

Evaluation of intraoperative radiotherapy for gastric carcinoma with D2 and D3 surgical resection

Huan-Long Qin, Chao-Hong Lin, Xiu-Long Zhang

Huan-Long Qin, Chao-Hong Lin, Xiu-Long Zhang, Department of Surgery, Shanghai Sixth People's Hospital Affiliated to Shanghai Jiaotong University, Shanghai 200233, China
Correspondence to: Dr. Huan-Long Qin, Department of Surgery, Shanghai Sixth People's Hospital Affiliated to Shanghai Jiaotong University, Shanghai 200233, China. hlqin@sjtu.edu.cn
Telephone: +86-21-64942226 Fax: +86-21-64368920
Received: 2006-09-07 Accepted: 2006-10-16

© 2006 The WJG Press. All rights reserved.

Key words: Gastric carcinoma; Intraoperative radiotherapy; Surgical resection

Qin HL, Lin CH, Zhang XL. Evaluation of intraoperative radiotherapy for gastric carcinoma with D2 and D3 surgical resection. *World J Gastroenterol* 2006; 12(43): 7033-7037

<http://www.wjgnet.com/1007-9327/12/7033.asp>

Abstract

AIM: To study the proper sites and doses of intraoperative radiotherapy (IORT) for gastric carcinoma and the effects of this treatment.

METHODS: A total of 106 patients with stage I-IV gastric carcinoma who received D2 or D3 radical operation combined with IORT were analyzed. Sixty-seven patients with gastric cancer of the antrum and body underwent distal gastrectomy. The sites of irradiation were at the celiac artery and hepatoduodenal ligament area. Another 39 patients with carcinoma of the cardia and upper part of the gastric body and whole stomach underwent proximal gastrectomy or total gastrectomy. The sites of irradiation for this group were the upper margin of the pancreas and the regional para-aorta. The therapeutic effects (including survival and complications) of these 106 cases received operation combined with IORT (IORT group) were compared with 441 cases treated during the same time period by a radical operation alone (operation group).

RESULTS: The radiation dose below 30 Gy was safe. The therapeutic method of the operation combined with IORT did not prolong the survival of patients with stage I and IV gastric cancer, but the 5-year survival rates of patients with stage II and III gastric cancers were significantly improved. The 5-year survival rates of the stages III cancer patients receiving D2 resection combined with IORT were markedly improved, while for those receiving D3 radical resection, only the postoperative 3- or 4-year survival rates were improved ($P < 0.005-0.001$). The 5-year survival rate for those patients was raised only by 4.7% ($P > 0.05$).

CONCLUSION: The 5-year survival rates of patients with stages II and III gastric carcinoma who received D2 lymphadenectomy combined with IORT were improved, and there was no influence on the postoperative complications and mortality.

INTRODUCTION

The fate of patients after surgical removal of a gastric carcinoma is determined to a large degree by regional failure of the operation (e.g. tumor recurrence in the tumor bed or in an adjacent structure). This is true for palliative resections with macroscopic tumor residues (D2) as well as for operations with microscopic involvement of resection margins (D1) or no discernible malignant cells (D0). Recurrent tumors may originate from extension of the primary tumor or from regional lymph node metastases not encompassed by the surgical procedure^[1]. It is desirable therefore to develop and study additional tumoricidal measures that might eliminate residual malignant tissues, thereby increasing the chance of regional tumor control^[2].

Intraoperative radiotherapy (IORT) as an adjunct to surgical excision of solid malignancies has been used, however, clear-cut evidence of its benefit for tumor control is still deficient. In IORT a large single dose of radiation is given to the area with greatest risk of local failure^[3-5]. Based on the available oncologic and radiotherapeutic data, radiation thus applied should be able to control tumor growth. The biologic and logistic advantages of radiation applied directly to the tumor bed at a single dose are obvious. For these reasons any information related to the efficacy of IORT is highly desirable and welcome.

Under these considerations, we have used IORT for gastric cancer and report the clinical results in comparison with that of patients treated by operation alone. The clinical results of IORT for gastric cancer were analyzed based on the histologic findings.

MATERIALS AND METHODS

Research subjects

A total of 106 patients were treated by radical resection and IORT between 1992 and 1998, including 13 cases in

Table 1 Clinical data of gastric carcinomas in different stages classified by intraoperative radiotherapy (IORT) and operation alone

Groups	Staging	n	Location of tumor n (%)			Operation method n (%)					
			Antrum	Body	Cardiac	TS	D2	D3	DG	PG	TG
IORT	I	13	8 (62)	2 (15)	3 (23)	0 (0)	9 (69.3)	4 (30.7)	10 (76.9)	3 (23.1)	0 (0)
	II	17	12 (70.6)	2 (11.8)	3 (17.6)	0 (0)	6 (35.3)	11 (64.7)	13 (76.5)	3 (17.6)	1 (5.9)
	III	48	25 (52.1)	6 (12.5)	8 (16.7)	9 (18.7)	9 (18.8)	39 (81.3)	30 (62.5)	5 (10.4)	13 (27.1)
	IV	28	13 (46.4)	2 (7.1)	5 (17.9)	8 (28.6)	3 (10.7)	25 (89.3)	14 (50)	6 (21.4)	8 (28.6)
Operation	I	70	50 (71.4)	16 (22.9)	4 (5.7)	0 (0)	50 (71.4)	20 (28.6)	66 (94.3)	4 (5.7)	2 (2.8)
	II	67	49 (73.1)	5 (7.5)	13 (19.4)	0 (0)	31 (46.3)	36 (53.7)	54 (80.6)	11 (16.4)	2 (3.0)
	III	244	164 (67.2)	37 (15.2)	28 (11.5)	15 (6.1)	110 (45.1)	134 (54.9)	201 (82.4)	28 (11.5)	15 (6.1)
	IV	60	36 (60)	10 (16.7)	6 (10)	8 (13.3)	8 (13.3)	52 (86.7)	42 (70)	4 (6.7)	14 (23.3)

TS: Total stomach; D2: Lymph node 2 dissection; D3: Lymph node 3 dissection; DG: Distal gastrectomy; PG: Proximal gastrectomy; TG: Total gastrectomy.

stage I, 17 in stage II, 48 in stage III and 28 in stage IV. There were 77 men and 29 women, aged from 31-80 years, averaging 52.4 years. Location of the carcinoma was: antrum 58, body 12, cardiac 19, and total stomach 17 cases. Operation method: D2 lymphadenectomy 27, D3 lymphadenectomy 79; distal gastrectomy 17, proximal gastrectomy 67 and total gastrectomy 22 cases. To evaluate the effectiveness of IORT, 441 patients who were treated by operation alone during the same time period were classified histologically, and their survival rates were compared with those of patients treated by IORT. In addition, a comparative study was performed on the survival rates of patients treated by IORT and those treated by operation alone based on the degree of staging (Table 1). Inclusion criteria for IORT^[6] were: (a) gastric adenocarcinoma confirmed through preoperative biopsy; (b) age between 25 and 80 years; (c) World Health Organization (WHO) performance status of 0-2; and (d) the availability of IORT facilities.

Patients were excluded if they had serious concurrent illness, active infection, symptomatic ischemic heart disease, congestive heart failure, a recent history of myocardial infarction, or symptomatic arrhythmia. Patients with significant gastrointestinal disturbance that could cloud the interpretation of gastrointestinal toxicity were also excluded. In addition, patients with severe malnutrition or severe nausea, or frequent vomiting were excluded.

Surgery was performed through a median laparotomy and surgeons were allowed to use either total or subtotal gastrectomy (according to the tumor location) combined with D2 and D3 lymphadenectomy. The same two senior surgeons were in charge of the operations during the whole protocol.

Radiation location

After the gastrectomy and lymphadenectomy and before alimentary reconstruction, the local region of the hepatoduodenal ligament and the upper margin of the pancreas or the gastric bed were irradiated in 67 patients who were treated with gastrectomy in the antrum and body of the stomach. The other 39 patients with total gastrectomy underwent removal of the pancreas capsule and extended lymph node dissection including the nodes along the splenic artery. In the patients with body, cardiac and total stomach cancer, the tail and body of the pancreas

were moved up to the right side margin of the abdominal aorta and the superior mesenteric vein and the region of the para-aorta received irradiation.

IORT was administered to the tumor bed and celiac axis at the time of gastric resection in those patients whose tumor appeared transmural and who were sufficiently stable to tolerate a transfer to the Radiation Therapy Treatment Room.

A variety of sizes and shapes of the pentagonal treatment cones were prepared so they fit the costal arch adequately and encompassed various anatomic situations of the tumor bed and the high risk lymph node groups noted above.

The field was clearly illuminated by an electric lamp fixed to a telescope attached to the treatment cone. The sterilized cone was inserted into the abdomen inclining degrees so the celiac axis was sufficiently covered.

Electronic energy and radiation dose of IORT

The electronic energy from 6 MeV to 16 MeV was selected. The radiation doses of IORT were selected according to the possibility of the radicality achieved by surgical operation. A single dose of 10-15 Gy was given to 41 patients who had no clinically undetectable lesions, a single dose of 20 Gy was given to each 27 patients who were suspected to have microscopic residual LN, 25 Gy was given to 37 patients who were suspected to have macroscopic residual LN or direct invasion of adjacent structure, and 30 Gy to one patient who had noncurative surgery because of incomplete excision of metastatic lesions.

RESULTS

Complications

When IORT is used for gastric cancer, critical organs to which exposure must be avoided, are the pancreas, duodenum and jejunum which must be shielded from radiation. Less than 40% of the pancreas was generally included in the radiation field. Acute and late damage to the pancreas was evaluated by changes in serum amylase and blood glucose levels after IORT. Temporary increases in both serum amylase and blood glucose occurred after IORT, but they returned to preirradiation levels within a week. Neither significant late complications nor deviation

Table 2 The 5-yr survival rate of patients with operation combined with intraoperative radiotherapy (IORT)

Groups	n	Stage I	Stage II	Stage III	Stage IV
IORT	106	13/13 (100%)	17/17 (100%)	29/48 (60.4%)	4/28 (14.3%)
Operation	441	65/70 (92.8%)	54/67 (80.6%)	110/22 (45.1%)	6/6 (10.0%)
P		> 0.10	< 0.001	< 0.005	> 0.05

Table 3 The 5-yr survival rate of patients with operation combined with intraoperative radiotherapy (IORT) in stage III

Groups	n	D2 resection						D3 resection					
		n	1 yr	2 yr	3 yr	4 yr	5 yr	n	1 yr	2 yr	3 yr	4 yr	5 yr
IORT	48	9	100%	100%	87.5%	87.5%	60%	39	100%	100%	93.1%	85.5%	61%
Operation	244	114	81.6%	70.4%	52.3%	43.3%	35.7%	128	92.1%	85%	66.5%	62.2%	56.3%
P			< 0.05	< 0.001	< 0.001	< 0.001	< 0.005		> 0.50	> 0.10	< 0.001	< 0.005	> 0.05

from the usual postoperative course was observed. There was no instance of delayed wound healing. One patient died from cardiac infarction, resulting in a death rate of 0.9% (1/106). Recovery of gut function in all of the patients with IORT was delayed for 24 h.

Survival

Table 2 demonstrates the survival rates based on an analysis of 106 patients treated by IORT and 441 patients treated by operation alone. The survival rate was calculated by the Kaplan-Meier method.

The 5-year survival rate (YSR) for patients treated by operation alone was 92.8% for stage I, 80.6% for stage II, 45.1% for stage III, and 10% for stage IV. On the other hand, the 5-YSR for patients treated by IORT was 100% for stage I and stage II, 60.4% for stage III, and 14.3% for stage IV. As shown in Table 2, there was no difference between the 5-YSR of patients in stage I, and stage IV in the two groups. The IORT procedure raised the survival of patients with stages II and III cancer from 15% to 20%, $P < 0.005-0.001$.

Table 3 demonstrates that the 5-YSR of the stage III cancer patients with D2 radical resection combined with IORT was improved as compared with operation alone. The 5-YSR of the stage III cancer patients with selective D3 radical resection combined with IORT was not improved as compared to an operation alone. However, the 3- and 4-YSR was significantly improved by IORT combined with operation as compared with operation alone. But the differences of the 3 and 4-YSR between the two groups were statistically significant.

DISCUSSION

As far as gastric adenocarcinoma is concerned, the prognosis remains poor with a high local failure rate estimated up to 67%^[7]. While a lot of trials using systemic chemotherapy are currently being made to decrease the general failure rate in gastric adenocarcinoma, using IORT as a boost to EBRT could be a way to improve local control rate on coeliac area after gastrectomy^[2,8]. IORT has been known as a feasible radiation treatment since 1907^[9]. Its main advantage is probably to spare normal tissues

while delivering a high dose precisely on the tumoral target. Extended lymph node dissection has been used mainly in Japan and the treatment results have improved remarkably as shown in many retrospective studies. But extended lymph node dissection is still controversial in the Western countries because of reported excessive postoperative morbidity and mortality and lack of proof in a recent retrospective study and in randomized controlled trials^[1,10]. The Dutch Gastric Cancer Trial and the Medical Research Council (MRC) randomized surgical trial were not able to prove the benefit of extended lymph node dissection.

Due to operating room planning reasons, a great number of patients with gastric adenocarcinoma were not included in the IORT protocol in the reported study, and therefore, no valid comparisons or conclusions can be made. However, it is important to notice that mortality and morbidity rates in patients treated with IORT (1/42 and 3/42) were not excessive when compared with the mortality and morbidity rates reported in the retrospective study of 350 gastric cancer patients treated by surgery alone in the same institution since 1970 (respectively 10.8% and 14%)^[11]. Glehen *et al.*^[12,13] did not detect any acute toxicity of IORT. Concerning the late toxicity of IORT, canine studies provide guidelines for human cancer treatment and the data provided by these canine studies are comparable with the data obtained in an autopsy study which validated the model for clinical use. With a long term follow-up, in the reported study we just detected one case of enteritis, 2 years after irradiation. But this late toxicity was controversial in the literature data because of the reported cases of other enteritis, gastrointestinal bleedings with or without arterioenteric fistulas, vertebral collapses and liver hemangiomas^[2,14,15].

Each surgical procedure that does not achieve a complete local excision of the primary tumor in all 3 dimensions (length, width, aboral, and depth of tumor) and of the area of lymphatic drainage is, according to the UICC classification of D1 or D2 resection (i.e. a resection leaving residual microscopic or macroscopic tumor), considered to be a "palliative resection". In addition to procedures that leave the entire tumor *in situ*, any type of operation that leaves residual macroscopic or microscopic tumor at the resection margin, tumor bed, or in the

lymphatic drainage area must also be considered to be a palliative procedure.

The rationale for IORT is to increase the irradiation dose to the tumor without exceeding critical normal tissue tolerance. IORT used as a neoadjuvant therapy, can increase the 5-YSR of patients with advanced gastric carcinoma. Special linear accelerators have been used for the application of high single-dose radiation to the tumor bed^[3,4]. Abe *et al*^[5] reported 115 gastric cancer patients treated by IORT. The 5-YSR survival of patients in stages II through IV treated by IORT increased by nearly 10%-20%. No difference in the survival of patients was observed between the two groups. IORT did not afford benefit if the lymph node metastases were limited with n₁ group or serosal invasion was not found. On the other hand, the 5-YSR for patients treated by IORT increased by nearly 10% when the serosal invasion was observed, and by nearly 18% when n₂ and n₃ lymph node metastases were found. Ogata *et al*^[16] reported that the 5-YSR and 8-YSR for 58 cases treated by IORT were both 100%, and 60% and 48% in control group with stage II cancer. The 8-YSR of the stage III cancer by IORT was 55%, and 35% in the control group. But these results were controversial. Coquard *et al*^[2] reported that the 5-YSR of patients with gastrectomy and local lymph node resection combined with IORT was the same as single expanded lymph node resection. However, the postoperative complications and mortality were lower than that in those who received only gastrectomy. Our results showed that operation combined with IORT is beneficial for patients in stage II and stage III cancer with a 5-YSR of 14.4%-20%. However, this procedure was ineffective for patients with stage I and stage IV cancer treated with D2 lymphadenectomy combined with IORT, the 5-YSR of stage II cancer patients was increased by 60% as compared with D2 lymphadenectomy only by 35.7%. With D3 lymphadenectomy combined with IORT, the 3- and 4-YSR were improved, but it was ineffective for the 1, 2 and 5-YSR. These encouraging results were already reported by Japanese authors^[5,17] with a 10%-20% increase in 5-YSR in stages II and III. However, this has not been reported in Western countries, especially for pN+ patients. But in a shorter follow-up, a local recurrence of under 15% after the use of IORT and EBRT was reported^[18,19].

The radiation target area in the region of the upper abdomen includes potential microscopic tumor extensions and known or suspected macroscopic disease^[13]. In order to reduce the injury of irradiation to the normal tissues near the stomach, the target area is restricted to the gastric bed. The inferior field border is generally at the level of the L3 to L4 vertebrae, but this depends on the location of the carcinoma and the position of the stomach before treatment. The target area includes the proximal and regional lymphatics, the right and left cardiac nodes, the nodal chains of the lesser and greater curvatures, the suprapyloric and infrapyloric chains, the splenic chains, and the lymph nodes along the hepatic artery. For the cardiac tumors, upper extension of the field to the terminal esophagus and paraesophageal lymph nodes is recommended. If the tumor is unresectable or if, after surgery, macroscopic disease remains, the

total irradiation dose can be increased in a coned-down volume, which is restricted to the area of gross disease. With regard to the optimization of IORT, we developed a new technique that provides a wider irradiation field for patients undergoing total gastrectomy. In these patients, total gastrectomy, splenectomy, removal of the pancreas capsule, and extended lymph node dissection including the nodes along the splenic artery were performed. Then the tail and body of the pancreas were moved up to the right side margin of the abdominal aorta and the superior mesenteric vein. These maneuvers provided a much wider irradiation field, which included the para-aortic lymph nodes. After irradiation, the pancreas was returned to its normal position and an esophagoenterostomy was performed. This method was adopted only in patients without cancer invasion of the pancreas or metastases in the lymph nodes along the splenic artery. The advantage of this method is that it produces a wide irradiation field including para-aortic lymph nodes and does not increase the complications and mortality. Meanwhile, one must be careful to protect the duodenum and jejunum before irradiation as those organs must be shielded from the irradiation field.

With regard to special radiotherapeutic techniques that include the potential of relatively high biologically effective doses, gastric cancer is one of the most convincing indications for intraoperative irradiation. Special linear accelerators have been used for the application of high single doses (15-35 Gy) to the tumor bed. One problem with IORT is to correctly cover tumor sites outside the midline area or under the left hemidiaphragm. In addition, the maximum tolerable dose administered in one session is limited from 15 to 35 Gy. Abe *et al*^[5] reported that doses of irradiation depended on the radicality achieved by the operation. In general, the irradiation doses from 15-30 Gy were applied in curative situations and 30-35 Gy in palliative situations. We selected the doses of IORT according to the residual tumor volume, including clinically undetectable lesions (10-15 Gy), microscopic residual (20 Gy), macroscopic residual (25 Gy), or noncurative surgery (30 Gy). No serious complications occurred in these cases. Our data strongly support the efficacy of IORT for local tumor control.

REFERENCES

- 1 Cuschieri A, Weeden S, Fielding J, Bancewicz J, Craven J, Joypaul V, Sydes M, Fayers P. Patient survival after D1 and D2 resections for gastric cancer: long-term results of the MRC randomized surgical trial. Surgical Co-operative Group. *Br J Cancer* 1999; **79**: 1522-1530
- 2 Coquard R, Ayzac L, Gilly FN, Rocher FP, Romestaing P, Sentenac I, Francois Y, Vignal J, Brailon G, Gerard JP. 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**: 1093-1098
- 3 Minsky BD. The role of radiation therapy in gastric cancer. *Semin Oncol* 1996; **23**: 390-396
- 4 Abe M, Yabumoto E, Takahashi M, Tobe T, Mori K. Intraoperative radiotherapy of gastric cancer. *Cancer* 1974; **34**: 2034-2041
- 5 Abe M, Nishimura Y, Shibamoto Y. Intraoperative radiation therapy for gastric cancer. *World J Surg* 1995; **19**: 544-547
- 6 World Health Organization. WHO Handbook for reporting

- results of Cancer treatment [WHO Offset Publication No 48]. Geneva, Switzerland: World Health Organization, 1979
- 7 **Gunderson LL**, Sosin H. Adenocarcinoma of the stomach: areas of failure in a re-operation series (second or symptomatic look) clinicopathologic correlation and implications for adjuvant therapy. *Int J Radiat Oncol Biol Phys* 1982; **8**: 1-11
 - 8 **Zhang ZX**, Gu XZ, Yin WB, Huang GJ, Zhang DW, Zhang RG. Randomized clinical trial on the combination of preoperative irradiation and surgery in the treatment of adenocarcinoma of gastric cardia (AGC)--report on 370 patients. *Int J Radiat Oncol Biol Phys* 1998; **42**: 929-934
 - 9 **Beck C**. On external roentgen treatment of internal structures. *N Y Med* 1909; **89**: 621-622
 - 10 **Hayes N**, Ng EK, Raimes SA, Crofts TJ, Woods SD, Griffin SM, Chung SC. Total gastrectomy with extended lymphadenectomy for "curable" stomach cancer: experience in a non-Japanese Asian center. *J Am Coll Surg* 1999; **188**: 27-32
 - 11 **Bonenkamp JJ**, Hermans J, Sasako M, van de Velde CJ, Welvaart K, Songun I, Meyer S, Plukker JT, Van Elk P, Obertop H, Gouma DJ, van Lanschot JJ, Taat CW, de Graaf PW, von Meyenfildt MF, Tilanus H. Extended lymph-node dissection for gastric cancer. *N Engl J Med* 1999; **340**: 908-914
 - 12 **Glehen O**, Traverse-Glehen A, Peyrat P, François Y, Gérard JP, Vignal J, Gilly FN. [Stomach adenocarcinoma. Evolution of surgical treatment in a series of 350 cases]. *Ann Chir* 2000; **125**: 744-751
 - 13 **Glehen O**, Peyrat P, Beaujard AC, Chapet O, Romestaing P, Sentenac I, François Y, Vignal J, Gérard JP, Gilly FN. Pattern of failures in gastric cancer patients with lymph node involvement treated by surgery, intraoperative and external beam radiotherapy. *Radiother Oncol* 2003; **67**: 171-175
 - 14 **Calvo FA**, Aristu JJ, Azinovic I, Abuchaibe O, Escude L, Martinez R, Tango E, Hernandez JL, Pardo F, Alvarez-Cienfuegos J. Intraoperative and external radiotherapy in resected gastric cancer: updated report of a phase II trial. *Int J Radiat Oncol Biol Phys* 1992; **24**: 729-736
 - 15 **de Villa VH**, Calvo FA, Bilbao JJ, Azinovic I, Balen E, Hernandez JL, Pardo F, A-Cienfuegos J. Arteriodigestive fistula: a complication associated with intraoperative and external beam radiotherapy following surgery for gastric cancer. *J Surg Oncol* 1992; **49**: 52-57
 - 16 **Ogata T**, Araki K, Matsuura K, Kobayashi M, Inomata T, Yasuhiro O, Yoshida S. A 10-year experience of intraoperative radiotherapy for gastric carcinoma and a new surgical method of creating a wider irradiation field for cases of total gastrectomy patients. *Int J Radiat Oncol Biol Phys* 1995; **32**: 341-347
 - 17 **Abe M**, Shibamoto Y, Ono K, Takahashi M. Intraoperative radiation therapy for carcinoma of the stomach and pancreas. *Front Radiat Ther Oncol* 1991; **25**: 258-269; discussion 330-333
 - 18 **Avizonis VN**, Buzydlowski J, Lanciano R, Owens JC, Noyes RD, Hanks GE. Treatment of adenocarcinoma of the stomach with resection, intraoperative radiotherapy, and adjuvant external beam radiation: a phase II study from Radiation Therapy Oncology Group 85-04. *Ann Surg Oncol* 1995; **2**: 295-302
 - 19 **Martínez-Monge R**, Calvo FA, Azinovic I, Aristu JJ, Hernández JL, Pardo F, Fernández P, García-Foncillas J, Alvarez-Cienfuegos J. Patterns of failure and long-term results in high-risk resected gastric cancer treated with postoperative radiotherapy with or without intraoperative electron boost. *J Surg Oncol* 1997; **66**: 24-29

S- Editor Wang GP L- Editor Ma JY E- Editor Bi L