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ORIGINAL ARTICLE

Image-guided intensity-modulated radiotherapy for patients with locally advanced gastric cancer: a clinical feasibility study

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Abstract
Background The aim of this study was to determine the medical and technical feasibility of intensity-modulated radiotherapy (IMRT) in high-risk nonmetastatic gastric cancer stage II and III after primary gastrectomy and D2 lymphadenectomy.
Methods and materials A prospective nonrandomized phase II trial was performed on 25 consecutive patients with gastric cancer with high risk (T3–4, N1–3, G2–3, R0–1). The dose delivered was 45 Gy (1.80 Gy per fraction) in IMRT technique. Concurrent 5-fluorouracil-based chemotherapy at 225 mg/m^2 was administered as a continuous intravenous infusion. Primary endpoints were acute gastrointestinal toxicity (CTC 4.0) and technical feasibility of IMRT in regard to dose planning and radiation delivery.
Results Early acute events were defined as clinical and chemical adverse effects of IMRT and concurrent chemotherapy during treatment. By definition, 90 days after the end of IMRT has been evaluated as acute-phase toxicity. No patient had grade 4 or higher acute adverse events. Clinical grade 3 toxicity occurred in two patients (8 %) with diarrhea and in one case (4 %) with nausea. Hematological changes with grade 3 occurred in three cases (12 %) with hemoglobin decrease, in five cases (25 %) as leukopenia, and in one case (4 %) with thrombocytopenia. The mean dose for liver was 16 Gy and the percentage volume exceeding 30 Gy (V30) was 21 %. Mean dose for right and left kidney was 9 and 13 Gy, respectively, and V20 was 9 % and 13 %, respectively. Heart received a median dose of 15 Gy and V40 was 17 %. The mean dose to the bowel was 11 Gy and V40 was 6 %. Spinal cord had at maximum 33 Gy in median. Specifics of dose distribution, including the coverage, for the target region were as follows: minimum was 33 Gy, maximum 48.6 Gy, and mean dose 44.6 Gy. The prescribed dose (45 Gy) covered 99 % and 95 % of planning target volume (OTV) in 66 % and 92 % of cases, respectively. Median PTV was 15.77 ml (range, 805–3,604 ml).
Conclusions The data support the practical feasibility of IMRT in adjuvant treatment in high-risk gastric cancer in the postoperative setting as a proof of principle. Acute toxicity has been tolerable.

Keywords Gastric cancer · Intensity-modulated radiotherapy · IMRT · Image-guided radiotherapy

Introduction

Surgery has been the treatment of choice for locally advanced gastric. However, even after complete resection and adequate D2 lymphadenectomy, high rates of locoregional recurrence continue to be reported [1–6]. Several approaches have been tried to improve the clinical outcome of resectable gastric cancer, including adjuvant chemotherapy (CT), concurrent radiochemotherapy (cRCT), and perioperative chemotherapy. Conventional radiotherapy ($_{con}$RT) combined with chemotherapy has been shown to decrease locoregional failure and improve overall survival in some retrospective studies on unresectable or residual disease after surgery. The landmark Intergroup 0116 trial [7] demonstrated an increase in the median overall survival from 27 to 36 months when postoperative conventional RT

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chemoradiation was used in addition to surgery. However, the trial was and still is criticized because of the low number of D2 lymphadenectomies and the high levels of toxicity. $_{con}$RT in this trial was delivered mostly as two-dimensional (2D) RT, although three-dimensional (3D) RT with large fields was used in some cases, and this was configured and verified by means of fluoroscopy and simple dose distribution models. This regimen led to significant acute and late abdominal toxicity, and 17 % of the patients assigned to $_{con}$RCT stopped treatment as a result. In addition, $_{con}$RT may affect normal structures including the liver, kidneys, lungs, and heart, resulting in late morbidity. Postoperative target volumes may include the stomach bed (including surgical clips), a portion of the left hemi-diaphragm, and draining lymphatics, thereby putting all these structures at risk. The standard target dose of 45 Gy far exceeds the tolerance of several surrounding, critical normal tissues (most notably the kidneys and liver). As a result, $_{con}$RT volumes are often significantly influenced by the need to avoid potential kidney and liver damage, but the resulting underdosing of some parts of the target can compromise local control and survival [8].

Intensity-modulated radiation therapy (IMRT) allows for more conformal dose delivery and selective sparing of critical structures such as the kidneys and liver, and may therefore allow for more complete target coverage to full dose; this in turn may substantially reduce acute toxicity and late sequelae. Theoretically, the improved target coverage and accuracy of IMRT could improve locoregional control and reduce toxicity.

The key to successful implementation of IMRT is to minimize the dose to the surrounding structures to prevent morbidity and compounded toxicity from chemotherapy while maintaining adequate coverage of the target by similar or even higher doses. This prospective feasibility study examined whether postoperative IMRT could be considered an effective and safe therapeutic option in clinical management of locally advanced gastric cancer.

Materials and methods

Between November 2008 and April 2011, 25 patients with newly diagnosed locally advanced gastric adenocarcinoma without distant metastases (T2–4 and N2–3, M0) were treated with postoperative IMRT and concurrent chemotherapy, all of whom were eligible for this study. All cases were discussed in a multidisciplinary team after surgery and selected by the team because of the risk factors related to T2–4 and N2–3. Patient and tumor characteristics are summarized in Table 1. The median age at the time of diagnosis was 60 years. Pretreatment evaluation included esophagogastroduodenoscopy, endoscopic ultrasonography, and computed tomography (CT) in all patients, as well as staging laparoscopy in 8 cases. Tumor stages were determined according the seventh edition of the American Joint Committee on Cancer staging system for gastric cancer, even for those treated before the new edition was published.

Table 1 Clinical and treatment characteristics

Parameter	Number of patients
Age (years)	
>60	18
<60	7
Gender	
Female	5
Male	20
Tumor location	
Antrum	11
Body	11
Pylorus	3
Grade	
G1–2	3
G3	22
Tumor size	
>5 cm	18
<5 cm	7
T stage	
3	20
4	5
N status	
1	5
2	14
3	6
Margin	
R0	22
R1	3
Extent of nodal dissection	
D2	25
D1	0
Extent of surgery	
Total gastrectomy	21
Subtotal gastrectomy	4
Intensity-modulated radiotherapy (IMRT) dose	
45 Gy	25
Other	0
Chemotherapy	
5-FU	25
Other	0

All patients received induction chemotherapy consisting of concurrent 5-fluorouracil (5-FU) at a dose of 225 mg/m^2 continuously administered intravenously. The actual IMRT

dose was 45 Gy in all cases. Patients had been instructed not to eat or drink for 3 h before each treatment to reduce variability resulting from stomach distension. IMRT started 6 weeks after surgery.

Target delineation

The magnitude of RT in general and of IMRT in this study is affected by the definition of the high-risk zone of the upper abdomen in the adjuvant setting. Postoperatively, there is no actual gross tumor volume (GTV), because the stomach has been removed. However, in all cases we attempted to define a "GTV" according to the preoperative endoscopic and CT findings.

In high-risk situations, the clinical treatment volume (CTV) had to be as accurate as possible. The CTV included the GTV with a 3-cm mucosal expansion and involved the node, celiac axis, splenic hilum, porta hepatis, and subpyloric/retropancreatic regions for tumors involving the antrum. In 14 cases (56 %), we performed additionally fluoroscopy of the upper abdomen with oral contrast agent, and in 18 cases (72 %), ultrasonography was performed to define the CTV more precisely. Positron emission tomography/CT was performed in addition to more conventional staging procedures in 12 cases (48 %) in which distant metastases were suspected.

The CTV was expanded circumferentially by 10 mm to form the planning target volume (PTV). Image guidance with daily kilovolt imaging was used for positioning according to the bony anatomy in all cases. Inverse treatment planning was performed using Eclipse and later ARIA oncology information systems (Varian Medical Systems, Palo Alto, CA, USA) and the direct machine parameter optimization algorithm. Generally, we used a median of five beams with an anterior or left anterior oblique beam angle configuration that would directly enter the stomach and exit posteriorly, thus sparing critical organs (Figs. 1 and 2). The V20 for each organ was the volume (percentage) receiving at least 20 Gy; V30, that receiving at least 30 Gy; and V40, that receiving at least 40 Gy. Normal tissue constraints included a V30 less than 30 % and a V20 less than 50 % for the liver, a V20 lower than 25 % for each kidney, a V40 less than 25 % and a V30 less than 35 % for the heart, and a maximum spinal cord dose of 45 Gy. The dose to the lungs and the left ventricle was reduced as much as possible.

Logistics and follow-up examination

The median time between surgery and IMRT was 5 weeks. During IMRT all patients were seen by a member of the study team (HB) at least once a week. Acute toxicity was graded according to the Common Terminology Criteria (CTC) for Adverse Events version 4.0.

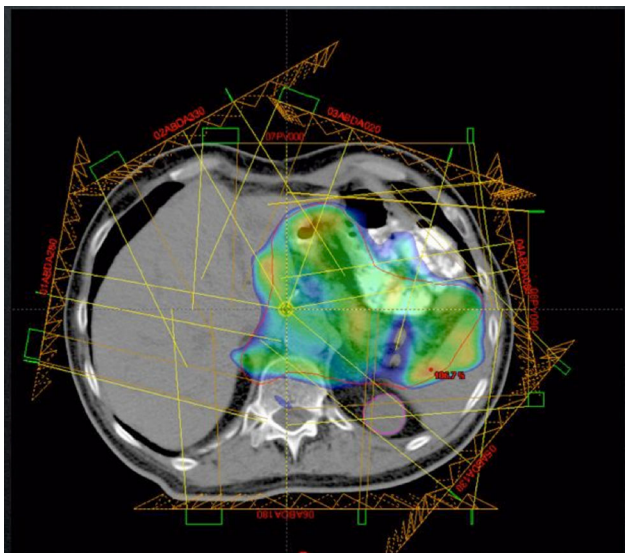

Fig. 1 Clinical target volume based on computed tomography (CT)

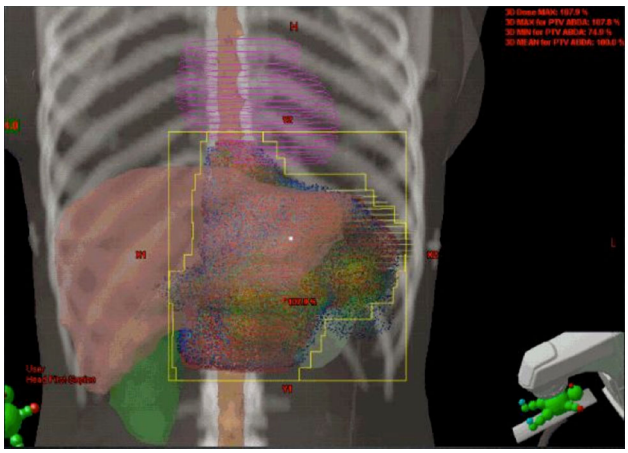

Fig. 2 Clinical target volume and field arrangement based on CT

Follow-up information was obtained from patient records and clinic notes.

The primary endpoint of this prospective feasibility study was acute toxicity and technical performance with regard to dose distribution to the PTV and organs at risk.

Results

Primary endpoint: acute toxicity

Early acute events were defined as clinical adverse effects of IMRT and concurrent chemotherapy during treatment, with acute-phase toxicity being defined as that occurring

Table 2 Acute toxicity

	Grade (CTC 4.0), number of patients				Total grade >2
	1	2	3	4	
Nausea	12	12	1	0	1
Vomiting	10	10	0	0	0
Diarrhea	4	4	2	0	2
Hb decrease	8	10	3	0	3
Leukopenia	5	5	5	0	5
Thromocytopenia	4	3	1	0	1
Pain	3	4	0	0	0

within 90 days of the completion of IMRT. No patient had a grade 4 or worse acute adverse event, but clinical grade 3 toxicity was experienced by two patients (8 %) with diarrhea, one (4 %) with nausea, three (12 %) with reduced hemoglobin levels, five (20 %) with leukopenia, and one (4 %) with thrombocytopenia (Table 2).

Primary endpoint: dosimetric characteristics of IMRT

The mean dose for liver was 16 Gy and the percentage volume exceeding 30 Gy (V30) was 21 %. Mean dose for right and left kidney was 9 and 13 Gy and V20 was 9 % and 13 %, respectively. Heart received a median dose of 15 Gy and V40 was 17 %. The mean dose to the bowel was 11 Gy and V40 was 6 %. The spinal cord had at maximum 33 Gy in median.

Specifics of dose distribution, including the coverage, for the target region was as it follows: minimum was 33 Gy, maximum 48.6 Gy, and mean dose 44.6 Gy.

The prescribed dose (45 Gy) covered 99 % and 95 % of planning target volume (OTV) in 66 % and 92 % of cases, respectively. Median PTV was 15.77 ml (range, 805–3,604 ml).

Secondary endpoint: local control

The median follow-up period was 16 months (range, 10–35 months). A year after completing IMRT, three patients (12 %) experienced local failure and another two experienced regional relapse (8 %). Distant metastases developed in six patients (24 %), five of whom died (20 %).

Discussion

This study was designed to assess the acute toxicity resulting from IMRT by using a validated standardized score (CTC 4.0) and by evaluating the dosimetric characteristics for organs at risk and the upper abdominal region of the tumor. We also examined the short-term clinical outcome, albeit as a secondary endpoint. There were no cases of grade 4 or worse adverse effects during combined IMRT and 5-FU-based chemotherapy, although there was a high incidence (12 %) of grade 3 clinical toxicity, most cases of which involved hematological changes including leukocytopenia (25 %) and reduced hemoglobin levels (12 %). All patients were treated in the clinical ward of the radiation oncology department, with strict clinical control and observation, and there were no interruptions to therapy, except in three cases with an IMRT delay of 2–3 days. Thus, therapy was more continuous than is usually achieved with $_{con}$RT [7–10].

Although IMRT does not provide a significant reduction in acute toxicity compared to $_{con}$RT, it does spare the kidneys and liver, as demonstrated in this study as well as previous studies [11–13]. The sparing of critical organs is clinically very important because concurrent chemotherapy also affects the kidneys, liver, and parts of the spinal cord and because it reduces potential long-term toxicity, especially for patients undergoing major abdominal surgery and for those who may subsequently need further chemotherapy.

Our findings are generally consistent with those of other studies on IMRT for gastric cancer. A previous comparison of patients treated with $_{con}$RT or IMRT indicated that IMRT reduces the dose to the liver but does not reduce acute gastrointestinal toxicity [11]. This finding was supported by another study in which IMRT was also shown to provide better protection of the liver and kidneys compared with 3D CRT [12], although this conflicts with a study that showed only marginal sparing of the kidneys [13].

Preoperative IMRT was previously shown to give rise to acute adverse effects of grade 3 acute toxicity in 14 patients (56 %), including dehydration in 10 cases, nausea in 8 cases, and anorexia in 5 cases, although there were no cases of grade 4 toxicity. The same study showed that the median target coverage was 0.97 (range, 0.92–1.01), with a median V30 for the liver of 26 %; a median V20 for the right and left kidneys of 14 and 24 %, respectively; and a median V40 (percentage of volume receiving at least 40 Gy) for the heart of 18 % [14]. In our study, we found that the doses to the left kidney and heart were lower than these previously reported values.

A number of other studies have also reported that IMRT is advantageous compared to $_{con}$RT. Jansen et al. [15] showed that if 20 % of one kidney receives a dose of more than 20 Gy, 11 % and 52 % of these patients will suffer from renal insufficiency within 6 months and 1 year of RT, respectively. Milano et al. treated seven gastric cancer patients with IMRT and compared the IMRT plan to that for $_{con}$RT. The former was found to have an advantageous

dose distribution in the target area and to provide better protection of high-risk organs [8].

In conclusion, our findings suggest that IMRT is a good option and a feasible method. The use of advanced IMRT techniques makes the side effects tolerable and manageable by protecting at-risk organs while providing good coverage of the target volume.

IMRT, combined with chemotherapy, may be considered a safe therapeutic option in addition to surgery in locally advanced gastric cancer. We encourage more prospective evidence generation in terms of testing effectiveness.

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Conflict of interest All authors confirm that there is no conflict of interest to any financial and personal relationships with other people or organization.

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