

IORT in Gastric Cancer

Myung Se Kim, M.D., Cheol Hoon Kang, M.D., Sung Kyu Kim, Ph.D.
Sun Kyo Song, M.D.,* Koing Bo Kwan, M.D.* and Heung Dae Kim, M.D.**

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

Total 28 patients with resectable, locally advanced gastric cancer were entered in our prospective randomized study from June 15, 1988 to Sep. 15, 1990 in Yeungnam University Hospital. This study consisted of curative resection, IORT, external irradiation and combination of chemotherapy. Twenty-four of 28 patients were treated with single dose of 1500 cGy with 9 MeV electron intraoperatively. External irradiation of 4300~4500 cGy with 180 cGy per fraction, 5 days per week was started within 4th weeks of postoperative days. Various chemotherapy with or without external irradiation were added for reducing hematogenous and/or peritoneal dissemination and determination of complication of each arm. Duration of follow up was 4~31 months. No serious complication related with radiation were reported compare to resection and chemotherapy only group.

Although our follow up period is too short to draw any conclusion, IORT appears to improve local control, hopefully further survival. Continuous follow up should be needed for evaluation of real therapeutic gain such as complication vs. improved survival.

Key Words: IORT. Prospective randomized trial. Locally advanced gastric cancer complication. Local control

INTRODUCTION

Gastric cancer is the most common malignancy in men 2nd in women in Korea¹⁾. Although remarkable development of techniques in surgery, anesthesiology and supportive therapy, overall survival rate has not much improved except early gastric cancer. Radical surgery has been considered as a treatment of choice, but complete resection of cancer cells, especially tumor nests around major vessels is impossible.

Loco-regional failure is the most common pattern of relapse²⁾, even after curative resection. More radical surgery with extended node dissection has been tried but it has not prevented local recurrence of gastric cancer⁴⁾. Even in the patients with intraabdominal dissemination, it did not occur without the localized recurrence in upper abdomen²⁾.

These data suggested that the local or regional control is the main problem for improving the survival rate in the patients of stomach cancer and surgery is no longer the only modality of choice in gastric cancer. Therefore, multidisciplinary approach including surgery, radiation therapy, chemotherapy, and immunotherapy should be the main stem of treatment for gastric cancer.

External irradiation also has been tried for increasing local control, but enough cancerocidal dose could not deliver to the gastric bed because of the normal tissue tolerance of adjacent organs such as liver, kidneys, small intestine, colon and spinal cord. Since current IORT was introduced by Abe, marked improvement of local control was reported by many authors^{3,5~13)}, but the propagation of IORT is still limited, because of expensive facilities and need of good interdepartmental cooperation.

The purpose of this article is to analyze our prospective randomized trial and to evaluate the effects and complication as a preliminary study even though duration of follow up is too short to draw the conclusion.

MATERIALS AND METHOD

Between June 15, 1988 and Sep. 15, 1990, total 28 patients with resectable, locally advanced gastric cancer who proved by histologically entered in our prospective randomized protocol. The detail of our protocol was described in Table 1.

Patients mean age was 58 years with a range of 34~72 years. Male to female ration was 1.5 : 1 (17 : 11 pts) and 61% of the patients were stage III and IV.

Table 1. Prospective Randomized Protocol for Gastric Cancer

Stage II	A	No Chemotherapy, No R. T.
	B	MMC + 5FU + UFT
	BR	MMC + 5FU + UFT + R. T.
Stage III	C	MMC + UFT
& IV	CR	MMC + UFT + R. T.
	D	FAM (5FU + ADR + MMC)
	DR	FAM + R. T.

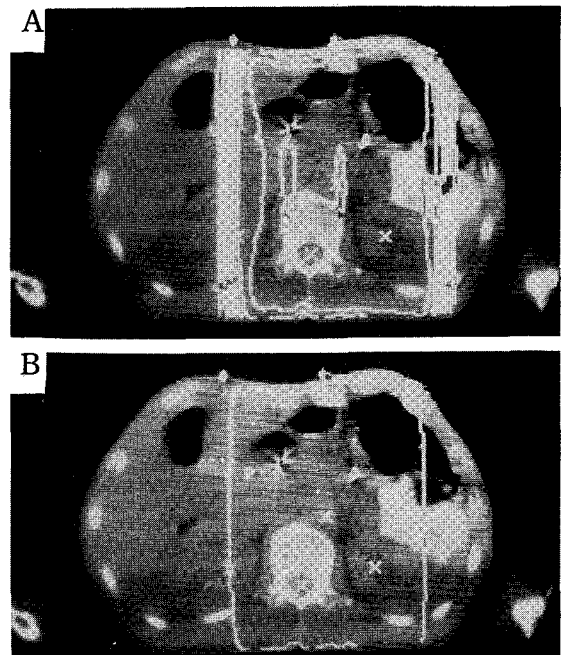
Table 2. Patients Characteristics

	No. of pts.	%
Sex Male	17	61
Female	11	39
Age 34–72 years (mean 58)		
Histology		
Adenocar. well differentiated	2	
moderate	8	
poorly	15	
signet ring cell	3	
Clinical stage		
Ia	1	3
Ib	6	22
II	4	14
IIIa	6	22
IIIb	7	25
IV	4	14

Adenocarcinoma was most common histologic type (Table 2).

Type of surgery was decided by surgeon, depend on the location and the extent of disease. Seventeen patients had subtotal gastrectomy and bypass surgery was selected in 3 patients because of the disseminated disease.

IORT was performed in 24 patients, because of early gastric cancer (1 case) and disseminated disease (3 patients). Single dose of 1500 cGy with 9 MeV electron was routinely delivered at 90% isodose level except 1st case (1000 cGy). Seven to nine cm individualized pentagonal cone with 15° beveled was used for covering all desired tumor bed area, especially celiac axis. Adjacent radiosensitive organs such as liver, duodenal stump, small intestine, colon were carefully excluded from the irradiated field by specially designed lead protec-

**Fig. 1.** Planning CT (uncorrected).

A: Isodose curve (X: Reference points of dose calculation on both kidneys, midline and spinal cords).

B: 90% isodose line include almost one-thirds of the right kidney.

tor because about 2% of leakage was calculated on outside of cone. IORT cone and protector will be published in other article. All IORT procedures including surgery and irradiation were performed in one Linac room, this needs the least movement of patients during whole procedure which will be the best condition for surgeon and radiotherapists.

External irradiation was designed to encompass the area of potentially nodal drainage and anastomosis area and exclude at least 1 whole kidney. Kidney shape and position was delineated by IVP at simulation and this is routinely double checked by planning CT to minimize the radiation dose of kidney (Fig. 1). All treatment field were corrected by optimization with our computer (Therac 2300)(Fig. 2). If there is the requirement of field correction, resimulation was done on the basis of CT planning (Fig. 3). Total 4300–4500 cGy daily fraction, 5 times per week were delivered using parallel opposing field. This treatment was started within 4th weeks of postoperative days. Chemotherapy was planned for reducing distant metastasis and started on postoperative day 0, according to our

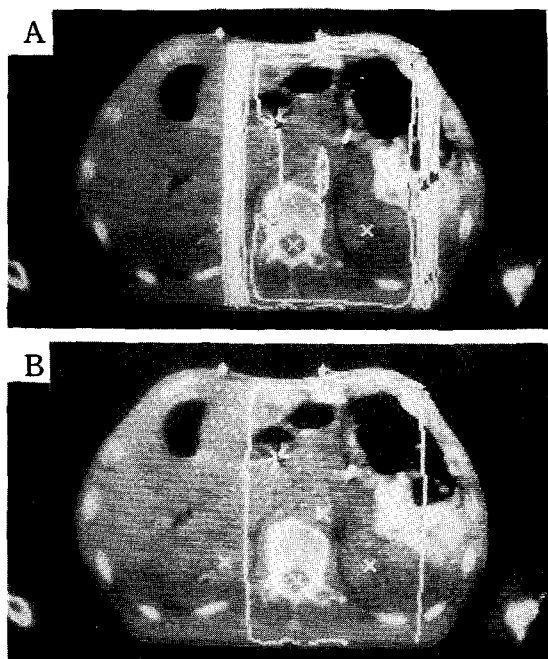


Fig. 2. Planning CT (corrected).

A: Isodose curve.

B: 90% isodose line include only the tip of the right kidney.

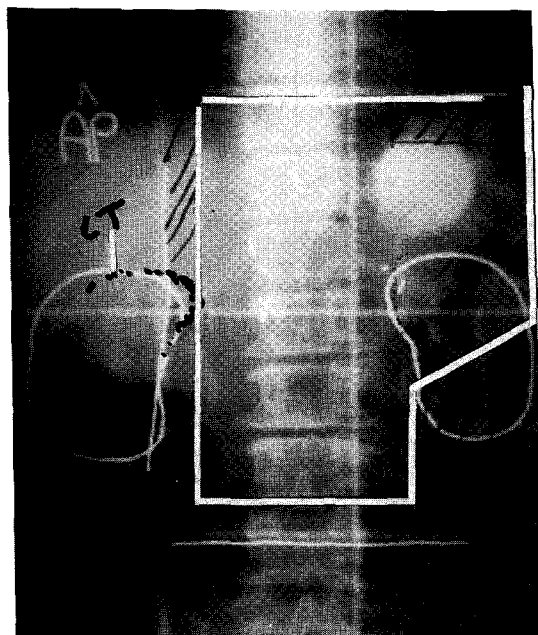


Fig. 3. Simulation film.

External irradiation fields (corrected by planning CT).

protocol.

Mean duration of follow up was 12.2 months with range of 4 months to 31 months and no patient was lost to follow up.

RESULT

Total 24 patients were underwent curative resection and IORT. Four patients were excluded because of early gastric cancer (1 case) and disseminated, unresectable cancer (3 cases). Curative resection include subtotal, nearly total or total gastrectomy, omentectomy, gastrojejunostomy and lymph node dissection as many as possible.

Six patients were died of 1, 4(2 cases), 7, 9 and 13 months after treatment. Two of them had bypass surgery only because of dissemination of disease and 1 case who had sudden death at 4 months after treatment could not prove the cause of death. One patient died because of severe gastric bleeding which was proved in exploratory laparotomy. Multiple ulcer were found in the remnant of stomach fundus with no evidence of marginal ulcer or residual gross tumor at laparotomy. Two patients were noted marked abdominal distension only by their family after their death, this suggested the dissemination of the disease. No patient had the evidence of local recurrence. No serious complication was noted in spite of IORT and/or external irradiation and chemotherapy.

DISCUSSION

Although remarkable improvements of surgical techniques, anesthesiology and supportive therapy increase resectability from about 30% in the 1940's to 50~60% at present, actual cure rates have little changed¹²⁾. Gunderson and Sosin²⁾ found that distant metastasis alone as a failure after curative resection was uncommon, locoregional failure was the most common pattern of failure. Local failure only was reported in 54% and any component in 88% in their reoperation series²⁾.

They also reported that locoregional failure was primarily limited to regional lymph nodes, gastric bed, anastomosis site, gastric remnant and/or duodenal stump. These suggest that aggressive locoregional treatment may decrease local failure and improve further survival.

Aggressive radical surgery was tried, but significant improvement of survival could not achieve because complete elimination of cancer nests around the major vessels is actually impossible and

the possibility which microscopic malignant lesions will be left behind even after extended radical surgery, always exists¹⁵⁾.

External irradiation was tried. But delivery of the enough cancerocidal dose above 6000~7000 cGy¹⁶⁾ is impossible without significant damage of adjacent radiosensitive organs, such as kidneys, spinal cord, liver, small bowel and colon.

Current intraoperative radiotherapy with a megavoltage machine was started by Abe in 1964¹⁵⁾. He irradiated 2500~3500 cGy with a single dose with cobalt or electron to the stomach bed area including celiac axis and regional nodes without external irradiation or chemotherapy. He insisted the benefits of IORT, 1) direct visualization of the lesion allowing an accurate determination of the site, 2) physical removal of all or part of the dose limiting normal organs from the field, 3) therefore, cancerocidal dose can be delivered primarily with least normal tissue morbidity and these result in more radical outcome than external irradiation only⁹⁾.

In United States, Golden and Henscke introduced IORT first in 1975 and performed the first case on Nov. 26, was followed by MGH(1978), NCI(1979)¹⁴⁾, Mayo clinic(1981) and New England Deaconess Hospital(1982). They used IORT as a boost of pre-or postoperative external irradiation which is quite different from Abe's philosophy.

In Korea, Yonsei University reported 7 cases of stomach cancer who received IORT in 1986. They stopped IORT soon because of some reasons.

Our institution, Yeungnam University Hospital started IORT on June 15, 1988 and performed 24 cases so far, mainly with resectable gastric cancer. We used IORT as a boost. Single dose of 1500 cGy with 9 MeV electron was usually delivered through transparent, pentagonal acrylic cone with 15° beveled to gastric bed and celiac axis area.

Dosimetry and special designs of IORT cone will be published in other article.

All procedure including surgery and irradiation were carried out in a Linac room which permit easy performance and minimal movement of patients. Dose limiting tissues, such as small intestine, liver and colon should be retracted outside the IORT field which may cause the possibility of marginal failure even though high IORT dose were delivered.

We added postoperative external irradiation for reducing possible locoregional failure, because Minnesota reoperation series reported significant failure in upper abdomen which could not covered by IORT field. 4000~4500 cGy were delivered to

upper abdomen with parallel opposing field. At least one whole kidney should be excluded from external field and maximum for other kidney.

Various regimens of chemotherapeutic agents were randomized for evaluation of the effects of chemotherapy, so that we expect to decrease distant failure because distant metastasis only failures were reported as 5~40%, any components were 22~50%^{2,17)}.

Six patients were reported as early death. Two of 6 patients had bypass surgery because of too advanced disease. One patient was noticed as sudden death at 4 months after surgery and IORT. He was very well until his death. Another 3 patients died at 1.5, 7 and 13 months after treatment. Although autopsy could not be performed, all patients had similar operation findings such as involvement of pancreas, omentum, mesocolon vascular invasion and regional lymph node involvement (N1 or N2) which suggest as poor prognostic factors.

So far, no evidence of the complication related with IORT or external irradiation, such as dehiscence of suture, fistula, biliary obstruction were noted.

Although follow up duration is too short (4~31 months) to draw any conclusion from our preliminary experience, no significant morbidity was evident and no evidence of local recurrence was reported. These suggest us the possibility of increased local control by our protocol and further improvement of survival. Further study should be accomplished for evaluation of real survival benefits without compromising complications.

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== 국문초록 ==

위암의 수술중 방사선 치료

영남대학교 의과대학 치료방사선과학교실, 일반의과학교실*, 마취과학교실**

김명세 · 강철훈 · 김성규 · 송선교* · 권평모* · 김홍대**

영남대학병원에서는 1988년 6월 15일부터 1990년 9월 15일까지 절제가능한 국소 진행된 위암 환자중 원격 전이를 확인할 수 없었던 환자 총 28명을 prospective randomized protocol에 의한 치료를 계획하였다. 28명중, 개복후 절제가 불가능했던 환자 3명과 stage Ia로 판명된 환자 1명을 제외한 24명에서 외과적 근치절제수술후 1500 cGy를 9 MeV의 전자선을 이용하여 1회에 조사하였다. 외부 방사선 치료는 수술후 4주 이내에 시작하여 하루 180 cGy 주 5회 치료법으로 4300~4500 cGy를 조사하였다. 항암요법은 protocol에 의하여 5-FU, Mitomycin-C, Adriamycin, Uraful을 여러가지 조합으로 투여하였다. 3개월에서 31개월 간의 추적기간 중에 방사선 조사와 관계되는 심한 부작용은 보고되지 않았다. 짧은 추적 기간이므로 생존율을 산출할 수 없겠으나 수술중 방사선치료, 외부방사선 치료와 여러가지 항암제를 병합 투여하였음에도 불구하고 심한 부작용이 발견되지 않았을 뿐 아니라 현재까지 국소재발이 한 예에서도 발견되지 않았으므로 수술중 방사선 치료의 국소 재발의 억제 및 방지의 효과가 확실시되며 계속되는 추적검사에서도 좋은 생존율이 기대된다.