Adjuvant Chemoradiation with 5-Fluorouracil or Capecitabine in Patients with Gastric Cancer after D2 Nodal Dissection

MATTIA FALCHETTO OSTI, LINDA AGOLLI, STEFANO BRACCI, FLAVIA MONACO, SLAVISA TUBIN, GIUSEPPE MINNITI, VITALIANA DE SANCTIS and RICCARDO MAURIZI ENRICI

Institute of Radiation Oncology, La Sapienza University, Sant’Andrea Hospital, Rome, Italy

Abstract. Aim: To evaluate outcome and prognostic factors in patients with locally advanced gastric cancer. Patients and Methods: From 2007 to 2011, 55 patients underwent adjuvant radiotherapy and concurrent chemotherapy with 5-fluorouracil (64%) or capecitabine (36%). D2 node resection was performed in all patients. The pathological stage was as follows: 13% IB; 29% II; 24% IIIA; 9% IIIB and 25% stage IV. Results: The median follow up was 21 months. Five-years overall and disease-free survival were 44.5% and 48%, respectively. Eighteen patients experienced disease relapse after combined treatment; in five of these patients, relapse was both locoregional and systemic. The most common toxicity was grade 1-2 leukopenia, reported in 32% of cases. Six patients developed grade 3 toxicity. Nodal ratio ≥0.4 and N3 stage were significant prognostic factors for survival and relapse. Conclusion: Adjuvant conformal radiotherapy and concurrent chemotherapy is a feasible and well-tolerated treatment for patients with locally advanced gastric cancer.

Gastric cancer (GC) is the sixth most common type of cancer in Europe, with 650,000 deaths every year (1). Gastric carcinoma has a poor prognosis, with 10-year survival rates of 20% for all stages, because most patients are diagnosed with advanced stage disease (2). Surgery is the principal treatment for patients with resectable cancer. Nevertheless, studies showed that cure rates after surgery alone are 10-40% in patients with extension beyond the gastric wall and/or lymph node involvement (3). Locoregional relapses occur principally in the gastric bed and nodes and less frequently in the anastomosis or duodenal stump (4).

Several randomized trials demonstrated superior outcomes with the addition of postoperative chemoradiation. Since 1969 Moertel et al. demonstrated that adjuvant radiotherapy (RT) associated with concurrent chemotherapy had favourable effects on survival and disease control (5). Postoperative combined treatment in high risk patients with GC reduced locoregional failure and increased survival rates compared to surgery alone (6, 7), or to adjuvant chemotherapy alone, and RT alone (8). In 2001, chemoradiation became the standard adjuvant therapy after curative surgery based on the randomized study by Macdonald et al. (7); this trial reported improved locoregional control and survival but high treatment-related toxicity rates. In Europe, the most frequent approach for resectable GC is preoperative chemotherapy as described in the Medical Research Council Adjuvant Gastric Infusion Chemotherapy (MAGIC) trial that demonstrated lower locoregional failure and survival benefit (9).

Several studies were performed in order to find the optimal chemotherapy regimen and RT pattern, to reduce toxicity rates and to increase the efficacy. Nowadays, a 3-dimensional (3D) treatment planning system is used for RT; this probably reduces toxicity rates and also allows a better dose distribution on the target volume. Here we aimed to evaluate disease control and toxicity rates after adjuvant RT and concurrent chemotherapy with 5-fluorouracil or capecitabine in patients with advanced GC. We also tried to assess the impact of prognostic factors on survival and local control.

Patients and Methods

Correspondance to: Linda Agolli, Radiation Oncology, Sant’Andrea Hospital, Via di Grottarossa 1035-1039 – 00189, Rome, Italy. Tel: +39 0633776160, +39 0633776164, Fax: +39 0633776608, e-mail: lindaagolli@yahoo.it

Key Words: Gastric cancer, radiotherapy, regional control, combined treatment, 5-fluorouracil, capecitabine, D2 node resection.
The study included 55 patients: 31 (56%) males and 24 (44%) females. The mean age was 63 years (range: 34-82 years). The performance status according to the Eastern Cooperative Oncology Group was 0-1 for all patients. Patients were staged according to the American Joint Committee for Cancer Staging System (AJCC) 2002. Patients’ characteristics are described in Table I. The most frequent histological grade was grade 3 (67%), followed by grade 2 (15%), grade 4 (10%), and grade 1 (4%). Histological grade was not stated for two (4%) patients.

Treatment. A total gastrectomy was performed in 24 patients (41%), while 35 patients (59%) underwent a sub-total gastrectomy. All patients underwent D2 lymph node dissection which involves resection of all perigastric nodes and some celiac, splenic, hepatic artery, and cardiac nodes, depending on the location of tumor. Five patients presented positive or close surgical margins. The lymph node ratio (LNR: defined as the ratio of the number of metastatic nodes to the number of removed nodes) was <0.4 in 40 patients and ≥0.4 in 15 patients (Table I).

All patients received concurrent chemotherapy with fluoropyrimidine-based schedule during all course of RT. Chemotherapy regimens consisted of 5-fluorouracil (5-FU) at 225 mg m²/day in continuous infusion (c.i.) for five days a week, administered to 35 patients (64%), or oral capecitabine at 825 mg m² twice daily for five days a week administered to 20 patients (36%). After combined treatment, the same agent was used as adjuvant therapy for an additional 2-3 cycles.

RT was started not later than 8 weeks after surgery and delivered using a 3 dimensional conformal technique. All patients underwent pre-treatment computed tomography (CT). Each patient required personalized irradiation fields depending on site of tumor, surgical resection and nodal involvement. The clinical target volume (CTV) included the tumor bed, the anastomosis region, the duodenal stump and locoregional lymph nodes (perigastric, celiac, suprapancreatic, splenic, suprapancreatic, porta hepatis, pancreaticoduodenal and para-aortic). A margin of 1.5-2 cm in all directions was added to the CTV to generate the planning target volume (PTV) taking into account the individual organ motion and setup margin. The organs at risk (OAR) contoured on the planning CT were: spinal cord, liver, distal esophagus, small bowel, kidneys and lungs. The dose-volume histogram (DVH) was in accordance with the accepted tolerance dose for OAR. RT was delivered by a linear accelerator using 15 MV photons using a four-field technique. The total prescribed dose to the PTV was 50.4 Gy distributed in 28 fractions of 1.8 Gy per day for five days a week over five weeks.

Follow up and statistics. All patients underwent weekly clinical evaluation and routine blood examinations during RT. Treatment related-toxicity was graded according to RTOG scale (10). Follow-up was performed every three months for the first two years after radiotherapy and every six months up to five years and annually afterwards. Performance status, treatment-related adverse effects, blood count, liver and renal function tests, tumor markers, abdominal ultrasonography and tomography, and endoscopy with histological examinations were assessed at follow-up.

Statistical analysis was performed using the SPSS statistical software package version 13.0 (SPSS, Inc., Chicago, Illinois, USA). The overall survival (OS) was recorded from the date of surgery to the date of death from any cause or last follow-up. The disease-free survival (DFS) was calculated from the date of surgery to the date of recurrence, local or distant or to the last follow-up. Locoregional recurrence was defined as any recurrence included in the irradiated field. Distant progression was defined as any evidence of disease...
outside of the irradiated field and in distant organs. Patient survival was estimated using the Kaplan–Meier method. The clinical prognostic factors age, gender, histological grade and type, Lauren classification, T stage, N stage, overall stage, LNR, surgical margins and lymphatic/vascular invasion were included in the statistical analysis. Univariate analysis was performed to determine significant prognostic factors using the log-rank test. Multivariate analysis was performed using Cox regression. The chi-square test was performed to determine statistical differences regarding toxicity rates between the two chemotherapy regimens administered. A $p$-value of less than 0.05 was considered as statistically significant.

**Results**

**Relapse and survival.** The overall mean and median follow up time were 25.1 and 21 months (range=7-62 months), respectively. Thirty-nine (71%) patients were alive at time of the analysis with a median follow up of 21 months. There were 16 deaths: 10 patients died due to disease progression and 6 patients died from other causes. Overall survival rates were 83% at 2 years, 59.3% at 3 years and 44.5% at 5 years. Disease-free survival rates were 75% at 2 years, 60% at 3 years and 48% at 5 years. Survival is shown in Figure 1. Mean and median duration of OS was 43.9 and 50 months, respectively. Mean and median duration of DFS was 42.2 and 47 months, respectively.

Five (9%) patients experienced disease relapse both locoregionally and systemically during the follow-up period. There was no patient who developed isolated local failure. Local control was 91.2% at 2 years and 73% at 5 years. Distant relapse occurred in 18 patients. Liver and diffuse metastasis (peritoneum, liver and bones) were the most common sites of relapse in seven (13%) and six (10%) patients, respectively. The patterns of failure are described in Table II. The median time to distant relapse was 11 months (range=6-47 months). Most recurrences (local and distant) occurred during the first two years after treatment.

**Toxicity rates.** Fifty-two patients completed combined treatment at the prescribed dose; three patients interrupted RT at a total dose of 45 Gy due to grade 3 toxicity (dysphagia: 1 patient; weight loss and diarrhea: 1 patient; reduced hemoglobin: 1 patient). Nevertheless, they were included in this analysis for reaching the effective dose according to the NCCN Guidelines in Oncology (11).

The most common hematological toxicity was grade 1-2 leukopenia reported in 18 (16%) cases. Grade 3 hematological toxicity was recorded in 3 patients. The most frequent grade 1-2 gastrointestinal adverse effect was nausea/vomiting recorded in 16 patients (29%), followed by dysphagia and diarrhea presented in 7 (12%) and 6 (10%) patients, respectively. Three patients developed grade 3 acute gastrointestinal toxicity: one patient had diarrhea and two patients presented dysphagia during combined treatment for tight stenosis at the site of anastomosis subsequently resolved with endoscopic treatment. Thirty-three (6%) patients lost weight during treatment, with a mean weight loss of 2.22 kg (range 0.5-16 kg). Treatment-related toxicities are included in Table III. We noted that grade 2
hematological toxicity occurred mainly in patients who received capecitabine, while patients receiving the 5-FU regimen more commonly presented gastrointestinal toxicities. No statistical correlation was found between type of chemotherapy regimen and adverse effect rates.

Prognostic factors. On univariate analysis, LNR ≥0.4 and N3 stage emerged as significant prognostic factors for OS (p=0.017 and p<0.0001, respectively), DFS (p=0.022 and p<0.0001, respectively), local control (p=0.02 and p=0.04, respectively) and distant progression (p=0.02 and p<0.0001, respectively). Advanced overall stage III-IV was identified as being a significant prognostic factor for OS (p=0.001), DFS (p=0.009), and distant progression (p=0.007), but there were no statistical correlations with local control (p=0.007). Therefore, no variables were found to be significantly associated with survival and local control on multivariate analysis.

Discussion

The prognosis of advanced GC remains poor, even after radical surgical treatment, with a 5-year overall survival of 20-30% for T3-T4/N+ patients. There is a high risk of locoregional and distant recurrence, and this requires multidisciplinary management in order to improve outcomes. Although meta-analysis has shown a small survival benefit after post-operative chemotherapy (12, 13), several studies did not demonstrate such survival improvement. However, a recent meta-analysis showed that the addition of RT for patients with resectable GC significantly improves survival (14).

Adjuvant chemoradiation has become the standard treatment in the USA since the randomized trial by McDonald et al. demonstrated a survival benefit compared to surgery alone, even after long-term follow up (7). The INT0116 group revealed significant improvement of OS at 3 years (50% in the chemoradiation arm vs. 41% in the surgery-alone arm, p=0.005) and DFS at 3 years (48% in the chemoradiation arm vs. 31% in the surgery-alone arm, p<0.001). Grade 3-4 toxicity rates were high, but that may be due to the conventional two-dimensional RT technique which increased the irradiated volume. The study was criticized because only 10% of patients included in the trial underwent a D2 node dissection. Thus, the benefit of extended lymphadenectomy remains a controversial question. In Asia, D2 node dissection is widely performed as standard radical surgery. A Korean study demonstrated the advantage of adjuvant chemoradiation for patients with GC who underwent D2 node resection (15). A Dutch randomized trial that compared D1 versus D2 dissection did not support a survival improvement (16), but an Italian study demonstrated benefit of D2 node resection (17).

In the present study, all patients underwent a D2 node resection and subsequent adjuvant 3D conformal RT
associated with concurrent chemotherapy with 5-FU or oral capecitabine. The 3- and 5-year OS was 59.3% and 44.5%, respectively, according to the present literature. The DFS rates found here were comparable to other studies conducted in similar series to ours (18). In a series of 70 patients who underwent D2 node resection and adjuvant chemoradiation, Leong et al. demonstrated a 3-year OS, DFS and local control of 60.6%, 54.1% and 84.3%, respectively (19). In our series, relapse occurred in 33% of the patients; five of these patients presented both locoregional and distant relapse. Others reported similar rates of distant relapse around 30-50% (20).

The treatment was well tolerated with only 10% of patients developing grade 3 toxicity. The most common hematological and gastrointestinal toxicities were grade 1-2 leukopenia reported in 16% patients and nausea/vomiting recorded in 29% of the patients, respectively. Our patients presented lower toxicity rates compared to other studies. The 3D conformal RT technique allows curative doses to be delivered sparing normal tissues and leading to lower toxicity rates. A Canadian study reported 33% and 56% of grade 3 hematological and gastrointestinal toxicities in patients who received adjuvant conformal radiotherapy and concurrent 5-fluorouracil (21).

Our study revealed that LNR and N-stage were the most important prognostic factors for OS, DFS and locoregional control as reported in other analyses (20, 22).

Nowadays, distant progression remains the major pattern of failure. Thus, chemotherapy is an irreplaceable treatment for gastric cancer, but the combined therapy is also associated with severe toxicities which may lead to treatment interruption, whilst reducing its efficacy. The role of systemic therapies, type of chemotherapeutic agents, schedules, dosages and timing has not been sufficiently defined. In 2006, the MAGIC study demonstrated a 5-year OS improvement (36% vs. 23%, p=0.009) in patients receiving preoperative chemotherapy [3 courses of epirubicin, cisplatin and 5-FU (ECF)] and subsequent postoperative chemotherapy (3 courses of ECF) compared to those receiving surgery alone (9). It should be noted that postoperative chemotherapy was administered to 55% of the patients in the MAGIC study and only 42% of them completed the entire treatment because of cancer progression, surgical complications and toxicity.

Several clinical studies reported similar survival rates using different chemotherapeutic agents. A pilot study by Orditura et al. reported no survival benefit using RT of 45 Gy and concurrent chemotherapy with a FOLFOX-4 regimen (leucovorin, fluorouracil and oxaliplatin) in a cohort of 29 patients with advanced GC; recurrence was observed in 55% of the patients (23). A retrospective analysis of 52 patients who underwent D1/D2 node dissection and adjuvant chemotherapy (cisplatin and 5-FU) followed by 3D conformal RT of 45 Gy with concurrent c.i. 5-FU, reported 5-year OS and DFS of 50% and 48%, respectively; relapse occurred in 52% of patients and 34% developed grade 3 gastrointestinal toxicity (24). A multicenter prospective study reported a 3-year OS of 62% after one cycle of ECF followed by conformal RT and concurrent infusional 5-FU and two additional cycles of ECF; grade 3-4 gastrointestinal and hematological toxicity rates were 66% and 28%, respectively (25).

The recent ARTIST trial randomized 458 patients submitted to D2 dissection undergoing adjuvant chemotherapy (6 cycles of capecitabine and cisplatin) alone or chemotherapy followed by combined therapy (RT of 45 Gy and concurrent capacitabine) and two subsequent cycles of the same agents (26). After a median follow up of 53.2 months, the authors concluded the addition of combined treatment did not significantly prolong DFS. However, the DFS was superior in patient with positive pathological lymph nodes who underwent chemoradiation (p=0.0365).

The ongoing CRITICS trial aims to improve clinical outcome in patients treated with preoperative chemotherapy (epirubicin, cisplatin and capecitabine) followed by surgery with adequate node dissection and concurrent chemoradiation (45 Gy, cisplatin and capecitabine) (27).

In conclusion, our study confirms that adjuvant conformal radiotherapy and concurrent chemotherapy after a radical D2 surgery offers adequate disease control with acceptable toxicity rates. Distant progression is the major pattern of failure, which is not sufficiently controlled by systemic therapy. Surgery remains the principal treatment but the extent of lymph node resection is still to be defined. Therefore, modern RT techniques such as intensity modulated RT and chemotherapy regimens need to be investigated in order to find the optimal treatment and to improve survival.

References


