Radiotherapy and Oncology 102 (2012) 51–55

Contents lists available at SciVerse ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

IORT in gastric cancer

Adjuvant chemoradiotherapy with or without intraoperative radiotherapy for the treatment of resectable locally advanced gastric adenocarcinoma

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ARTICLE INFO

Article history:
Received 17 October 2010
Received in revised form 26 September 2011
Accepted 16 October 2011
Available online 16 December 2011

Keywords:
Gastric
Carcinoma
Intraoperative radiotherapy
Chemoradiotherapy
Gastrectomy

ABSTRACT

Purpose: To document the long-term efficacy of intraoperative electron radiotherapy (IOERT) followed by concurrent chemotherapy and external-beam radiotherapy (EBRT) in the management of locally advanced gastric cancer.

Materials and methods: A total of 97 consecutive patients with T3/4 or N+ gastric adenocarcinoma were enrolled. Fifty-one patients received adjuvant chemoradiotherapy (EBRT group) and 46 received IOERT (dose range, 12–15 Gy) followed by chemoradiotherapy (EBRT + IOERT group).

Results: The 5-year locoregional control rates were 50% and 35% in the two groups with or without IOERT, respectively ($p = 0.04$). Two patients had recurrence within the IOERT field in the EBRT + IOERT group and 14 patients recurred in the same area in the EBRT group ($p = 0.02$). Multivariate analyses revealed that adjuvant IOERT was an independent prognosticator for both local–regional control ($p = 0.02$) and disease-free survival ($p = 0.05$). G3/4 late toxicity was observed in 5 patients in the EBRT + IOERT group, but none in the EBRT group ($p = 0.02$).

Conclusions: Higher radiation dose may contribute to the improvement of local control, especially in the field encompassed by IOERT. The addition of IOERT to surgery and adjuvant chemoradiation deserves further investigation in a randomized trial.

Despite advances in surgical techniques, the outcome of patients with locally advanced gastric cancer remains dismal after surgery, with 5-year survival rates of 8–34% [1]. Forty to 90% of gastric cancer patients develop locoregional recurrence after complete resection, and nearly 80% deaths are due to locoregional recurrence, especially in patients with gastric serosal involvement or nodal metastases [2,3].

Postoperative chemoradiotherapy for locally advanced gastric cancer has demonstrated its efficacy in a randomized clinical trial, and is currently the standard of care for resectable high-risk disease in North America. However, local or regional recurrence rates after adjuvant chemoradiotherapy remained at 19% and 65%, respectively [4]. The suboptimal outcome is due to, at least in part, dose limitation of the normal organs at risk (OARs) in the planning treatment volume (PTV): the dose of radiotherapy is limited to 40–45 Gy. Higher doses necessary for disease control cannot be safely delivered with conventional EBRT.

IOERT enables the delivery of relatively large doses of radiation in a single fraction, immediately after tumor removal, to the "at-risk" site within the surgical bed, with adjacent dose-limiting tissues surgically displaced [5]. Abe et al. have documented that IOERT improved 5-year overall survival (OS) in patients with locally advanced gastric cancer [6]. Preliminary results of IOERT used in combination with adjuvant concurrent chemoradiotherapy for T3/4, or N+ gastric adenocarcinoma were previously reported [7]. However, the tolerability of this aggressive regimen as well as patients' long-term prognosis has never been addressed.

The aim of this report is to document the long-term efficacy and toxicity profile of this treatment combination in the management of locally advanced gastric cancer.

Materials and methods

Patients and staging evaluation

From March 2003 to October 2005, 97 consecutive patients who had pathologically confirmed and staged T3/T4 or N+ gastric adenocarcinoma (AJCC /UICC staging classification) were treated by a combination of radical gastrectomy and postsurgical chemoradio-

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doi:10.1016/j.radonc.2011.10.008

therapy according to an institutional research protocol. Pretreatment evaluation consisted of a complete history and physical examination, complete blood count (CBC), serum chemistry, chest X-ray, endoscopy, computed tomography (CT) of the abdomen, and ultrasound of pelvis. Patients with metastatic disease or T1–2 disease without enlarged regional lymph nodes were excluded.

Radiotherapy regimen included IOERT followed by EBRT or EBRT alone. The use of IOERT was based on patients' preference and availability of the facility at the time of surgery: 46 and 51 patients received radical surgery followed by IOERT and adjuvant chemoradiation or adjuvant chemoradiation (same regimen) alone. Patient's characteristics are detailed in Table 1. No significant difference among the two groups was observed.

Treatment

Surgery

Surgery was performed through a median laparotomy with either total or subtotal gastrectomy combined with D2 lymph node dissection.

IOERT

IOERT was delivered with single electron beam by a dedicated linear accelerator (Varian 1800C) located next to the operation room and before the reconstruction of digestive anastomosis. PTV included lymph node groups along the common hepatic, left gastric, splenic arteries and around the celiac axis. Tumor bed was also irradiated with IOERT if surgical margins were anticipated by the surgeons' judgment. Lucite collimators were used to produce circular, elliptical, and hexangular IOERT fields (range, 6×5 cm–10×11 cm). Gauze pads were used to displace/immobilize the surrounding sensitive structures such as small bowel and liver out of the radiation field. Electron beams with a median energy of 12 MeV (range 9–16 MeV) were used depending on the depth of the original tumor extension and completeness of resection at the time of surgery. IOERT dose ranged from 12 to 15 Gy based on a previous report [8], according to the probability of residual disease assessed by the surgeon, and was prescribed to the 90% isodose line.

Table 1
Patient, tumor and treatment characteristics.

Variable	IOERT + EBRT	EBRT	X^2	*P*
Age				
Median	58	60	0.01	0.93
Mean	56	57		
Range	35–74	30–75		
Gender			0.13	0.72
Male	30 (65%)	35 (69%)		
Female	16 (35%)	16 (31%)		
Pathology				
Adenocarcinoma	46 (100%)	51 (100%)		
Location of tumor			1.1	0.61
Cardia	4 (9%)	6 (12%)		
Body	19 (41%)	16 (31%)		
Antrum/pylorus	23 (50%)	29 (57%)		
pT classification			3.15	0.51
T1	1 (2%)	1 (2%)		
T2	12 (26%)	10 (19%)		
T3	24 (52%)	35 (69%)		
T4	9 (20%)	5 (10%)		
pN classification			0.54	0.92
N0	4 (9%)	4 (8%)		
N1	20 (43%)	24 (47%)		
N2	18 (39%)	17 (33%)		
N3	4 (9%)	6 (12%)		
Overall stage (AJCC)			0.46	0.94
II	9 (20%)	9 (18%)		
IIIa	15 (33%)	20 (39%)		
IIIb	14 (30%)	14 (27%)		
IV	8 (17%)	8 (16%)		
Residual disease			0.03	1
R0	41 (89%)	46 (90%)		
R1	5 (11%)	5 (10%)		
Distal margins (duodenal)	2 (40%)	2 (40%)		
Proximal margin	3 (60%)	3 (60%)		

Abbreviations: IOERT = intraoperative electron beam radiotherapy; EBRT = external beam radiotherapy; pT = pathology proved T staging; R0 = no residual tumor; R1 = microscopic residual tumor; AJCC = american joint committee on cancer.

EBRT

The details of the EBRT techniques were previously described [4,5]. Briefly, the target volume included the tumor bed, anastomosis, gastric remnant, and regional draining lymph nodes based on preoperative CT scan, surgical clips and barium examination. Barium swallow was required for simulation to define the intestines, gastric remnants and the motion of the stomach. Both kidneys were identified on simulation films after intravenous pyelography. Patients were instructed to practice shallow breaths during simulation and treatments. Treatment was delivered with 6 MV photons using multi-field techniques (anteroposterior/posteroanterior, with 1–2 lateral fields depends on dose coverage and the volume of kidney). A three-dimensional dose calculation was made during the treatment planning. The EBRT doses were 39.6 Gy and 45 Gy (1.8 Gy/daily fraction) for patients treated with or without IOERT, respectively.

The biological equivalent doses of combined IOERT + EBRT were calculated using alpha/beta ratio of 10 for tumor and acute/late normal tissue reaction with the formula described previously [9].

Chemotherapy

All patients received chemotherapy during and after the completion of EBRT. The chemotherapy regimen delivered with concurrent radiotherapy consisted of 5-FU (400 mg/m^2, D1–5), cisplatin (30 mg/m^2, D1–3), docetaxel (65 mg/m^2, D1), and Leucovorin (200 mg/m^2, D1–5). All patients received 4–6 additional cycles of chemotherapy consisting of 5-FU (425 mg/m^2, D1–5), cisplatin (75 mg/m^2, D1–3), docetaxel (75 mg/m^2, on day 1), and Leucovorin (200 mg/m^2, D1–5).

Follow-up

All patients were followed up according to protocol every 3 months after the completion of treatment in the initial 3 years, then every 6 months for 3 additional years thereafter. Follow-up examinations included complete history, physical examination, CBC, serum chemistry, ultrasound of liver, CT of the chest and abdomen, as well as endoscopy were performed routinely every 6 months, or earlier if recurrence was suspected.

Adverse effects

Acute and late toxicities from treatment were graded according to Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC) criteria [10]. Late toxicities were defined as symptoms first occurring or lasting >90 days after the completion of radiotherapy. Toxicities from surgery, IOERT, and EBRT were reported together, since accurately differentiating the underlying cause from each treatment was not possible.

Statistical analysis

Time to locoregional failure and distant metastases were measured from the completion of EBRT until documented treatment

failure. The duration of OS was calculated from the completion of EBRT until death or until the date of the last follow-up visit for patients still alive. Kaplan–Meier method was used to estimate the OS, disease-free survival (DFS), metastaic free survival (MFS), and local control rates for the entire cohort. The difference regarding the local recurrence rate in the radiation area encompassed by IOERT between the two groups was analyzed using Fishers exact tests. The association between each of the candidate prognostic factors with local control, DFS, MFS and OS rates was tested using the log rank test. Multivariate analysis was performed using the Cox regression model.

Results

The median follow-up for all patients was 37.5 months (range, 8.7–81.3 months). Fifty-five Patients had subtotal gastrectomy and 42 had total gastrectomy. R0 resection was achieved in 87 cases and R1 (40% proximal/gastric mucosal, 60% distal/duodenal) resection in 10 patients. Two patients developed postoperative gastric atony. No other postoperative complications including anastomotic fistula, gastric remnant necrosis, bowel block, pancreatitis, upper digestive tract bleeding, and wound dehiscence were observed.

95.8% (93 patients) of patients completed the entire treatment course. Reason for cessation was mainly due to treatment toxicity. Five patients had delay in starting adjuvant chemoRT, 12 patients had chemotherapy delay due to G3/4 adverse treatment events. The total biological equivalent dose of combined EBRT and IOERT ranged 68.7–78 Gy.

Treatment outcome

The median survival time was 37.5 months (95% confidence interval [CI: 29.892, 45.042] for the entire group of patients. At the time of this analysis, 80 (82%) patients had disease recurrence (EBRT $n = 44$; IOERT + EBRT $n = 36$) and 76 (78%) patients were deceased (EBRT $n = 40$; IOERT + EBRT $n = 36$). The 5 year OS rates were 26% vs. 28% for EBRT and IOERT + EBRT groups respectively ($p = 0.4$).

Local–regional recurrences developed in 34 patients (EBRT $n = 21$; IOERT + EBRT $n = 13$), and distant recurrences developed in 55 patients (EBRT $n = 30$; IOERT + EBRT $n = 25$) as their first site of recurrence, respectively. In addition, 12 patients (EBRT $n = 8$; IOERT + EBRT, $n = 4$) developed both local and distant relapses synchronously.

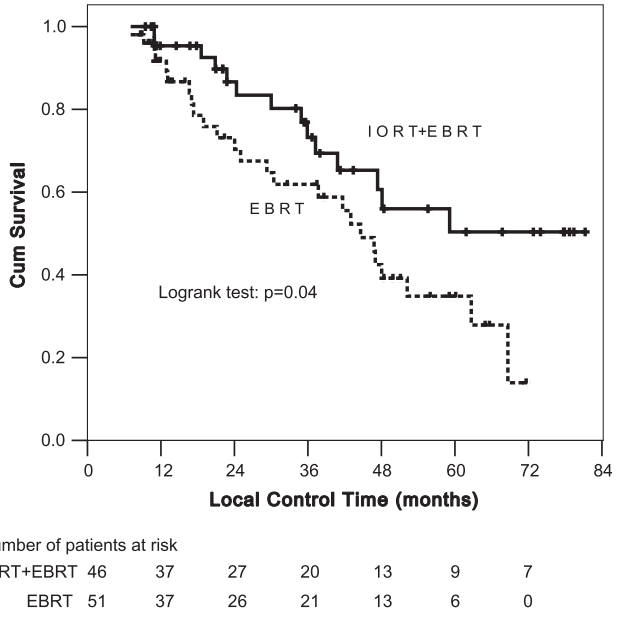

Fig. 1. Local control rate after radiotherapy.

Table 2
Patterns of local regional failure after adjuvant chemoradiotherapy.

Patterns of failure	Group	
	IOERT + EBRT (%)	EBRT (%)
Anastomosis	8 (57%)	9 (36%)
Posterior to pancreatic head	4 (29%)	2 (8%)
Hepatoduodenal ligment	1 (7%)	4 (16%)
Tumor bed	1 (7%)	7 (28%)
Common hepatic artery	0 (0%)	2 (8%)
Celiac axis	0 (0%)	1 (4%)
Total	14 (100%)	25 (100%)

The 5-year locoregional control, DFS, and MFS were 35% vs. 50% ($p = 0.04$) (Fig. 1), 15% vs. 22% ($p = 0.34$) and 22% vs. 25% ($p = 0.77$) for EBRT and IOERT + EBRT groups respectively.

Site of recurrence

Thirty-nine patients presented with local–regional recurrence (IOERT $n = 14$; EBRT $n = 25$). The most common site of recurrence was the anastomosis (Table 2). Twelve of seventeen patients had biopsy confirmed anastomotic recurrence after laparotomy. Two (14%) patients developed locoregional recurrence in the radiation area encompassed by IOERT in the IOERT + EBRT group, while 14 (56%) patients developed locoregional recurrence in the same area in the EBRT group ($p = 0.02$).

Of the 68 patients with distant metastases (IOERT $n = 33$; EBRT $n = 35$), the most common metastatic sites were liver, supraclavicular lymph node, and peritoneum.

Prognostic factors

The impact of pT and N classifications, completeness of surgery, and IOERT on local control, MFS, DFS, and OS were studied in both univariate and multivariate analyses. Multivariate analysis revealed that adjuvant IOERT was an independent prognosticator for both locoregional control ($p = 0.02$) and DFS ($p = 0.05$); pT and N classifications were independent prognostic factors for locoregional control, OS, DFS, and MFS (Table 3). Presence of residual disease was an independent prognostic factor for DFS and MFS ($p < 0.05$) (Table 3).

Adverse effects

No significant difference was observed between the 2 groups for acute toxicities. Of the 97 patients, 93 (95.8%) completed the entire treatment course without interruption. The most commonly observed G3/4 acute toxicity was leucopenia which developed in 20 (43%) and 23 (45%) of patients in the IOERT + EBRT and EBRT groups, respectively. G3/4 acute gastrointestinal toxicity, such as nausea/vomiting, weight loss, dyspepsia, and diarrhea occurred in 18 (39%) and 19 (37%) patients in the IORT + EBRT and EBRT groups, respectively. Anastomotic fistula and wound dehiscence were not observed.

G3/4 late toxicity were observed in 10.9% and 0% of patients who received IOERT + EBRT or EBRT only groups, respectively ($p = 0.02$). One patient (2%) had G3 enteritis. Four patients (8.7%) experienced G3/G4 upper alimentary tract hemorrhage: 3 recovered after medical treatment, and 1 suffered from massive gastrointestinal hemorrhage caused by arterioenteric fistula requiring interventional angiography. No grade 5 toxicity was observed.

Table 3
Multivariate analysis for overall survival, local control, metastatic-free and disease-free survival.

Variable	*P* value			
	Overall survival	Local regional control	Metastatic free survival	Disease free survival
IOERT (Yes vs. No)	0.06	0.02	0.10	0.05
T (T1–2 vs.T3 vs. T4)	<0.001	0.03	<0.001	<0.001
N (N0 vs. N1 vs. N2 vs. N3)	<0.001	0.002	<0.001	<0.001
R (R0 vs. R1)	0.07	0.14	0.01	0.006

Discussion

Despite significant improvement in disease control, outcome after surgery followed by surgery and adjuvant chemoradiotherapy remained suboptimal, with local or regional recurrences approximated 19% and 65%, respectively, after the tri-modality therapy [4].

Local control by radiation for subclinical disease is a function of radiation dose. In addition, extended interval between surgery and radiation allows accelerate proliferation of cancer cells under stress [11]; Therefore, it is reasonable to postulate that a larger dose delivered early in the course of treatment could further improve disease control of gastric cancer after surgical resection. However, the radiation dose to the intra-abdominal target volume is limited to 45–50 Gy due to adjacent dose-limiting organs such as small bowel and kidney. Such dose might not be sufficient for eradicating subclinical residual disease [12]. However, dose escalation using conventional radiation to surgical bed and regional nodal areas is usually not feasible.

In the present study, patients with T3/4 or N+ gastric cancer were treated with D2 gastrectomy, followed by IOERT and concurrent chemoradiotherapy, to a substantially greater biologically equivalent dose of 68.7–78 Gy (1.8-Gy equivalent total dose range, 58.2–66.1 Gy) to the "at risk" region. Compared to other literatures, there were more advanced stage in our study with 75% T3–4 disease and 90% N1–3 disease. The long-term overall survival of both groups was low. But this regimen seemed significantly to improve locoregional control compared with adjuvant chemoradiotherapy alone. The 5-year locoregional control and DFS of patients treated with and without IOERT were 50% vs. 35% ($p = 0.04$), and 22% vs. 15% ($p = 0.34$) respectively. These results confirmed our preliminary findings at 3 years after treatment and previously published results on the efficacy of IOERT in gastric cancer treatment [7,13].

A total of 39 patients (40%) developed local relapse as a component of failure but the recurrence patterns between the two groups were different: Only 14% of recurrences occur within the IOERT field, as compared to 56% of recurrences in the same area after EBRT alone. The recurrences posterior to pancreas head were not considered IOERT in-field relapse. The pancreas was pushed outside the IORT field or we use lead to shape the pancreas in order to prevent pancreatitis. Long-term analysis is needed to evaluate the precise patterns of failure, which may help in the defining of radiation volumes. On the other hand, patients can recur with peritoneal carcinomatosis or distant metastases [14]. Despite the improvement in locoregional control, about 70% of patients had distant metastases in our series, emphasizing the need for more effective systemic therapies.

Treatment-induced toxicities remain a challenge in the treatment of gastric cancer using chemoradiation [4,15]. In our series, the most common acute complications were hematological and GI toxicities. Although 93 patients (95.8%) completed the entire treatment without interruption, acute Grade 3/4 toxicities occurred in 43% and 45% of patients in the IOERT + EBRT and EBRT group, respectively ($p > 0.05$). The toxicity profile is comparable to that reported in the chemoradiotherapy arms of the INT-0116 with published incidence of G3/4 toxicity of 41/32% and G3–4 toxicity of 43% in AIO/ARO/ACO study [16], respectively. The toxicity profile of 5-FU with docetaxel and cisplatin was within acceptable limits for treatment.

Large radiation dose per fraction increases late toxicity; however, reports on late toxicity after IOERT are scant. Our long term follow-up demonstrated only 1 case of enteritis and 4 cases of gastrointestinal bleeding. Severe vascular toxicity was observed in the IOERT + EBRT group with an incidence of 2% and is in concordance with previous published reports [13,17]. The tolerance of vasculature and stomach after surgery to IOERT with or without EBRT has been investigated in animal experiments [18,19]. The late effects observed in animal experiments suggest that 10–20 Gy IOERT plus EBRT dose of 45–50 Gy do not compromise the outcome of healthy adult animal. The damage to the intrinsic vasculature and connective tissue of organs observed in the examined specimens seems to be responsible for the damage to the organ with an increasing degree of severity depending on IOERT dose escalation [20]. In the clinical setting, long-term tissue changes are rarely histologically evaluated, and long-term survivors usually experience multiple treatment protocols. However, animal experiments in IOERT radiobiology cannot completely mirror human response. Second malignancy is another concern [21]. Undifferentiated or sarcoma-like tumor has been reported within the IOERT field after long term follow-up [22]. The median follow-up of 37.5 months in our series is clearly too short to address the issue of second malignancy.

To our knowledge, this is the only report on the efficacy of IOERT in combination with adjuvant chemoradiation in the treatment of locally advanced gastric adenocarcinoma. However, we consider our results far from conclusive, and several important issues need to be addressed. First, although patients accrued for the IOERT plus adjuvant chemoradiotherapy regimen in the present series were treated according to an institutional treatment protocol, calculation of sample size for a set level of statistical power was not performed. This was partly due to the lack of affirmative data after D2 gastrectomy and adjuvant chemoradiotherapy at the time of protocol design, as well as a newer chemotherapy regimen used. Second, in the recently published Medical Research Council Adjuvant Gastric Infusional Chemotherapy trial, the role of neoadjuvant plus adjuvant chemotherapy in the management of advanced gastric cancer became clear [23]. Whether the addition of preoperative chemotherapy can further improve the treatment outcome needs to be addressed. Third, we believe the improvement in the treatment outcome is associated with a greater biologic radiation dose. It remains to be determined whether a comparable improvement in outcome can be obtained by precise high-dose RT to a similarly planned tumor volume using intensity-modulated RT or proton therapy without IOERT. Finally, our patients' treatment was not prospectively randomized and this was certainly a substantial pitfall of our study. All these issues need to be further addressed in future prospective clinical trials.

Conclusion

IOERT followed by adjuvant chemoradiotherapy after D2 gastrectomy is an efficacious and well tolerated treatment for patients with locally advanced gastric adenocarcinoma. It significantly improves locoregional control and marginally improves

disease free survival. Escalated radiation doses with concurrent chemotherapy used in an adjuvant setting is a strategy that deserves to be optimized and then evaluated in randomized clinical trials.

Conflict of interest statement

None.

Acknowledgements

Qing Zhang, M.D. and Jeremy Tey, M.D. contributed equally on this manuscript.

This article is funded by a research Grant (Grant 044017) from the Shanghai Municipal Health Bureau and research grants (Grant 09JC411900, 09411951100) from the Science and Technology Commission of Shanghai, Shanghai, People's Republic of China.

References

[1] Hundahl SA, Philips JL, Menck HR. The National Cancer Data Base report on poor survival of U.S. gastric carcinoma patients treated with gastrectomy: Fifth edition American Joint Committee on Cancer staging, proximal disease, and the "different disease" hypothesis. Cancer 2000;88:921–32.
[2] Wisbeck WM, Becher EM, Russell AH. Adenocarcinoma of the stomach: Autopsy observations with therapeutic implications for the radiation oncologist. Radiother Oncol 1986;7:13–8.
[3] Gunderson LL. Gastric carcinoma–patterns of relapse after surgical resection. Semin Radiat Oncol 2002;12:150–61.
[4] Macdonald JS, Smalley SR, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med 2001;345:725–30.
[5] Glehen O, Peyrat P, Beaujard AC, et al. Pattern of failures in gastric cancer patients with lymph node involvement treated by surgery, intraoperative and external beam radiotherapy. Radiother Oncol 2003;67:171–5.
[6] Abe M, Nishimura Y, Shibamoto Y. Intraoperative Radiation Therapy for gastric cancer. World J Surg 1995;19:544–7.
[7] Fu S, Lu JJ, Zhang Q, Yang Z, Peng L, Xiong F. Intraoperative radiotherapy combined with adjuvant chemoradiotherapy for locally advanced gastric adenocarcinoma. Int J Radiat Oncol Biol Phys 2008;72:1488–94.
[8] Coquard R, Ayzac L, Gilly FN, et al. Intraoperative radiation therapy combined with limited lymph node resection in gastric cancer: an alternative to extended dissection? Int J Radiat Oncol Biol Phys 1997;39:1093–8.
[9] Okunieff P, Sundararaman S, Chen T. Biology of large dose per fraction radiation therapy. In: Gunderson LL, Willet CG, Harrison LB, editors. Intraoperative irradiation: techniques and results. Totowa, New Jersey: Humana Press; 1999. p. 19–46.
[10] Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys 1995;31:1341–6.
[11] Cividalli A, Creton G, Ceciarelli F, et al. Influence of time interval between surgery and radiotherapy on tumor regrowth. J Exp Clin Cancer Res 2005;24:109–16.
[12] Withers HR, Peters LJ, Taylor JM. Dose–response relationship for radiation therapy of subclinical disease. Int J Radiat Oncol Biol Phys 1995;31:353–9.
[13] Calvo FA, Aristu JJ, Azinovic I, et al. Intraoperative and external radiotherapy in resected gastric cancer: updated report of a phase II trial. Int J Radiat Oncol Biol Phys 1992;24:729–36.
[14] Beaujard AC, Glehen O, Caillot JL, et al. Intraperitoneal chemohyperthermia with mitomycin C for digestive tract cancer patients with peritoneal carcinomatosis. Cancer 2000;88:2512–9.
[15] Kim S, Lim DH, Lee J, et al. An observational study suggesting clinical benefit for adjuvant postoperative chemoradiation in a population of over 500 cases after gastric resection with D2 nodal dissection for adenocarcinoma of the stomach. Int J Radiat Oncol Biol Phys 2005;63:1279–85.
[16] Kollmannsberger C, Budach W, Stahl M, et al. Adjuvant chemoradiation using 5-fluorouracil/folinic acid/cisplatin with or without paclitaxel and radiation in patients with completely resected high-risk gastric cancer: two cooperative phase II studies of AIO/ARO/ACO. Ann Oncol 2005;16:1326–33.
[17] De Villa VH, Calvo FA, Bilbao JI, et al. Arteriodigestive fistula: a complication associated with intraoperative and external beam radiotherapy following surgery for gastric cancer. J Surg Oncol 1992;49:52–7.
[18] Calvo FA, Meirino RM, Orecchia R. Intraoperative radiation therapy part 2. Clinical results. Crit Rev Oncol Hematol 2006;59:116–27.
[19] Schulz-Hector S, Brechenmacher P, Dorr W, et al. Complications of combined intraoperative radiation and external radiation of the upper abdomen: an experimental model. Radiother Oncol 1996;38:205–14.
[20] Sindelar WF, Kinsella TJ. Normal tissue tolerance to intraoperative radiotherapy. Surg Oncol Clin N Am 2003;12:925–42.
[21] Gillette SM, Gillette EL, Powers BE, Withrow SJ. Radiation-induced osteosarcoma in dogs after external beam or intraoperative radiation therapy. Cancer Res 1990;50:54–7.
[22] Johnstone PA, Sindelar WF, Kinsella TJ. Experimental and clinical studies of intraoperative radiation therapy. Curr Probl Cancer 1994;18:249–90.
[23] Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for respectable gastroesophageal cancer. N Engl J Med 2006;335:11–20.