

Complication of Intraoperative Radiation Therapy (IORT) in Gastric Cancer

Myung Se Kim, M.D., Sung Kyu Kim, Ph.D., Sung Kyo Song, M.D.,* Hong Jin Kim, M.D.,*
Koing Bo Kwan, M.D.* and Heung Dae Kim, M.D.*

Department of Therapeutic Radiology, General Surgery, and Anesthesiology**, Yeungnam University
College of Medicine, Taegu, Korea*

Local control is the important prognostic factor in cancer treatment because local control decrease the relative risk of metastatic spread and increase distant metastasis free survival.

IORT is the modality which could increase local control without increasing complication, combined with curative operation. Eventhough we could achieve significant decreased local failure by IORT and curative resection, it should not be committed as a main treatment modality without proving acceptable complications.

Therapeutic Radiology Department of Yeungnam University Medical Center have tried 58 IORT from June 15, 1988, and performed 53 IORT in patients with gastric cancer.

No local failure has been reported by regular follow up so far. Nine cases (17%) of treatment related complicaiton were reported including intestinal obstruction, hemorrhage, sepsis, and bone marrow depression.

These complications could be comparable to Jo's 25.2% (chemotherapy + operation), Kim's 18% (chemotherapy only in inoperable patients), because our treatment regimen is consisted of IORT (1500 cCy), external irradiation (--4500 cGy) and extensive chemotherapy (FAM, 5FU + MMC, BACOP).

Our data encouraged us to re-inforce further IORT in stomach cancer treatment.

Key Words: IORT, Gastric Cancer, Complication, External irradiation, Chemotherapy.

INTRODUCTION

Loco-regional failure is the significant problem not only in gastric cancer but also in most locally advanced cancer. National Cancer Institute in USA reported 37.6% of recurrence after local treatment only¹⁾. Park et al²⁾ reported 34.3% of confirmed recurrence in operable gastric cancer patients in Seoul national University Hospital, Korea, which is similar to NCI's overall recurrence rate.

Park et al²⁾ also reported 65.2% of local failure and 32.9% of distant metastasis among confirmed recurrent patient, which showed that local failure is much higher compared to distant metastasis.

Fuks et al³⁾ emphasized the importance of local control. They insisted 4 fold increased relative risk of metastasis in locally failed patients compared to locally controlled patients.

They also stressed high distant metastasis free survival with local control, compared to locally relapsed patients.

IORT combined with curative resection is the modality which could decrease local failure and

further increase survival. But, we should not committ IORT as a main treatment modality without proving acceptable complications, even though IORT could achieve remarkably decreased local failures.

The purpose of this article is to evaluate complicaiton rate and problems of our IORT trial and to reinforce our IORT protocol, because we already published the excellent local control⁴⁾.

We hope that our data can encourage to all doctors who try IORT in their cancer treatment.

MATERIALS AND METHODS

Total 58 patients of gastric cancer entered to our protocol from June 15, 1988 to August 30, 1992.

Fifty-three patients were performed IORT because of too early (1 case) and far advanced cancer (4 cases).

Patient's median age was 56 and male to female ratio was 1.23 : 1. Most patients (96.6%) were categorized into adenocacinoma and about 60% of patients belonged to stage II-IV (Table 1). Curative resection was the aim of surgery, and 75.9% of

Table 1. Patients Characteristics

	No. of Patients	(%)
Age		
range	31--71 (yr)	
median	56	
Sex		
male	32	(55)
female	26	(45)
M:F	1.23 : 1	
Pathology		
Adenocarcinoma	56	(97)
well differentiated	5	
moderately differentiated	14	
poorly	35	
mucinous	1	
signet ring cell	1	
Non-Hodgkins Lymphoma	2	
Stage		
Ia	4	(7)
Ib	9	(16)
II	11	(19)
IIIa	13	(22)
IIIb	15	(26)
IV	6	(10)
Duration of follow up (months)		
--6	8	(14)
--12	12	(21)
--24	20	(35)
--36	13	(22)
--48	3	(5)
>49	2	(3)

patients had subtotal gastrectomy.

Single dose of 1,500 cGy of IORT with 9 MeV electron were given routinely, except the first case (1,000 cGy). Over 4,000 cGy of external irradiation within 4 weeks of POD was planned but only 44.8% of patients were given over 3,000 cGy because of poor inter-departmental cooperation.

Various combinations of chemotherapy were given according to our protocol and 86.2% of patients had more than 3 cases of chemotherapy

Table 2. Summary of Treatment

	No.	(%)
Operation		
Subtotal Gastrectomy	44	(76)
Total Gastrectomy	9	(15)
By-pass	4	(7)
Whipple's Operation	1	(2)
Radiation Therapy		
IORT		
no	5	(8)
1,000 cGy	1	(2)
1,500 cGy	52	(90)
External		
no	27	(46)
Irradiation		
<3,000 cGy	5	(9)
>3,000 cGy	26	(45)
Chemotherapy		
No	8	(14)
FAM	29	(50)
MMC + 5 FU	16	(27)
5 FU	4	(7)
BACOP	1	(2)

Table 3. Analysis of Complication (9/53; 17%)

Complication	Case	Sex/Age	Stage	Type of op.	Ext.RT	ChemoTx	Remark
GI bleeding	Bae	M/59	IIIb	S.G.	1620	FAM	Endoscopy + POD3mo, Exp
	Lee	M/62	IIIb	S.G.	4500	FAM	POD 2mo. Hematemesis Exp
	Shin	M/68	IIIa	T.G.	3960	FAM	Endoscopy + POD 5mo. Exp at 7mo.
Intestinal obstruction	Park	M/35	IIIa	S.G.	4320	FAM	A-loop syndrome Reop. POD 9mo.
	Choi	M/58	IIIa	S.G.	No	BACOP	Band adhesion Reop. POD3mo.
	Kim	M/54	Ib	T.G.	No	FAM	Int. obstr. POD 3mo. Conservative
Perioperation Sepsis	Lee	F/61	IIIb	S.T.			Pancreas abscess Exp at POD 31
	Kim	M/58	IIIb	S.T.	720	FAM	POD 40 bleeding + Reop. POD3, Exp
Bone marrow depression	Lee	F/35	IIIb	S.T.	4500	5 FU+ MMC	POD 19mo. Exp

S.G.: subtotal gastrectomy T.G.: total gastrectomy Exp: expire

Table 4. Comparison of Complication

University Reference	Total (%)	Treatment	complication (%)				
			Bleeding	Int. Obstr.	Sepsis	Bone	Others*
Yeungnam	17.0	OP + IORT + Ext RT + ChemoRx	5.7	5.7	3.8	1.9	
Kyunghee	25.2	OP + ChemoRx	0.6	0.4	10.4	20.0	13.6
Kyunghee		ChemoRx (inoperable)			4.0	(Gr. III 1)	
Hanyang	18.5	OP	0.5	2.4	5.9		10.2
Kwangju Christian NCI**		OP + ChemoRx (MFC)			8.9 (9.5)		
	17	OP + Ext RT + IORT	2	4	10		1
	23	OP	1	7	10		5
HJ Kramhing	35.3	OP + IORT		5.9	11.8		17.6

*include pulmonary infection, pericarditis, pericaditis, fistula, dermatitis severe nausea / vomiting

**number of patients

(Table 2). About 80% of patients were followed up regularly more than 12 months (Table 3), which is thought to be acceptable follow up period to evaluate complication, because most complications developed within 1 year after treatment.

RESULTS

IORT was performed for 53 cases, fifty-five cases were given 1,500 cGy except the first case. 44.8% of these patients received over 3,000 cGy of external irradiation on area of tumor bed and major lymphatic draining.

Eighty six percentage of IORT patients received at least 3 courses of chemotherapy. Total 9 cases (17%) of complication were noted including GI bleeding (3 cases), perioperative sepsis (2 cases), and bone marrow depression (1 case) (Table 4).

GI bleedings were developed on POD 2 months, 3 months, and 5 months and 2 were confirmed by endoscopy. Other 1 patient had operation due to bleeding but he expired on POD (2nd) 6 without recovery from operation this patients was included in sepsis category. Exposed external irradiation for these patients was 1,620 cGy, 3,960 cGy and 4,500 cGy. All 3 patients had FAM chemotherapy. Intestinal obstruction developed on 3 months, 9 months, and 19 months of POD.

Two patients had reoperation and 1 patients had conservative treatment. Only one case of intestinal obstruction had 4,320 cGy of external irradiation and other 2 cases had no external irradiation. 2 patients received FAM regimen, 1 case had BACOP chemotherapy. No local recurrence were found in reoperated field.

Two cases of perioperative sepsis were noted

and expired on POD 31 and POD 3 of 2nd operation because of uncontrolled bleeding after on POD 31 and POD 3 of 2nd operation because of uncontrolled bleeding after subtotal gastrectomy. One patient had 720 cGy of external irradiation and FAM chemotherapy other had no external irradiation and chemotherapy.

One case of bone marrow depression (wbc < 2000, Hb < 7, PLT < 80000) was expired on POD 19 month. She had received 5FU + MMC regimen for 9 months and 4,500 cGy of external irradiation. She had intermittent ascites but it was easily controlled by medication. All patients had advanced stage (3 cases of IIIa, 5 cases of IIIb) except 1 case (Ib). Age range was 35-69 patients.

DISCUSSION

Loco-regional failure is the most common problem even after curative resection in gastric cancer treatment. Gunderson and Sosin⁵⁾ reported 68.6% of loco-regional failure which was confirmed by second-look operations. They also reported that almost 100% of recurrence could find in the cases of tumor extension through stomach wall (B2 and B3) at some time. Frequent local failures were found in stomach bed, anastomosis or stump and very few in abdominal or stab wound.

Park et al²⁾ reported 65.2% of local failure and 32.9% of distant metastasis in their study at Seoul National University Hospital, Korea, which showed that local recurrence rate is much higher than metastasis in gastric cancer. Local control is an important factor for decreasing metastasis^{3,6,7)}, increasing survival⁷⁾ and higher life quality, not only in gastric cancer but also most of other cancer

management. Suit⁷⁾ insisted that administration of higher dose can increase local control and further survival. IORT was suggested as a local treatment modality for administration of high dose of radiation without increasing complication. Many authors^{8~11)} reported good local control with acceptable complication in their IORT trials and we also reported good local control⁴⁾. But we shouldn't admit IORT as a main treatment modality unless reasonable therapeutic gains, namely good local control with acceptable complications.

Cromack et al¹⁰⁾ compared survival and complications in IORT and conventional treatment in 119 patients of prospective randomized NCI protocol. IORT group was treated with IORT (2000 cGy) and conventional group was treated with operation + external irradiation (5000 cGy). Their complication rate was 17% in IORT group and 23% in conventional group. The majority of complication occurred in gastrointestinal category such as enteritis, bowel obstruction and hemorrhage. Sepsis was greater in conventional group than IORT group with retroperitoneal sarcoma. GI bleeding and sepsis were more than 50% of complication episodes and results in ten of the 11 postoperative death. They concluded that complication rate was no different between IORT and conventional group. They also demonstrated that GI bleeding after IORT and conventional group. They also demonstrated that GI bleeding after IORT in pancreas carcinoma, typically occurred at 4-6 months POD was due to ischemic necrosis of mucosa on the medial duodenal wall which was included in IORT field. These complication rate was 20-30% in pancreas cancer patients but these bleeding were self-limiting.

Calvo et al¹¹⁾ reported 2 cases of dehiscence of the esophago-jejunal suture which is not related to IORT and could manage medically.

Gunderson et al¹²⁾ reported 4 cases of perioperative infections but he insisted that these infection could come from spillage of bowel content. In our trials total 9 cases (17%) of complications were noticed so far, including 3 cases of GI bleeding, 3 cases intestinal obstruction, 2 cases of perioperative sepsis and 1 case of bone marrow depression. GI bleeding were closely located on anastomosis area. Two cases were confirmed by endoscopy and one case was reopened, but he was dead at POD 6 of 2nd operation without recovery from operation. Surgeon found diffuse, continuous bleeding on remnant stomach area which could not control adequately. These bleeding area were not included

in external irradiation field and exposed dose was 1620, 3960, and 4500 cGy. All 3 patients had FAM chemotherapy. Of 3 cases of intestinal, 2 were treated surgically, and one was medically. Surgeon cannot find any local recurrence except moderate fibrosis. Only one case received 4320 cGy of external irradiation but other 2 had only chemotherapy (FAM, BACOP).

Of 2 perioperative sepsis cases, one had pancreas abscess and other case had reoperation for correction of bleeding. Both patients could not recover from operation and dead at POD 31 and Re-POD 3 (POD 43). One reoperated patient had FAM chemotherapy and 720 cGy of external irradiation but other patient had no further treatment.

One patient with bone marrow depression had 4500 cGy of external irradiation and Mitomycin + Furtulon chemotherapy for about 10 months. Since fluctuation of bone marrow was noticed, her regimen was changed as Furtulon + Copolang + Tamoxifen for 1 more month. Her condition showed down-hill course continuously and expired at POD 19 months.

Influencing factors for our relatively high mortality rate (11.3%, 6/53) should be investigated, because external irradiation, chemotherapy, surgical skill and perioperative care might be a courses. IORT could be excluded as a cause of GI bleeding and intestinal obstruction because all intestines were pulled out from IORT field. External irradiation could be a cause of GI bleeding and bone marrow depression. But only 1620 cGy, 3960 cGy, 4500 cGy were exposed which is lesser than conventional dose (5000 cGy) for pelvic irradiation.

Chemotherapy also might be a cause of bleeding, intestinal obstruction due to fibrosis, and bone marrow depression. Cho et al¹³⁾ reported the pathological finding after chemotherapy (C-DDP + 5 FU + VP). They found some remission of tumor and very similar findings to radiation, such as fibrosis, necrosis, and ulceration. These finding suggested that chemotherapy may be a forceful influencing factor. There is doubt that experienced surgical skills and excellent postoperative care could decrease perioperative complications.

However, overall complication rate of our protocol was 17% (9/53) which thought to be acceptable compare to Joo et al¹⁴⁾ (25.2%, op + chemotherapy), Kim et al¹⁵⁾ (18%, EAP chemotherapy only), Lee et al¹⁶⁾ (18.5%, surgery only) and Kramling et al¹⁷⁾ (35.3%, op + IORT 2800--3500 cGy). Our mortality rate (11.3%) was relatively high compare to others (2.4%¹³⁾--7.8%¹⁸⁾) but very similar to Kramling

ing's result (11.8%).

If we consider our aggressive protocol including operation, IORT (1500 cGy), external irradiation and aggressive chemotherapy, overall complication rate was acceptable.

Our results encourage us to reinforce our protocol. We hope that our data also encourage all doctors who are trying IORT in their field.

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= 국문초록 =

위암의 수술중 방사선 치료의 합병증

영남대학교 의과대학 치료방사선과학교실, 일반외과학교실*, 마취과학교실**

김명세 · 김성규 · 송선교* · 김홍진* · 권광보* · 김홍대**

영남대학교 의료원 치료방사선과에서 1988년 6월 15일에 위암 환자의 수술중 방사선치료를 시작한 이래 1992년 8월 30일까지 총 58예에서 시도하여 그중 53예에서 IORT를 실시하였으며, 정기적인 추적검사에서 한명의 국소재발 환자도 보고되지 않고 있다.

출혈(3예), 장관폐쇄(3예), 폐혈증(2예), 골수기능저하(1예)를 포함한 총 9예(17%)의 합병증이 보고되었고, 이중 6예(13%)가 사망하였다.

IORT(1500 cGy), 외부 방사선치료(-4500 cGy)와 강한 항암제를 병합치료 하였음에도 불구하고 주등(수술과 항암제 치료)의 25.2%, 김등(수술 불가능한 환자에서 항암제 투여)의 18%, 리등(수술)의 18.5%, Kramling등(IORT 2800-3500 cGy)의 35.3%에 비해 낮은 합병증을 보여 IORT가 위암의 치료에 공헌할 수 있음을 시사하였다. 그러나 비교적 높은 치사율(11.3%)은 더욱 세심한 수술수기 및 수술 후 환자의 치료가 필요하며 외부 방사선치료와 항암제치료의 적절한 시기 조절 및 치료선량의 가감이 필요할 것으로 생각된다.