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ORIGINAL ARTICLE

# Clinical outcome and toxicity of 3D-conformal radiotherapy combined with chemotherapy based on the Intergroup SWOG 9008/INT0116 study protocol for gastric cancer

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## Summary

***Purpose:*** *To retrospectively evaluate the efficacy and toxicity of adjuvant radio-chemotherapy in patients with gastric cancer and to relate them to the outcome of the landmark INT0116 study that is criticized because of the high toxicity and poor treatment compliance.*

***Methods:*** *A total of 102 patients who underwent postoperative fluorouracil (5-FU)-based radio-chemotherapy in our institution between 2004 and 2010 for stage IB-IV (AJCC 6th Edn.) gastric cancer were selected. Radiotherapy to 45 Gy was defined individually and delivered with 3D conformal technique. Chemotherapy was carried out during the first 4 and the last 3 days of radiotherapy with continuous infusion of 5-FU (400mg/m²/day) and leucovorin. Patients received an additional 3 cycles of chemotherapy of 5-FU (425mg/m²/day), mostly 1 before and 2 after radio-chemotherapy. Acute hematological and gastrointestinal toxicities were evaluated according to the CTC v3.0 scale.*

***Results:*** *Stage distribution was as follows: IB-5 (5%), II-32 (31%), III-49 (48%), and IV-14 (14%). There were 96% R0 resections; 15% of the patients had a D2 resection. Seventy-four patients (72.5%) received all 5 planned cycles and 98 (96%) completed radiotherapy. The 3- and 5-year overall survival (OS) rates were 57% and 48%, respectively. Multivariate analysis showed that variables significantly affecting OS were pT3-T4, pN2-3, R1 resection and female gender. Only 2% of the patients experienced grade 3 gastrointestinal toxicity; 7% had grade 3 or higher hematological toxicity.*

***Conclusions:*** *We demonstrated better treatment tolerance, compliance, OS of adjuvant radio-chemotherapy for gastric cancer in comparison with INT0116 study. Conformal radiation techniques might have contributed to this improvement.*

***Key words:*** *adjuvant treatment, conformal radiotherapy, gastric cancer, INT0116 study, radio-chemotherapy, toxicity*

## Introduction

Although gastric cancer incidence is decreasing, it is still one of the most frequent malignancies in the world. In Poland in 2011, there were 3510 new cases of gastric cancer in men and 1858 in women. Gastric cancer is the 5th and the 8th most prevalent solid tumor diagnosed in Poland in men and women, respectively [1]. Gastric cancer is often diagnosed at an advanced stage. Surgery remains a standard treatment; however, the results of surgery for advanced-stage disease are not satisfactory. Five-year OS of patients with T3-4N0M0 or T1-4N(+)M0 gastric cancer treated with surgery alone is only 20-30% [2]. To improve the outcome of locally advanced gastric cancer, adjuvant and/or neoadjuvant therapy have been largely employed. The results of the Intergroup

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**Table 1.** Patient and treatment characteristics

| *Characteristics* | *N* | *%* |
|---|---|---|
| *No. of patients* | *102* | *100* |
| Sex | | |
| Females | 38 | 37 |
| Males | 64 | 63 |
| Age, years | Median: 57; Range: 35-77 | |
| ≤65 | 84 | 82 |
| >65 | 18 | 18 |
| Anatomic localization | | |
| Pylorus | 17 | 16.5 |
| Cardia | 17 | 16.5 |
| Body | 63 | 62 |
| Multifocal localization | 1 | 1 |
| Unknown | 4 | 4 |
| Clinical stage (TNM-UICC/ AJCC; 2002) | | |
| IB | 5 | 5 |
| II | 32 | 31 |
| IIIA | 34 | 33 |
| IIIB | 15 | 15 |
| IV | 14 | 14 |
| Unknown | 2 | 2 |
| T stage | | |
| T1 | 2 | 2 |
| T2 | 32 | 31 |
| T3 | 61 | 60 |
| T4 | 7 | 7 |
| N stage | | |
| N0 | 17 | 17 |
| N1 | 49 | 48 |
| N2 | 26 | 25 |
| N3 | 8 | 8 |
| Nx | 2 | 2 |
| Grade (G) | | |
| G1 | 2 | 2 |
| G2 | 36 | 35 |
| G3 | 60 | 59 |
| Unknown | 4 | 4 |
| Extent of resection | | |
| R0 | 98 | 96 |
| R1 | 4 | 4 |
| Type of surgery | | |
| Total gastrectomy | 65 | 64 |
| Subtotal gastrectomy | 37 | 36 |
| Type of lymphadenectomy | | |
| D1 | 85 | 83 |
| D2 | 15 | 15 |
| No lymphadenectomy | 2 | 2 |
| Number of lymph nodes removed | | |
| <15 | 48 | 47 |
| >15 | 50 | 49 |
| Unknown | 4 | 4 |
| Planned dose of radiotherapy (GY) | | |
| 45 | 97 | 95 |
| 50.4 | 4 | 4 |
| 54 | 1 | 1 |
| Total cycles of chemotherapy | | |
| 5 | 73 | 71.6 |
| 4 | 9 | 8.8 |
| 3 | 10 | 9.8 |
| 2 | 4 | 3.9 |
| Unknown | 6 | 5.9 |

trial SWOG 9008/INT0116 have established postoperative radio-chemotherapy as a recommended treatment schedule for patients with completely resected gastric cancer. Patients who received bolus 5-FU and leucovorin before and after concurrent radio-chemotherapy (the same chemotherapy plus 45 Gy) after surgery had improved OS and locoregional control in comparison with patients treated with surgery alone [3,4]. Currently, the alternative method to postoperative radio-chemotherapy is perioperative chemotherapy. In a prospective randomized trial, 3 cycles of chemotherapy (epirubicin, cisplatin, 5-FU ) given before and after surgery improved OS and locoregional control compared with surgery alone [5].

One of the main objections raised against the use of postoperative radio-chemotherapy according to the Intergroup (INT)0116 schedule [3] was a high percentage of acute toxicity and treatment discontinuations. Hematological toxicity (mainly leukopenia) of grade 3 and higher was noted in 54% of the patients, and severe gastrointestinal toxicity in 33%. Treatment was completed in accordance with the planned schedule only in 64% of included patients. Besides the outdated chemotherapy schedule, radiotherapy was also suboptimal i.e. 2D-planned, with most of the patients being treated with two opposite (anterior and posterior) fields. This probably contributed to the observed side-effects and poor compliance to treatment.

Postoperative 5FU-based radio-chemotherapy for adenocarcinoma of the stomach in T3-4N0M0 or T1-4N(+)M0 stage is a standard treatment in

our department. However, in contrast to the original INT0116 protocol, we were using 3D conformal radiotherapy (3D-CRT) with strict quality assurance criteria. Our hypothesis is that the use of conformal radiotherapy techniques may decrease toxicity and increase treatment compliance and finally improve treatment outcome in comparison to the INT0116 results.

The aim of this study was to retrospectively evaluate the toxicity and efficacy of postoperative 3D-CRT combined with chemotherapy in gastric cancer patients treated in our institution.

## Methods

One hundred and two consecutive patients with locally advanced gastric adenocarcinoma treated with surgery and postoperative radio-chemotherapy in our institution between 2004 and 2010 were included into this study. The list of patients was generated from the institutional database. The medical records of all patients were available for the purpose of this study.

Patients were referred for adjuvant radio-chemotherapy having pathological stage ≥ IB (T3-4 N0-3 or T1-2 N1-3) without distant metastases according to the TNM/AJCC 2002 classification [6]. Patient and treatment characteristics are presented in Table 1.

All patients were treated with concurrent radio-chemotherapy according to the published schedule [3]. The treatment consisted of 5 cycles of chemotherapy given every 28 days (5-FU: 425mg/m$^2$/day 24-h continuous i.v. infusion; and leucovorin: 20mg/m$^2$/day short i.v. infusion, days 1-5). Radiotherapy was given concurrently with the 2$^{nd}$ and 3$^{rd}$ or 3$^{rd}$ and 4$^{th}$ cycle of chemotherapy. During radiotherapy the dose of 5-FU was reduced to 400mg/m$^2$/day. Chemotherapy was given at the first 4 and the last 3 days of radiotherapy.

Patients were treated with 3D-CRT using 3-6 photon beams with 15 MV energy. Standard radiotherapy schedule consisted of 45 Gy in 25 fractions. In 4 patients with R1 operation the total dose was increased to 50.4 Gy in 28 fractions. Clinical target volume (CTV) included tumor bed, anastomosis with margin and regional lymph nodes (along the lesser and the greater curvature, cardial, supra- and infra-pyloric, along the left gastric and the common hepatic artery, in the hepatoduodenal ligament, celiac, gastroduodenal, suprapancreatic, inclusion of splenic hilum, periesophageal and retropancreaticoduodenal lymph nodes dependent on tumor location). To a such defined CTV, one cm margin was added in view of the creation of planning target volume (PTV). Reduction of margin to 0.6 cm was permitted in the posterior part (in direction to kidneys and spinal cord). The range of PTV size was 476-4236 cm$^3$ (average: 1563 cm$^3$, median: 1450 cm$^3$). The averages of mean doses were 19.74 Gy for liver, 3.26 Gy for right kidney, and 32.3 Gy for left kidney.

Patients were evaluated for hematological and gastrointestinal toxicity according to the Common Toxicity Criteria of Adverse Events score (CTCAE v3.0; 2003) [7]. The lowest level of blood count parameters - hemoglobin (Hgb), leucocytes (WBC), neutrophils (Neut), and platelets (PLT) during radio-chemotherapy - was scored for each patient as the endpoint of the study. The grade of nausea/vomiting and diarrhea was scored once weekly for each patient during treatment. Renal toxicity was not systematically evaluated. Additional evaluated indicators of treatment toxicity was WHO performance status (PS) deterioration and weight loss during radiotherapy. The time frame for the evaluation of the change of these parameters was restricted within the duration of radiotherapy only, because of incomplete data (retrospective character of analysis) after radiotherapy completion. The rate of completion of radiotherapy and/or chemotherapy in relation with the schedule was also analyzed to evaluate early tolerance/intolerance of treatment.

The following variables were analyzed with regard to the rate of discontinuation of radiotherapy and chemotherapy: WHO PS deterioration, weight loss, grade of hematological and intestinal toxicity, age (≤65 vs >65 years), sex (women vs men), PTV size (≤1450 vs >1450cm$^3$), and baseline WHO PS (0 vs 1-2). Baseline WHO PS was scored at the start of radiotherapy.

The efficacy of postoperative radio-chemotherapy was estimated by survival analysis from the date of surgery to the last follow-up visit/death. The variables that could impact patient survival (sex, age, baseline WHO PS, stage, tumor size, lymph node involvement, grade, extent of resection, type of gastrectomy and lymphadenectomy, number of lymph node removed, and PTV size) were analyzed.

### *Statistics*

Chi-square test was used to compare proportions of treatment complications in relation to the treatment- and patient-related factors. OS was calculated with the Kaplan-Meier method. Univariate analysis (log-rank test) was performed to compare the impact of prognostic factors on survival. Then the variables that were related to OS with p value ≤0.1 were included in the multivariate analysis using the Cox's regression model. A p value ≤0.05 was considered as statistically significant. Statistical analysis was performed using STATISTICA software (version 10; 2012) (StatSoft, Poland).

## Results

The time interval between surgery and the first course of chemotherapy ranged from 15 to 122 days (median 45). Ninety-eight patients (96%) completed radiotherapy in accordance to the schedule. Radiotherapy was discontinued in 3 cases at 19.8 Gy, 21.6 Gy, and 30.6 Gy, because of poor tolerance and deterioration of PS. One

**Table 2.** Compliance to treatment and toxic effects of radio-chemotherapy

| *Compliance and complications of treatment* | *Patients, N* | *%* |
|---|---|---|
| | *102* | *100* |
| Radiotherapy completed in accordance with schedule | | |
| Yes | 98 | 96 |
| No | 4 | 4 |
| Chemotherapy completed in accordance with schedule | | |
| Yes | 74 | 72.5 |
| No | 23 | 22.5 |
| Unknown | 5 | 5 |
| WHO PS change during RT | | |
| No change | 85 | 83 |
| Deterioration | | |
| by 1 grade | 14 | 14 |
| by 2 grade | 2 | 2 |
| Unknown | 1 | 1 |
| Weight change | | |
| No change | 15 | 15 |
| Loss of weight (%) | | |
| <5 | 43 | 42 |
| 5-10 | 36 | 35 |
| >10 | 2 | 2 |
| Unknown | 6 | 6 |
| Hematological toxicity - CTC | | |
| Leukopenia | | |
| 0 | 41 | 40 |
| 1 | 29 | 28 |
| 2 | 24 | 24 |
| 3 | 6 | 6 |
| 4 | 0 | 0 |
| Unknown | 2 | 2 |
| Neutrocytopenia | | |
| 0 | 67 | 65 |
| 1 | 16 | 16 |
| 2 | 11 | 11 |
| 3 | 5 | 5 |
| 4 | 0 | 0 |
| Unknown | 3 | 3 |
| Anemia | | |
| 0 | 50 | 49 |
| 1 | 35 | 34 |
| 2 | 13 | 13 |
| 3 | 1 | 1 |
| 4 | 1 | 1 |
| Unknown | 2 | 2 |
| Thrombocytopenia | | |
| 0 | 80 | 78 |
| 1 | 16 | 16 |
| 2 | 3 | 3 |
| 3 | 0 | 0 |
| 4 | 1 | 1 |
| Unknown | 2 | 2 |
| Intestinal toxicity - CTC | | |
| Nausea/vomiting | | |
| 0 | 51 | 50 |
| 1 | 38 | 37 |
| 2 | 10 | 10 |
| 3 | 2 | 2 |
| Unknown | 1 | 1 |
| Diarrhoea | | |
| 0 | 79 | 77 |
| 1 | 20 | 20 |
| 2 | 2 | 2 |
| 3 | 0 | 0 |
| Unknown | 1 | 1 |

CTC: common toxicity criteria

patient did not receive the last fraction because of technical problem (breakdown of the accelerator). Seventy-four patients (72.5%) received all 5 planned cycles of chemotherapy. The deterioration of PS, treatment toxicity, or patient refusal were the reasons of unplanned earlier termination of chemotherapy in 23 patients. The total number of chemotherapy cycles received was not determined in 5 patients.

Radio-chemotherapy was well tolerated. There was no grade 4 gastrointestinal toxicity. Grade 3 nausea and vomiting were noted in 2 individuals. In all other patients, the maximum of gastrointestinal toxicity was grade 2. Grade 4 hematological toxicity was observed in 2 patients (one anemia and one thrombocytopenia). Grade 3 leukopenia, neutropenia and anemia were observed in 6, 5 and 1 patient, respectively. Weight loss during radiotherapy, as an additional indicator of treatment toxicity, was observed in 81 patients (79%), while in 43 cases (42%) did not exceed 5% of the baseline weight. Loss of weight of more than 10% was noted in 2 cases. WHO PS deterioration by more than one grade was observed in 2 patients, whereas in 85 patients (83%) WHO PS did not change (Table 2). There was a significant interaction between baseline WHO PS and percentage of completed treatment: 90% of patients with baseline WHO PS 0 completed chemotherapy in accordance with the

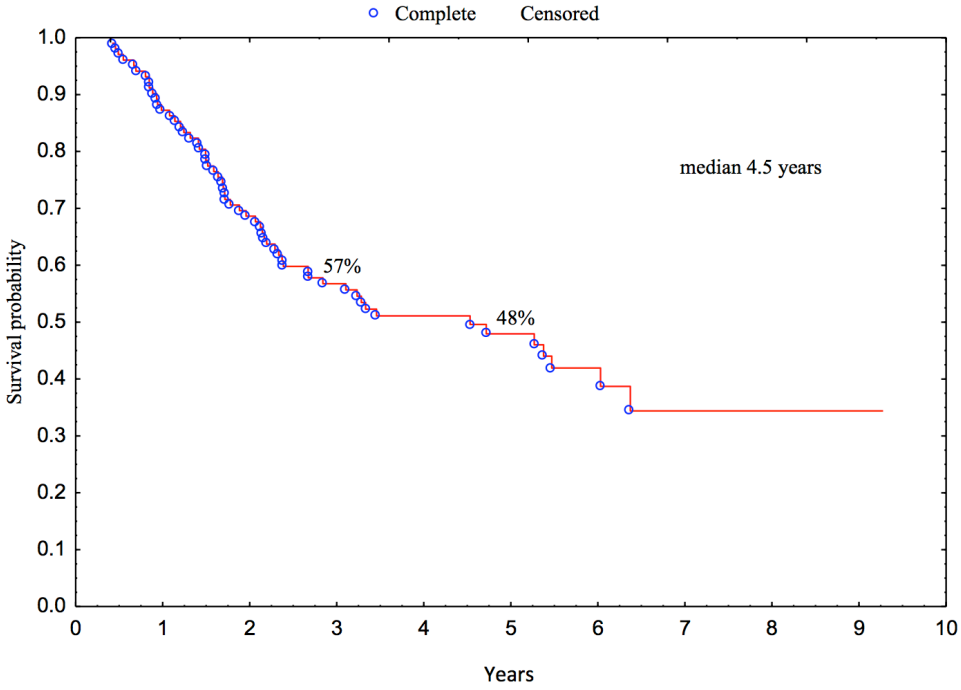


**Figure 1.** Overall survival of all treated patients.

schedule, whereas 5 cycles of chemotherapy were given only to 63% of the patients with baseline WHO PS 1 or 2 (p=0.004). There was a significant interaction between PTV size and the incidence of diarrhea (p=0.009). In patients older than 65 years, nausea and vomiting were more frequent (p=0.03) and also more frequently among women (p=0.008) (Table 3).

At the time of analysis 56 patients (55%) died. Follow-up after surgery ranged from 0.4 to 9.3 years (median 3.1) for all patients and 2.6 – 9.3 years (median 5) for survivors. Three- and five-year OS rates were 57 and 48%, respectively, with a median of 4.5 years (Figure 1). In univariate analysis, significant influence on OS was demonstrated for clinical stage (p<0.001), T stage (p=0.005), N stage (p=0.014), extent of resection (p=0.044), type of gastrectomy (p=0.043), and sex (p=0.046) (Table 4). Multivariate analysis showed T stage (T1-2 vs T3-4, HR:1.58, 95% confidence interval [CI]: 1.15-2.17, p=0.005); N stage (N0 vs N1 vs N2-3, HR:1.55 95%CI: 1.05-2.29, p=0.028); extent of resection (R0 vs R1, HR:3.3 (95%CI: 1.14-9.54, p=0.27); and sex (women vs men), HR:0.56 95%CI: 0.33-0.96, p=0.034) as independent factors for OS.

## Discussion

We related our results to the landmark publication of the INT0116 randomized study [3] with a recent update [4] in which survival improvement for patients with gastric cancer treated with adjuvant radio-chemotherapy in comparison with surgery alone was demonstrated. The characteristics of our patients were very similar to that of the INT0116 study - median age 57 and 60 years, T3-T4 67 and 70%, N(+) 81 and 85%, D2 resection 15 and 10% for our study and INT-0116 study, respectively. The demonstrated OS in our study, with a median of 54 months, differs favorably from the randomized study in which the median OS was only 36 months. The benefit of adjuvant radio-chemotherapy shown in the INT0116 study is often criticized, because this improvement was achieved at the cost of the relatively high toxicity. Grade 3 hematological and gastrointestinal toxicities were observed in 54 and 33% of the patients, respectively. Toxicity demonstrated in our study was minimal: only 7 and 2% of patients developed grade 3 or higher hematological and gastrointestinal toxicity, respectively.

It is postulated that the out-dated radiation techniques used in the INT0116 study might have contributed to the observed high rate of serious side-effects. Radiotherapy was two-dimensionally planned and delivered with two opposed anterior and posterior fields. In our study, the 3D-CRT was used. Conformal techniques give an opportunity to cover a target volume with homogeneous

**Table 3.** Distribution of treatment complications in relation to patients' and treatments' related factors

| *Treatment complications* | *Factors* | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Age (years)* | | | | | *Sex* | | | | | *PTV size (cm³)* | | | | | *Initial WHO* | | | | |
| | *≤65* | | *>65* | | $x^2$ | *Females* | | *Males* | | $x^2$ | *≤1450* | | *>1450* | | $x^2$ | *0* | | *1-2* | | $x^2$ |
| | *N* | *(%)* | *N* | *(%)* | | *N* | *(%)* | *N* | *(%)* | | *N* | *(%)* | *N* | *(%)* | | *N* | *(%)* | *N* | *(%)* | |
| WHO PS change | | | | | | | | | | | | | | | | | | | | |
| deterioration | 12 | (14) | 4 | (24) | p=0.56 | 8 | (21) | 8 | (13) | p=0.4 | 8 | (17) | 7 | (14) | p=0.96 | 10 | (20) | 6 | (12) | p=0.44 |
| no deterioration | 72 | (86) | 13 | (76) | | 30 | (79) | 55 | (87) | | 40 | (83) | 42 | (86) | | 41 | (80) | 44 | (88) | |
| Weight change | | | | | | | | | | | | | | | | | | | | |
| loss <5% | 48 | (60) | 10 | (62.5) | p=0.93 | 17 | (49) | 41 | (67) | p=0.07 | 28 | (65) | 28 | (57) | p=0.43 | 29 | (62) | 29 | (59) | p=0.80 |
| loss ≥5% | 32 | (40) | 6 | (37.5) | | 18 | (51) | 20 | (33) | | 15 | (35) | 21 | (43) | | 18 | (38) | 20 | (41) | |
| Planned chemotherapy | | | | | | | | | | | | | | | | | | | | |
| received | 60 | (76) | 14 | (78) | p=0.89 | 26 | (74) | 48 | (77) | p=0.92 | 33 | (73) | 39 | (81) | p=0.51 | 43 | (90) | 30 | (63) | p=0.004 |
| not received | 19 | (24) | 4 | (22) | | 9 | (26) | 14 | (23) | | 12 | (27) | 9 | (19) | | 5 | (10) | 18 | (37) | |
| Planned radiotherapy | | | | | | | | | | | | | | | | | | | | |
| received | 81 | (96) | 17 | (94) | p=0.78 | 35 | (92) | 63 | (98) | p=0.29 | 46 | (94) | 49 | (100) | p=0.24 | 49 | (96) | 48 | (96) | p=0.62 |
| not received | 3 | (4) | 1 | (6) | | 3 | (8) | 1 | (2) | | 3 | (6) | 0 | (0) | | 2 | (4) | 2 | (4) | |
| Hematological toxicity | | | | | | | | | | | | | | | | | | | | |
| Leukopenia | | | | | | | | | | | | | | | | | | | | |
| 1-2 | 43 | (90) | 10 | (91) | p=0.67 | 24 | (83) | 29 | (97) | p=0.18 | 26 | (90) | 24 | (89) | p=0.73 | 24 | (89) | 29 | (91) | p=0.83 |
| 3-4 | 5 | (10) | 1 | (9) | | 5 | (17) | 1 | (3) | | 3 | (10) | 3 | (11) | | 3 | (11) | 3 | (9) | |
| Neutrocytopenia | | | | | | | | | | | | | | | | | | | | |
| 1-2 | 22 | (88) | 5 | (71) | p=0.63 | 13 | (87) | 14 | (82) | p=0.88 | 14 | (78) | 12 | (92) | p=0.55 | 14 | (100) | 13 | (72) | p=0.097 |
| 3-4 | 3 | (12) | 2 | (29) | | 2 | (13) | 3 | (18) | | 4 | (22) | 1 | (8) | | 0 | (0) | 5 | (28) | |
| Anemia | | | | | | | | | | | | | | | | | | | | |
| 1-2 | 39 | (95) | 9 | (100) | p=0.79 | 25 | (96) | 23 | (96) | p=0.51 | 25 | (93) | 21 | (100) | p=0.59 | 22 | (100) | 26 | (93) | p=0.58 |
| 3-4 | 2 | (5) | 0 | (0) | | 1 | (4) | 1 | (4) | | 2 | (7) | 0 | (0) | | 0 | (0) | 2 | (7) | |
| Thrombocytopenia | | | | | | | | | | | | | | | | | | | | |
| 1-2 | 16 | (94) | 3 | (100) | p=0.31 | 6 | (86) | 13 | (100) | p=0.75 | 9 | (90) | 10 | (100) | p=1.0 | 13 | (100) | 6 | (86) | p=0.75 |
| 3-4 | 1 | (6) | 0 | (0) | | 1 | (14) | 0 | (0) | | 1 | (10) | 0 | (0) | | 0 | (0) | 1 | (14) | |
| Intestinal toxicity | | | | | | | | | | | | | | | | | | | | |
| Nausea/vomiting | | | | | | | | | | | | | | | | | | | | |
| 0 | 47 | (56) | 4 | (24) | p=0.03 | 15 | (39) | 36 | (57) | p=0.085 | 23 | (48) | 26 | (53) | p=0.61 | 28 | (55) | 23 | (46) | p=0.37 |
| 1-3 | 37 | (44) | 13 | (76) | | 23 | (61) | 27 | (43) | | 25 | (52) | 23 | (47) | | 23 | (45) | 27 | (54) | |
| Diarrhea | | | | | | | | | | | | | | | | | | | | |
| 0 | 64 | (76) | 15 | (88) | p=0.44 | 31 | (82) | 48 | (75) | p=0.60 | 43 | (90) | 32 | (65) | p=0.009 | 44 | (86) | 35 | (70) | p=0.08 |
| 1-2 | 20 | (24) | 2 | (12) | | 7 | (18) | 16 | (25) | | 5 | (10) | 17 | (35) | | 7 | (14) | 15 | (30) | |
| Nausea/vomiting | | | | | | | | | | | | | | | | | | | | |
| 1 | 28 | (76) | 10 | (77) | p=0.77 | 13 | (57) | 25 | (93) | p=0.008 | 20 | (80) | 17 | (74) | p=0.87 | 19 | (83) | 19 | (70) | p=0.50 |
| 2-3 | 9 | (24) | 3 | (23) | | 10 | (43) | 2 | (7) | | 5 | (20) | 6 | (26) | | 4 | (17) | 8 | (30) | |
| Diarrhea | | | | | | | | | | | | | | | | | | | | |
| 1 | 18 | (90) | 2 | (100) | p=0.41 | 5 | (71) | 15 | (100) | p=0.17 | 4 | (80) | 16 | (94) | p=0.94 | 6 | (86) | 14 | (93) | p=0.83 |
| 2 | 2 | (10) | 0 | (0) | | 2 | (29) | 0 | (0) | | 1 | (20) | 1 | (6) | | 1 | (14) | 1 | (7) | |

**Table 4.** Overall survival in subgroups

| *Variables* | *Overall survival* | | | *p value* |
|---|---|---|---|---|
| | *3-year %* | *5-year %* | *Median (years)* | |
| Sex | | | | |
| Females | 45 | 39 | 1.95 | 0.046 |
| Males | 64 | 53 | 5.4 | |
| Age, years | | | | |
| ≤65 | 58 | 50 | 5.3 | 0.40 |
| >65 | 50 | 38 | 1.7 | |
| Baseline WHO PS | | | | |
| 0 | 66 | 58 | 5.5 | 0.08 |
| 1-2 | 48 | 38 | 2.3 | |
| Clinical stage | | | | |
| I-II | 78 | 67 | 6.4 | 0.00097 |
| III-IV | 43 | 35 | 2.3 | |
| T stage | | | | |
| 1-2 | 73 | 67 | - | 0.0048 |
| 3-4 | 48 | 37 | 2.7 | |
| N stage | | | | |
| 0 | 65 | 54 | 6.4 | |
| 1 | 63 | 56 | 6 | 0.014 |
| 2-3 | 41 | 31 | 1.7 | |
| Grade | | | | |
| 1-2 | 58 | 49 | 4.7 | 0.38 |
| 3 | 55 | 46 | 3.4 | |
| Extent of resection | | | | |
| R0 | 59 | 50 | 5 | 0.044 |
| R1 | 0 | 0 | 1.2 | |
| Type of gastrectomy | | | | |
| Total | 49 | 41 | 2.8 | 0.043 |
| Subtotal | 70 | 60 | 6 | |
| Type of lymphadenectomy | | | | |
| D1 | 56 | 45 | 3.3 | 0.196 |
| D2 | 60 | 60 | - | |
| Number of lymph nodes removed | | | | |
| <15 | 58 | 48 | 3.3 | 0.9 |
| >15 | 54 | 48 | 4.5 | |
| PTV size ($cm^3$) | | | | |
| ≤1450 | 51 | 43 | 3.3 | 0.3 |
| >1450 | 59 | 52 | 5.3 | |

dose and to adequately spare organs at risk; this is considered as a potential tool for decreasing radiotherapy toxicity [8,9]. As the tissues adjacent to the surgical bed after gastrectomy are at high risk of radiation damage, because their tolerance dose is lower, equal, or slightly higher than a dose prescribed to the target volume, it is crucial to limit the contouring of CTV to the region with the highest probability of the presence of microscopic disease. From the time of publication of the results of INT0116 study, the new guidelines for delineation of targets for postoperative radiotherapy were published [10,11]. CTV has been defined individually depending on tumor localization, T and N stage, and type of lymphadenectomy. Such an individualized concept of CTV definition used in our patients besides conformal radiotherapy planning might have contributed to the observed low treatment-related toxicity. Similar results of improved tolerance with the use of conformal techniques were shown in some other reports. Ciepiela et al. showed that in 66 patients treated with postoperative 3D-CRT and chemotherapy there were only 6% of grade 3 and higher hematological toxicity and no serious gastrointestinal side effects [12]. Skowronska-Gardas reported no grade 4 and higher toxicity in 69 patients undergoing conformal radio-chemotherapy [13]. Similarly, no grade 4 gastrointestinal toxicity was observed in 26 patients treated with 3D-CRT at Stanford University [14]. Liu et al. [15] reported only one case of grade 3 toxicity in 24 patients. Some other authors, however, reported opposite results. In 82 patients treated between 2000 and 2004 with conformal techniques, there were 34 and 33% grade 3 or higher acute gastrointestinal and hematologic toxicity, respectively [16]. These conflicting results from retrospective, mostly small series, do not enable us to conclude that the use of conformal planning improves treatment tolerance in comparison with the INT0116 study. On the other hand, it is not conceivable that we were not using newer acquired treatment modalities for careful planning in view of the limiting dose to normal structures. Limitation of the target volume to the region of the highest probability of subclinical disease is also of value. We demonstrated increased rate of diarrhea with increased size of PTV.

We proved that older age was not correlated with poorer treatment compliance or higher treatment toxicity except for higher percentage of any grade of nausea and vomiting. Survival was also not compromised by age. Only baseline poor PS

was an indicator of worse treatment compliance. Such a finding is of value, because data on the outcome of elderly patients undergoing postoperative radio-chemotherapy in gastric cancer, similarly to other cancer locations, are scarce, due to the rare inclusion of elderly patients into prospective clinical trials. Treatment outcomes of elderly patients with gastric cancer should be investigated because the mean age of gastric cancer diagnosis is 71 years and almost 2/3 of the patients with this diagnosis are older than 65 years [17]. There are conflicting data on the treatment tolerance and outcome of adjuvant therapy in elderly patients with gastric cancer [18-20]. Nevertheless, a general suggestion from these studies is that the most important prognostic factor is PS, thus elderly patients in good PS benefit from adjuvant treatment at the same extent as their younger counterparts.

Unexpectedly, aside from the prognostic significance of local advancement, as well as the completeness of resection (R0 vs R1), female gender appeared to negatively impact survival. One can speculate that this may be a result of statistical hazard. Despite a poorer treatment tolerance caused by a significantly higher rate of grade 2 and higher nausea and vomiting and a trend for a higher rate of leukopenia and weight loss during treatment, women completed adjuvant therapy as often as men. This higher rate of toxicity in women is in line with the worse tolerance of 5-FU-based chemotherapy by women shown also in other studies. In a meta-analysis of 6 NCCTG studies, worse tolerance of 5-FU-based chemotherapy in the form of higher rate of acute gastritis, diarrhea and leukopenia was shown [21,22].

Referral of patients with D2 lymphadenectomy to postoperative radio-chemotherapy is a subject of debate. In the INT-0116 study only 10% of patients had D2 lymphadenectomy. In our study also only 15% of patients underwent optimal regional lymph nodes removal. This reflects the clinical practice in most surgical departments from which patients are referred for adjuvant therapy to our tertiary cancer centre. Improvement of survival with adjuvant radio-chemotherapy is not questioned for D0 or D1 resections. It is only uncertain for patients after D2 resection. Some studies confirm improvement of outcome also for those patients [23,24]. However, in the ARTIST study that compared adjuvant chemotherapy with capecitabine and cisplatin and radio-chemotherapy with the same chemotherapy and 45 Gy radiotherapy concurrent with capecitabine after D2 lymph node dissection, there was no survival benefit demonstrated with the addition of radiotherapy to chemotherapy in the whole group. Subgroup analysis revealed that N(+) patients had longer disease-free survival with the use of radiotherapy [24]. In our study, only 2 (13%) out of 15 patients with D2 dissection were N0, which indicates a value of the use of postoperative radio-chemotherapy for most patients also in D2 subgroup.

Quite narrow therapeutic window of postoperative radio-chemotherapy and some indications that accurate radiotherapy planning may improve treatment outcome incited us to introduce newer radiation techniques in the postoperative management of gastric cancer patients. Currently, for several months we have treated gastric cancer patients with the Volumetric Modulated Arc Therapy (V-MAT) technique. V-MAT technique appears very promising for this indication in planning studies [26,27]. We expect to further improve treatment results with this technique by better sparing the organs at risk. However, data on the value of IMRT for reduction of treatment toxicity in this indication did not confirm the benefit of the use of these techniques. Benefit may be confined to the sparing of kidney and possibly liver only and its clinical meaning is still uncertain [14,28-30]. In our study, we did not analyze renal toxicity because of the retrospective nature of the study and the institutional database did not provide us complete data on this issue. We were only able to evaluate the issue of acute toxicity and survival outcome.

Finally, we should acknowledge that our comparison of patients treated between 2004 and 2010 with those treated in the frame of randomized trials between 1991 and 1998 suffers from all biases that are related to the comparisons with historical controls. Firstly, a retrospective analysis may show better results than a prospective trial, because of the selection bias, i.e. patients with early disease progression or deterioration of PS during the first cycle of chemotherapy are not included in the analysis, whilst such patients have been registered into the INT0116 study and analyzed with the principle of intention to treat. Secondly, besides radiation techniques improvement, there is also major progress in supportive care. In the INT0116 study, 5 HT3 receptor antagonists as drugs for prevention of nausea and vomiting were not in use, and also knowledge on the need of nutritional support during radiotherapy might have been lower than during treatment of patients from our study. In addition, the use of infusional

5-FU instead of bolus injections as in the INT0116 study may have contributed to better toxicity profile of radio-chemotherapy in our study.

To conclude, we demonstrated improved treatment tolerance and compliance (with possibly better survival) of postoperative radio-chemotherapy for gastric cancer patients in comparison with the landmark randomized INT0116 study that first proved survival benefit with use of such a treatment. Conformal radiation techniques might have contributed to this improvement. Ongoing trials will probably define appropriate sequencing of radio-chemotherapy in relation to surgery and the role of adjuvant radiotherapy itself.

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