

Role of Radiation Therapy for Locally Advanced Gastric Carcinoma Management

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Thirty-five patients with locally advanced gastric carcinoma were treated with combined modalities of external radiation therapy (RT) and 5-FU based chemotherapy at the Division of Radiation Therapy, Department of Radiology, Kangnam St. Mary's Hospital, Catholic University Medical College from May 1983 to May 1987.

The purpose of this retrospective study is for the evaluation of the palliative response to RT. There were 25 men and 10 women. The age ranged from 38 to 80 years (median: 56 years). The pathologic classification showed 14 (40%) poorly differentiated, 12 (34%) moderately differentiated, 3 (9%) well differentiated adenocarcinomas, 2 mucinous cystadenocarcinomas, 1 signet ring cell and 3 not specified ones.

The time intervals from the initial surgicopathologic diagnosis to the starting day of RT was within 1 year for 18 (51%), 1 to 2 years for 8 (23%) and 2 to 3 years for 5 (14%), respectively. The major symptoms to be treated were pain in 30 (86%), mass for 29 (83%), obstruction for 11 (31%) and jaundice for 9 (26%) patients. The response rate (patient number of positive response/total patient number) according to treated radiation doses were observed as follows; 14/16 (88%) for 40~50 Gy, 8/10 (80%) for over 50 Gy, 6/8 (75%) for 30~40 Gy and 8/15 (53%) for 20~30 Gy in decreasing order. The over all survival was 3.6 months and that of 5FU+RT, FAM+RT and RT alone groups were 4.6 months, 3.7 months and 2.5 months respectively. Complications induced by RT were nausea and vomiting in 16 (46%), diarrhea in 7 (20%), leukopenia in 6 (17%) and anemia and intercurrent pneumonia in each 3 (9%) patients in decreasing order.

Key Words: Radiation Therapy, Locally advanced gastric carcinoma, Adenocarcinoma, Combined modality, Palliative response, Symptom, Complication

INTRODUCTION

Radiation has been a very minor role in the treatment of locally advanced gastrointestinal lesions, especially carcinoma of the stomach, because most have attempted to utilize it as the only modality of treatment. In that case, the chance for cure is minimal due to the limited tolerance of the surrounding organs and tissues¹⁻⁵.

Recently, available literatures reported the concepts that adenocarcinoma of the stomach is a radioresponsive lesion, and that radiation alone has been shown to have good palliative and occasional curative potential in patients with residual disease after resection or with unresectable lesion¹⁻¹⁰. Its greatest benefit, however, has been when used in combination with chemotherapy.

We have experience thirty-five patients with locally advanced gastric cancer who were tried chemoradiation (CRT) or RT alone for palliative effects at the Division of Radiation Therapy, Department of Radiology, Kangnam St. Mary's Hospital, Catholic University Medical College from May 1983 to May 1987.

The purpose of this retrospective study was to analyze the therapeutic effectiveness of CRT and/or RT alone for patients with the locally advanced stage of gastric cancer.

METHODS AND MATERIALS

1. Indications and Aims

Thirty-five patients with unresectable, residual or recurrent gastric cancer after initial diagnosis were treated by external irradiation in order to reduce palpable epigastric mass, stop gastrointestinal bleeding and relieve the obstructive symptoms

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of gastrointestinal tracts and/or obstructive jaundice.

All patients had been diagnosed as adenocarcinoma of the stomach, histologically. Thirty-three were postsurgically and the remaining two were diagnosed by endoscopic biopsy because of their poor general conditions. We used criteria for palliative treatment suggested by Haslam¹¹⁾ in this study.

The criteria for palliation were as follows;

Good at least 2 of following;

1. complete relief of pain, sustained for at least 4 weeks.
2. weight gain not due to ascites or edema.
3. relief of obstructive symptoms & jaundice.
4. decrease in size of mass, if palpable.

Fair one of the following;

1. partial relief of pain, sustained for at least 4 weeks.
2. arrest of weight-losing tendency, with restored appetite.
3. clearly improved energy & activity level

None no reversal of adverse symptoms or signs

2. Radiation

All patients were treated with 6 MV linear accelerator. The radiation fields usually included the tumor or tumor bed encompassing major nodal chains (lesser and greater curvature, celiac axis, gastroduodenal, pancreaticoduodenal and porta hepatis, splenic, suprapancreatic; when feasible para-aortic and level of mid L-3 level; paraesophagogastric junction with proximal lesion). Such idealized portals need to be modified depending on the initial extent of disease and patients performance status as well as expected life span. Most patients were used recent abdominal CT scans to adjust and apply the anatomical informations to be used by the therapeutic planning computer.

Average radiation field measured (10-11) × (10-11) cm in AP & PA, (6-8) × (10-12) cm in bilateral ports, that is, box technique, by way of simulation. With single daily schedule the usual dose aim was 45-52 Gy delivered in 1.6-1.8 Gy fraction over five to five and a half weeks with a field reduction after 40 Gy. The posterior shield for kidney which was inevitably involved in upper half, was done from the beginning of RT. During the RT, patients were seen at least once a week with record of tolerance, weight and blood count and also treatment related complications. If chemotherapy preceded or it was given concomitantly with RT, blood count was obtained twice a week.

3. Patient Selection and Characteristics

Characteristics of these 35 patients are displayed in table 1. The age ranged from 38 to 80 years of age (median age was 56 years). The male to female ratio was 25 to 10. All patients were diagnosed as adenocarcinoma of the stomach by histopathologically. By the disease extent of 35 patients at the time of RT, locoregionally advanced cancer were 23(66%). Eight (23%) were locoregional plus liver metastasis, resulting in obstructive jaundice and pain. Two (6%) were revealed locoregional disease with thoracolumbar junctional spine metastasis. Two (6%) were sustained of locoregional problem plus malignant ascites.

The intervals between the time of surgery and RT were noted in Table 1 and 2. All but three patients (9 %) who tried RT alone have been treated with chemotherapy as soon as their initial pathologic diagnosis was made. FAM regimen and 5 FU were

Table 1. Patient Characteristics (n=35)

| | |
|---|---|
| Age | : 38 – 80 years (median ; 56 years old) |
| Sex | : Male : Female = 25 : 10 |
| Pathology | |
| Adenocarcinoma | |
| Well differentiated | 3 |
| Moderate differentiated | 12 |
| Poorly differentiated | 14 |
| Not specified | 3 |
| Mucinous cystadenocarcinoma | 2 |
| Signet ring cell | 1 |
| Status | |
| 1. Recurrent and/or unresectable locoregional disease | 23 |
| 2. 1. + liver metastasis | 8 |
| 3. 1. + spine metastasis | 2 |
| 4. 1. + carcinomatosis peritonei | 2 |
| Time interval from surgery to RT | |
| below 1 year | 18 |
| 1 – 2 years | 8 |
| 2 – 3 years | 5 |
| 3 – 4 years | 1 |
| 4 – 5 years | 1 |
| over 5 years | 2 |
| Distribution of chemoradiation | |
| 5-FU + XRT | 12 |
| FAM + XRT | 20 |
| XRT | 3 |

used in 20(57%) and 12(34%) patients, respectively before and after these combined modalities (Table 1).

RESULTS

1. In view of pathologic differentiation, 14(40%) poorly differentiated, 12(34%) moderately differentiated, 3 (9%) well differentiated adenocarcinomas, 2 mucinous cystadenocarcinomas, 1 signet ring cell and 3 not specified ones were noted (Table 1). The time intervals from the initial surgical pathologic diagnosis to the starting day of RT was within 1 year for 18(51%), 1 to 2 years for 8(23%) and 2 to 3 year for 5(14%) respectively (Table 2).

2. The major symptoms to be treated were 30(86%) for pain, 29(83%) for mass reduction, 11(31%) for obstruction and 9(26%) for jaundice. The response rate (patients number of positive

response/total patient number) according to the treated radiation dose were as follow; 14/16(88%) for 40~50 Gy, 8/10(80%) for over 50 Gy, 6/8(75%) for 30~40 Gy and 8/15(53%) for 20~30 Gy (Table 3).

3. The higher the treated radiation doses, the better responses were observed (Table 4).

4. The overall mean survival was 3.6 months and that of each group of 5 FU+RT, FAM+RT, and RT alone were 4.6 months, 3.7 months and 2.5 months in order (Table 5, Fig 1).

5. Complications observed during RT were nausea and vomiting in 16(46%), diarrhea in 7(20%), leukopenia in 6(17%) and anemia and intercurrent pneumonia in each 3(9%) patients in decreasing order (Table 6).

Table 2. Relation between Time Intervals from Gastric Cancer Surgery to RT and Pathologic Types

| Year Differentiation | - < 1 | 1 ≤ - < 2 | 2 ≤ - < 3 | 3 ≤ - < 4 | 4 ≤ - < 5 | 5 ≤ - |
|-------------------------|-------|-----------|-----------|-----------|-----------|-------|
| Well | 2* | 0 | 1 | 0 | 0 | 0 |
| Moderate | 8* | 2 | 0 | 0 | 1 | 1 |
| Poorly | 6 | 5 | 3 | 0 | 0 | 0 |
| Not specified | 0 | 1 | 0 | 1 | 0 | 1 |
| Mucinous | 1 | 0 | 1 | 0 | 0 | 0 |
| Signet ring | 1 | 0 | 0 | 0 | 0 | 0 |
| Total | 18 | 8 | 5 | 1 | 1 | 2 |

* One of 2 well differentiated and 1 of 8 moderate differentiated were diagnosed only by endoscopic biopsy.

RT : Radiation therapy

Table 3. Relationship of Radioresponsiveness between Palliative Symptoms and Treated Doses

| Symptom RT responses | Pain (n=30) | Mass (n=29) | Obstruction (n=11) | Jaundice (n=9) | Ascites (n=6) | Total |
|-------------------------|----------------|----------------|-----------------------|-------------------|------------------|-------|
| Dose (Gy) | c/s | c/s | c/s | c/s | c/s | c/s |
| - < 10 | 0/7 | 0/7 | 0/0 | 0/1 | 0/3 | 0/18 |
| 10 ≤ - < 20 | 2/4 | 0/5 | 0/2 | 2/2 | 0/0 | 4/13 |
| 20 ≤ - < 30 | 5/0 | 3/4 | 0/2 | 0/0 | 0/1 | 8/ 7 |
| 30 ≤ - < 40 | 4/0 | 2/1 | 2/1 | 0/0 | 0/1 | 8/ 2 |
| 40 ≤ - < 50 | 6/0 | 4/2 | 1/0 | 3/0 | 0/0 | 14/ 2 |
| 50 ≤ - | 2/0 | 1/0 | 2/1 | 1/0 | 0/1 | 6/ 2 |
| Total | 19/11 | 10/19 | 5/6 | 6/3 | 0/6 | 40/45 |

c : With. s : Without

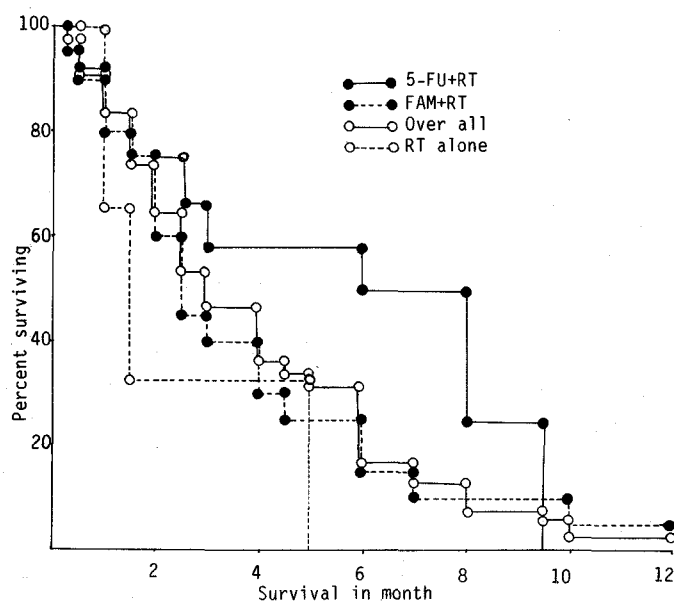
Table 4. Effects of Treated Radiation Doses for Gastric Cancer Associated with Each Degree of Symptomatic Improvement

| Dose (Gy) | - < 10 | 10 ≤ - < 20 | 20 ≤ - < 30 | 30 ≤ - < 40 | 40 ≤ - < 50 | 50 ≤ - | Total |
|-----------|--------|-------------|-------------|-------------|-------------|--------|-------|
| Good | | 1 | | 2 | 6 | 3 | 12 |
| Fair | | 4 | 4 | 3 | 1 | | 12 |
| None | 8 | 2 | 1 | | | | 11 |
| Total | 8 | 7 | 5 | 5 | 7 | 3 | 35 |

Table 5. Distribution of Patients Treated with Chemoradiation in Stomach Cancer (n=35)

| Dose (Gy) Regimen | - < 10 | 10 ≤ - < 20 | 20 ≤ - < 30 | 30 ≤ - < 40 | 40 ≤ - < 50 | 50 ≤ - | Total |
|---------------------------|--------|-------------|-------------|-------------|-------------|--------|-------|
| 5-FU + RT (m = 4.6 mo) | 2 | 2 | 1 | 2 | 4 | 1 | 12 |
| FAM + RT (n = 3.7 mo) | 6 | 4 | 2 | 3 | 3 | 2 | 20 |
| RT (m = 2.5 mo) | | 1 | 2 | | | | 3 |

*One of each group was tried intraperitoneal cisplatin for malignant ascites or carcinoma peritonei.
m = mean survival rate, mo = month, FAM ; 5-FU, adriamycin, mitomycin, 5-FU ; 5-fluorouracil

**Fig. 1.** Survival curve of 35 patients with locally advanced gastric cancer treated with chemoradiation (K-M method).

DISCUSSION

Surgery remains the main stay of treatment for

cancer of the stomach, but over the past three decades the course of disease has changed a little. Although resectability has increased from about 30 percent in the 1940s to 80 percent at present, cure

Table 6. Complications Observed during RT

| Complications | Number (%) |
|-------------------|------------|
| Nausea & vomiting | 16 (46) |
| Diarrhea | 7 (20) |
| Leukopenia | 6 (17) |
| Anemia | 3 (9) |
| Pneumonia | 3 (9) |
| Thrombocytopenia | 2 (6) |

rate by extent of disease have changed only slightly¹⁻⁵.

In the therapeutic view², three stages of stomach cancer can be appreciated. These are local disease in which the treatment is surgery and in which radiotherapy, chemotherapy and immunotherapy have been and are being studied as adjuvant therapy, disseminated disease in which treatment is principally palliative and symptomatic, and locally advanced nonresectable disease in which the treatment with chemotherapy and/or radiation therapy can improve survival of a percentage of patient. In locally advanced unresectable gastric cancer, together with partially resectable or locally recurrent states have been considered as good candidates for treatment with RT.

Radiation alone has been shown to have palliative and occasional curative potential in patients with residual disease after resection or with unresectable lesions. Its greatest benefit, however, has been seen when radiation is used in combination with chemotherapy. Most reports on combined irradiation and chemotherapy of patients with residual or unresectable disease have shown an advantage for combined over single modality treatment.

Combined therapy would be attractive for the resected but high risk subgroups with gastric carcinoma. The preferred use of radiation, as an aid to local control, would be in combination with the operative removal of all gross disease in the primary area and lymph nodes, utilized for the microscopic or subclinical residuum¹⁻¹⁰.

In a randomized double blind series from the Mayo Clinic⁶, 5-FU (fluorouracil) was utilized during the first three days of irradiation in one half of the group. For the combined treatment group, mean and over all survival were improved (13 months versus 5.9 months and 12 percent versus 0 survival at 5 years). In the recent randomized GITSG study⁵, the combination of irradiation and

5-FU, followed by maintenance with 5-FU and methyl-CCNU was statistically superior to 5-FU and methyl-CCNU alone for long term survival, with a plateau of 15~20 percent between the second and third years of follow up.

Patients who had a resection but residual disease had better long term survival than those who were never resected in the GITSG series. In a series of 46 patients with localized gastric cancer treatment at Massachusetts General Hospital (MGH) by Gunderson et al⁴ problem with excessive acute or chronic toxicity due to combination treatment with irradiation and chemotherapy were not seen. Takahashi reported a 28% survival at 30 months in irradiated patients with locally advanced gastric cancer⁹.

Weiland & Human with trying doses in the range of 6000 cGy reported a 11%(9/82) survival at 36 months and 7%(5/72%) at five years¹⁰. But a similar study at the Mayo Clinic, fail to demonstrate survival benefit in 26 patients treated to 3500~4000 cGy in four weeks, no survival advantage was seen when compared to 43 patients who received no specific antineoplastic therapy. Current megavoltage technique permit the delivery of between 4500 cGy in 5 to 5.5 weeks with acceptable toxicity, complication rates being less than 10%¹⁻⁵.

In this situation, definite palliation can be obtained using external irradiation. The duration of palliation appears to increase as the dose of radiation is increased from 4000 cGy in 4.5 to 6 weeks to 6000 cGy in 7 to 10 weeks (using a split course technique with the long time periods). In order to deliver doses in excess of 4500 to 5000 cGy with safety, care must be taken minimize the amount of normal tissue in the radiation fields. This requires having an accurate deliniation of the tumor volume (from CT scans and/or small postsurgical clips around tumor volume) and use of multiple ports irradiation. Authors observed also the higher to treated radiation doses, the better response rate. Our survival rate was very poor showing the range from 0.5 months to 12 months. Because most of patients were the advanced candidates for palliative and supportive cares.

This study was the beginning of multidisciplinary team approaches for gastric cancer management. In future, prospective study should be promised in combination with using hyperthermia and/or hypoxic cell sensitizer for residual or recurrent and unresectable gastric cancer in CUMC.

CONCLUSIONS

Authors have experienced external RT for 35 patients with locally advanced gastric cancer to achieve the palliative responses such as reducing or ameliorating the palpable mass, pain, bleeding and/or obstruction. The results were not much remarkable comparing with those of available literatures. However, we observed fair palliative responses in locally advanced gastric cancer patients and in terms of rates of responsiveness the higher the treated radiation doses, the better clinical results were obtained.

During the radiation, most patients tolerated clinically with minor complications. We need new randomized prospective clinical study for gastric cancer treatment in future along with using hyperthermia, hypoxic cell sensitizer and/or radiation protectors.

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== 국문초록 ==

재발성 또는 국소진행된 위암의 방사선치료

—35예의 치료성적 분석—

가톨릭의대 강남성모병원 방사선과 · 외과* · 내과학교실**

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가톨릭의대 강남성모병원 방사선치료실에서는 1983년 5월 부터 1987년 5월 사이 수술후 재발되거나 국소적으로 진행되어 절제 불가능한 위암환자 35예에 대하여 외부방사선치료를 실시하였다.

방사선치료는 6 MV 선형가속기를 사용하여 매일 160~180 cGy씩, 주 5회 분할 조사하여 총 4500~5500 cGy를 시도 하였으며, 전예에서 Box Technique을 이용하였다. 방사선치료만을 실시하였던 3예를 제외한 전예에서 5-FU 또는 FAM 화학요법을 병행하였다.

1. 총 35예는 남자 25명 여자 10명이었으며 연령은 38세에서 80세사이에 (평균 56세)분포하였다. 조직학적으로는 전 예가 선세포암이었다.

2. 수술후 재발되어 방사선치료하기까지의 기간은 수술후 1년이내에 18(51%)명, 1~2년내 8(23%)명, 그리고 2~3년내에 5(14%)명이었다.

3. 방사선치료를 하게된 주된 증상으로는 통증 30명(86%), 종괴 29명(85%), 위장관폐쇄 11(31%)명 및 폐쇄성 황달이 9(26%)명이었다.

4. 이증상들의 방사선치료후 반응은 총치료선량에 따라 40~50 Gy에서 14/16(88%), 50 Gy이상에서 8/10(80%), 30~40 Gy에서 6/8(75%), 및 20~30 Gy에서 8/15(53%)의 호전율을 관찰할 수 있었다.

5. 국소 진행된 위암환자의 방사선치료후 평균 생존율은 3.6개월이었으며 방사선치료에 의한 부작용으로서는 오심, 구토(46%), 설사(20%), 백혈구 감소증(17%), 그리고 빈혈 및 폐염(9%) 등의 순을 보였다.