastric carcinoma has acceptable toxicity, and is effective particularly in regard to LRC. High incidence of distant metastases calls for more effective systemic regimens.

Key words: gastric cancer; adjuvant therapy; radiochemotherapy; survival; toxicity

### Introduction

In Slovenia as well as worldwide, gastric carcinoma is considered as a disease with poor prognosis. Radical surgery which can be performed in only 50-70% of patients<sup>1,2</sup> is a common treatment for localized disease. Long-term outcomes with surgery alone are still relatively poor because disease recurrence was observed in 75% of patients, and in 40-65% of them, the disease recurred

Received 21 August 2009

Accepted 28 August 2009

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**Table 1.** Pathohistological characteristics of tumors (n = 123)

Characteristics		No.	%
pT – stage	1	9	7.3
	2	39	31.7
	3	66	53.7
	4	9	7.3
pN – stage	0	4	3.3
	1	53	43.1
	2	42	34.1
	3	24	19.5
Overall stage	Ib	6	4.9
	II	26	21.1
	IIIa	37	30.1
	IIIb	24	19.5
	IV	30	24.4
Pathohistological tumor grade	1	5	4.1
	2	25	20.3
	3	87	70.7
	unknown	6	4.9
	Bormann type	1	4
	2	14	11.4
	3	43	35
	4	24	19.5
	unknown	38	30.9
Growth type according to Lauren	diffuse	61	49.6
	intestinal	55	44.7
	unknown	7	5.7
Perineurial invasion	yes	59	48
	no	45	36.6
	unknown	19	15.4
Lymphovascular invasion	yes	66	53.7
	no	23	18.7
	unknown	34	27.6
Angioinvasion	yes	23	18.7
	no	45	36.6
	unknown	55	44.7

locally and/or regionally.<sup>2-4</sup> A number of studies have been conducted to improve the treatment outcome of these patients and, as a result, postoperative radiochemotherapy was established as a routine treatment in the USA as well as in other countries.<sup>6-17</sup> The authors believe that the INT 0116 protocol is safe and acceptable for clinical use.<sup>3,5,8-11</sup>

Data on late side effects are scarce. It is suspected that the used radiation fields can cause the damage to the left kidney in some patients, resulting in hypertension and other renal problems.<sup>17</sup> Six months after radiochemotherapy for gastric cancer, Jansen *et al.* observed a 20% decrease in the function of the left kidney. They believe that the renal impairment may increase over time.<sup>18</sup>

In 2001, at the Institute of Oncology Ljubljana, Slovenia, postoperative radiochemotherapy was established as a standard clinical practice in the treatment of patients who had undergone radical resection of non-metastatic gastric adenocarcinoma of stages Ib-IV. The short-term results of this treatment regimen have already been published.<sup>10</sup> The aim of the present report is to present the long-term results of postoperative radiochemotherapy for gastric adenocarcinoma, including late treatment-related toxicity.

## Patients and methods

Between 2001 and 2004, 123 patients (79 males, 44 females) with the mean age of 60 years (range: 31-76 years), were treated for gastric adenocarcinoma of TNM stages Ib-IV (nonmetastatic), with postoperative concomitant radiochemotherapy. One hundred and seven (87%) patients had radical resection (R0) of the tumor, and in the remaining 16 (13%) patients, non-radical (R1) resection was made. Distal subtotal, total,

and multivisceral resection of the stomach was performed in 40.7%, 29.3%, and 27.6% of patients, respectively, and three patients (2.4%) had resection of the carcinoma on gastric stump. In 92 (74.7%) patients, at least 15 lymph nodes were removed and histologically examined, in 27 (22%) patients, less than 15 lymph nodes were examined, while for 4 (3.3%) patients, no data on the lymph node status was available. Most frequently, the primary tumor originated in the antrum (38.2%). Sixty-one percent of patients had advanced disease and 96.7% of patients had N+ disease (Table 1).

After surgery, all patients with the disease of pathological stage Ib or more were presented to a multidisciplinary advisory team, consisting of a surgeon, radiation oncologist and medical oncologist, in order to assess the prospects of eventual adjuvant treatment. Eligibility of patients for adjuvant therapy was assessed with respect to the blood test results and performance status ( $\geq 2$  according to the World Health Organisation [WHO]). More extensive radiologic investigations already performed before surgery to rule out metastatic disease, were repeated only in the patients with clinically suspected progression of the disease.

During the therapy, the patients were clinically examined and referred for hematological and biochemical blood testing once a week. The therapy-related local and systemic toxicity was assessed according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0.<sup>19</sup> WHO scale was used to determine the performance status of patients and their body weight was measured on weekly basis.

Adjuvant treatment was initiated six weeks after surgery. It consisted of concomitantly applied chemotherapy and radiotherapy. In the chemotherapy part of the protocol, five cycles of 5-FU (425mg/m<sup>2</sup>)

and LV (20 mg/m<sup>2</sup>) administered as five-day intravenous infusions were planned. The treatment cycle was repeated every 28 days. During radiotherapy, the intensity of chemotherapy was decreased. In the second and third cycle, only 4 and 3 applications of the drugs were administered, respectively. After the completed radiotherapy, the patients received two more five-day chemotherapy cycles.

Irradiation was applied during the second and third cycle of chemotherapy. The patients were irradiated on linear accelerator with 5-15 MV photon beams for 5 days per week, at a daily dose of 1.8 Gy. The irradiation field involved the primary tumor site and regional lymph node areas with a safety margin of 1.5-2 cm. Two opposite (AP-PA) beams were applied. Total irradiation dose was 45 Gy and total irradiation time 5 weeks.

After the completed treatment, follow-up examinations were performed every three months in the first two years and then at six month intervals to the end of five years. The patients were then referred back to their general practitioner's care and attended follow-up examinations only once per year. The follow-up examination consisted of clinical examination, complete blood count, liver and renal functional tests and measurements of CEA and Ca 19-9. Ultrasound (US) or computed tomography (CT) of the abdomen were performed every six months, chest radiography or CT once a year and endoscopic examination of the upper gastrointestinal tract as clinically indicated. During the follow-up period, any suspected disease relapse or recurrence was confirmed by biopsy.

### Statistics

Statistical analysis was performed using personal computer and software statistical package SPSS, version 13 (SPSS Inc., USA).

**Table 2.** Toxicity of adjuvant radiochemotherapy

Toxicity	NCI grade (%)					Total
	0	1	2	3	4	
Stomatitis	48	10.6	15.4	26	0	100
Radiodermatitis	95.2	1.6	1.6	1.6	0	100
Diarrhoea	79.7	5.7	5.7	8.9	0	100
Dysphagia	44.7	12.1	21.2	22	0	100
Nausea, vomiting	56.9	11.4	13	18.7	0	100
Infection	50.4	18.7	18.7	12.2	0	100
Leukocyte count	30.1	29.3	30.1	9.7	0.8	100
Haemoglobin level	19.5	70.7	9.8	0	0	100
Platelet count	92.7	7.3	0	0	0	100

The main endpoints were as follows: locoregional control (LRC, the event was local and/or regional recurrence); disease-free survival (DFS, the event was local, regional or systemic recurrence); the disease-specific survival (DSS, the event was death due to gastric adenocarcinoma), and overall survival (OS, the event was death from any cause).

The survival of patients was computed from the date of surgery to the 1<sup>st</sup> of May, 2009 (close out date). Survival probability was calculated using Kaplan-Meier estimate<sup>20</sup>, and log rank test<sup>21</sup> was used to evaluate the differences between individual groups of patients. Independent prognostic values of variables that appeared statistically significant on univariate analysis were tested by multivariate Cox regression analysis model.<sup>22</sup> Two-sided tests were used and the differences at  $p < 0.05$  were considered as statistically significant.

## Results

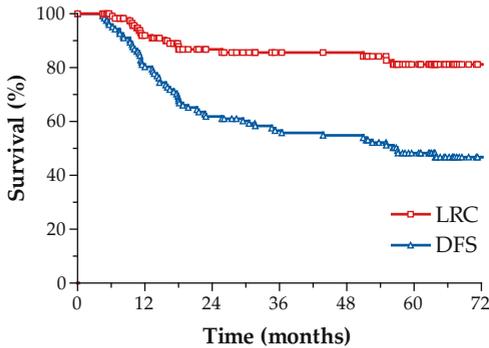
### Treatment outcome

All 123 patients were evaluable for analysis. Postoperative chemotherapy started 3.6-11.9 weeks after surgery (median 5.9 weeks). Total postoperative treatment time ranged from 4.9- 32.6 weeks

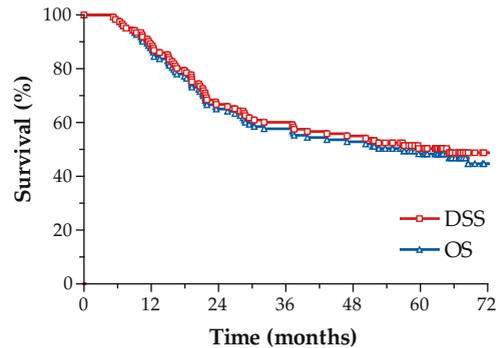
(median 17.6 weeks), whereas the duration of the radiotherapy part of the protocol ranged from 3.3-18 weeks (median 5.3 weeks). In regard to the intensity of radiotherapy and chemotherapy doses, 82% of patients completed the treatment according to the protocol. There was no treatment-related death. The frequency and severity of early toxic effects of radiochemotherapy are shown in Table 2. In regard to the late side effects, only renal functional impairment (the rise of creatinine level of grade 1, but without hypertension or other renal impairment) was observed in 5 patients (4.1%). The observed median time interval of creatinine level elevation was 10.5 months (range: 8.9-13.4 months).

On the close-out date, median follow-up time of all treated patients was 51.8 months (range: 5.3-96.4 months), with the median follow-up time of 64.5 months (range: 51.7-96.4 months) for 56 survivors. In 56 (45.5%) patients, alive at the time of analysis, 53 had no signs of disease. Of 67 (54.5%) dead patients, 60 died of gastric carcinoma, 4 of other causes (stroke, lung cancer, cancer of the *caecum*, myocardial infarction; 1/4 patients with simultaneous locoregional recurrence), and in 3 patients, the cause of death could not be determined.

After adjuvant radiochemotherapy, disease re-appeared in 62 (50.4%) patients. Local and/or regional recurrence developed in 7 (5.7%) patients in the median time of 18 months (range: 9.7-56.3 months) after surgery. Locoregional failure and systemic dissemination were diagnosed in 11 (8.9%) patients in the median time of 11 months (range: 6.2-25.7 months), and



**Figure 1.** Locoregional control (LRC) and disease-free survival (DFS).



**Figure 2.** Disease-specific survival (DSS) and overall survival (OS).

systemic metastases alone in 44 (35.8%) patients in the median time of 16 months (range: 4.5-63.8 months). The 5-year LRC, DFS, DSS and OS were 81%, 48.3%, 50.4%, and 48.4%, respectively (Figures 1,2).

### Prognostic factors

On univariate analysis of survival, locally advanced disease (pT3-4, pN3, overall TNM stage IV) was predictive for worse LRC and survival compared to early disease stages. In addition, poor outcome of patients was associated also with higher degree of stomach involvement with cancer (whole stomach vs. involvement of individual stomach areas), tumor location in the stomach (cardia vs. other subsites), Borrmann type 4, growth type according to Lauren (diffuse type vs. others), with the presence of vascular and perineurial invasion and intensity of chemotherapy (<5 cycles vs. 5 cycles of chemotherapy) (in all instances  $p < 0.05$ ).

The multivariate analysis showed that the tumor involvement of cardia and low intensity of chemotherapy were independent adverse prognostic factors for DSS and OS. More advanced pT-stage and tumors with diffuse growth type according to Lauren were identified as negative independent prognostic factor for OS. They

were also on the threshold of statistical significance for DSS (Table 3).

### Discussion

Short-term results of pooperative treatment with radiochemotherapy for gastric cancer in our population of patients have already been published.<sup>10</sup> As some other authors, we may also conclude that the combined radiotherapy and chemotherapy with 5-FU is feasible, with acceptable toxicity, and seems to have a potential to improve treatment outcome compared to surgery as the sole mode of treatment for this poor prognosis group of patients.<sup>5-15</sup> After a longer follow-up, excellent LRC and acceptable DFS, DSS and OS were confirmed, which concurs with the results from other studies.<sup>5,6,8,9,11,13,23</sup>

In the present analysis, the patients with more advanced tumors, cardia involvement, perineurial and vascular invasion had poorer survival. With the prolongation of follow-up time, the diffuse growth type according to Lauren, Borrmann type 4 and low number of chemotherapy cycles, were also recognized as negative prognostic factors for disease outcome. All these factors are considered to be well established negative prognosticators in clinics for patients

**Table 3.** Multivariate analysis of survival

Prognostic factors	n	Locoregional control	Disease free survival	Disease specific survival	Overall survival
		P	P	P	P
pT- stage					
pT 1+2	48			0.06	0.04
pT 3+4	75				
pN- stage					
pN 0+1+2	98				
pN 3	25				
Overall stage					
Stage Ib –III	93				
Stage IV	30				
Stomach involvement					
Whole stomach	7				
Individual areas	116				
Primary tumour site					
Cardia	16			0.01	0.01
Other sites	107				
Perineurial invasion					
Yes	45				
No	59				
Angioinvasion					
Yes	45				
No	23				
Borrmann type					
Type 1-3	61				
Type 4	24				
Growth type according to Lauren					
Diffuse	61			0.09	0.05
Intestinal	56				
No of ChT cycles					
Less than 5 cycles	24			0.03	0.04
Five cycles	99				

pT – pathological T-stage; pN – pathological N-stage; ChT – chemotherapy.

with gastric cancer or with another malignancies and are also usually mentioned as such in pertinent literature.<sup>4,24-27</sup> The subgroup of patients with early, distal tumors in whom distal subtotal resection was per-

formed had no better outcome compared to those who had more advanced disease and, consequently, underwent more extensive surgery. This observation pointed out the potential of adjuvant therapy to neutralize otherwise well established prognostic power of higher tumor stage and tumor's localization. Contrary to our previous analysis<sup>10</sup>, the dose of 5-FU per cycle and pretreatment Hb concentration  $\leq 110$  g/l lost their influence on survival. The reason for this finding could be longer follow up and consecutively more adequate statistical analysis.

The results of both multivariate analyses (*i.e.* the one from the past and the present one) exposed tumors located in the cardia as negative and independent prognosticators, which was pointed out also in other similar studies.<sup>26,27</sup>

In the present analysis, like at the most of analysis of other

malignancies<sup>25</sup>, to no surprise, a more advanced pT-stage was established as negative independent prognostic factor for OS, while for DSS it was on the threshold of statistical significance. The patients who

received less than five cycles of chemotherapy had worse DSS and OS. It is well known that the intensity of chemotherapy can have an influence on treatment outcome neoplasma.<sup>24,28</sup> In our series of patients, we didn't notice other serious late toxicities than the rise of creatinine blood level of grade 1. Jansen *et al.* observed a progressive decrease in the function of the left kidney which was 11% and 52% after 6 and 18 months, respectively.<sup>18</sup> Due to the more accurate conformal radiotherapy planning, we hope there will be less late renal toxicity<sup>29,30</sup>, however, to approve this, longer follow-up of our patients is needed.

Because of high incidence of unresectable disease and distant metastases, this issue is to be addressed in future prospective studies exploring new systemic drugs and regimens. We should pay greater attention to preoperative radiochemotherapy, which could be the best treatment approach also in this type of malignancy, as it is in rectal, esophageal and breast cancer<sup>31</sup>, although more randomized trials are needed to evaluate the survival benefits of this approach.

## Conclusions

From the analysis of the treatment results of a group of 123 patients with operable gastric carcinoma and median follow up time of almost 5 years (more than 5 years in survivors), we may conclude that postoperative adjuvant radiochemotherapy with 5-FU and LV can efficiently improve the treatment outcome, particularly in regard to LRC, with acceptable early and late toxicity. Because of high incidence of distant metastases, this issue has to be addressed in well designed future prospective studies exploring new systemic drugs and regimens.

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