Medical Journal of the
Islamic Republic of Iran

Volume 9
Number 3
Fall 1374
November 1995

INTRAOPERATIVE RADIATION THERAPY FOR GASTRIC ADENOCARCINOMA

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ABSTRACT

Intraoperative radiation therapy (IORT) is a multidisciplinary approach in which residual tumors or tumor beds are directly irradiated during a surgical procedure. To evaluate its efficacy, from 1985, we conducted a prospective study including non-metastatic gastric adenocarcinoma treated by surgery, IORT (15 Grays) and postoperative external beam radiotherapy (44 Grays). Up to 1993, 51 cases of gastric adenocarcinoma (20 pN_0 and 31 pN_{1-2}) have been included in the study. Mortality and morbidity rates were not different from those of surgery alone. The overall 5 year survival rate was 59.1%, and the pN_1N_2 5 year survival rate was 50.6%. These promising results are comparable with those of Asian randomized studies which demonstrate the possible value of IORT in the treatment of gastric adenocarcinoma.

Keywords: Gastric adenocarcinoma, Radiotherapy, Intraoperative radiation therapy.

MJIRI, Vol. 9, No. 3, 183-187, 1995.

INTRODUCTION

The overall 5 year survival rate for gastric adenocarcinoma remains extremely poor (5 to 10%); the main reason for this poor prognosis, according to autopsy findings, appears to be local treatment failures.[1]

In order to try to improve local control (and so the survival rate), we decided in 1985 to initiate a prospective non-randomized study using surgery, intraoperative radiation therapy (IORT) and postoperative external beam radiotherapy in the treatment of gastric adenocarcinoma.[2]

First described in 1907 by C. Beck in Germany,[3] IORT was then forgotten because of technological problems; in 1971, M.Abe in Japan[4] again described IORT using a linear accelerator and reported in 1985 very encouraging results in locally far advanced gastric carcinoma treated by surgery and IORT.[5]

IORT consists of direct irradiation of a tumor or of a tumor bed during a surgical procedure; it allows the delivery of a high dose of irradiation with excellent targetting, thereby providing good protection for normal surrounding tissues.

MATERIAL AND METHODS

From January 1986 to November 1993, 251 patients underwent the IORT procedure in our department. Fifty-one were included in our IORT protocol for gastric adenocarcinoma.

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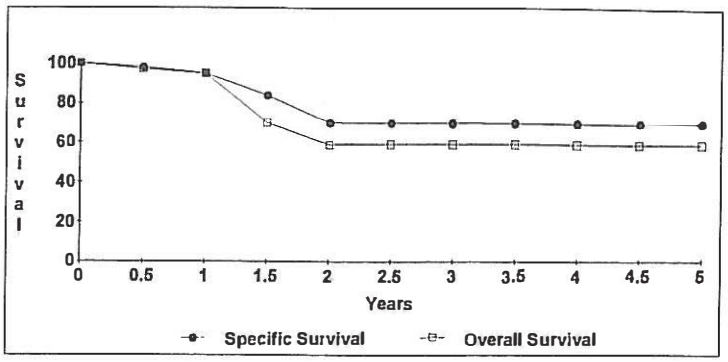


Fig. 1. Overall and specific survivals of gastric adenocarcinoma treated by surgery and IORT.

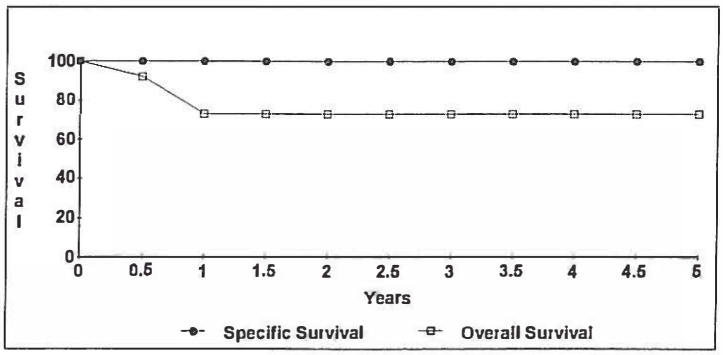


Fig. 2. Overall and specific survivals of pN_0 gastric adenocarcinoma treated by surgery and IORT.

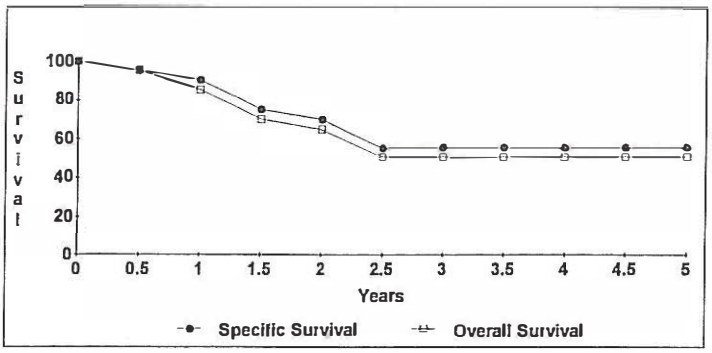


Fig. 3. Overall and specific survivals of pN_1N_2 gastric adenocarcinoma treated by surgery, IORT and external postoperative complementary irradiation.

IORT protocol

We used the Lyon Intraoperative System (LIS)[6] using a linear accelerator (Saturne 42) with 1cm thick altuglass collimation cones between the tumoral target and the accelerator.

Inclusion criteria were a) gastric adenocarcinoma histologically proven, b) patients without distant metastasis at the time of diagnosis, c) patients without previous oncologic disease, and d) patients with an OMS status of 0 to 2 regardless of age.

The LIS protocol was a) total or subtotal gastrectomy with R_2 lymph node dissection, b) IORT with linear accelerator using 12 to 15 Grays through 9 cm diameter collimation cones located on the celiac area, c) postoperative external beam irradiation of 44 Grays, 1 month after surgery, for patients with serosal erosion and/or lymph node involvement, and d) postoperative systemic chemotherapy when the age and status of the patient made it possible.

Patients

Fifty-one patients were included in the IORT study: 39 males and 12 females, mean age 61.7 years (S.D.= 14.7 years, range from 26 to 85 years). Forty-three patients underwent a total gastrectomy (9 with an extended total

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gastrectomy) while 8 underwent a subtotal gastrectomy. Concerning tumor localization, the angulus (n= 15), antrum (n= 14), upper part of the lesser curvature (n=5), pre-pyloric area (n= 5), greater curvature (n= 5), anterior face of the stomach (n= 3), the whole stomach (diffuse involvement) (n= 3) and the gastric stump (n= 1) were affected. Mean tumor size was 5.3 cm (S.D.= 1.9cm, range 1-12 cm). Histologic confirmation of adenocarcinoma was obtained for all patients; the histologic types were "well differentiated" (n=33), "poorly differentiated" (n= 12) and "undifferentiated" (n= 6). According to UICC staging, p TNM were 20 pN_0, 6 pN_1 and 25 pN_2 (Table I).

All patients underwent a curative resection of their tumor except for two patients with microscopic involvement of the duodenum discovered on histological examination.

Statistical analysis

Statistical analyses were performed on STATITCF software and survival rates were calculated by using the Kaplan Meier method.

RESULTS

Mean hospitalisation time of the patients was 11.5 days (S.D.= 2.4 days, range= 8-18 days).

The mortality rate was 2/51, with 1 myocardial infarction in a patient (pT_1N_0) without a previous cardiac history, and 1 case of hepatic failure in a patient (pT_2N_0) with a past history of alcoholism.

The morbidity rate was 3/51: 1 gastric fistula (treated by surgery), 1 evisceration on the 27th postoperative day (treated by surgery) and 1 case of severe esophagojejunal anastomosis edema on the 10th postoperative day which was treated medically.

A late complication was observed in a 54 year old man treated by total gastrectomy and IORT (15 Grays, 18 MeV) for a pT_1N_0 gastric adenocarcinoma; four months postoperatively, just after an endoscopic control (no evidence of disease), he died suddenly from massive hematemesis. No autopsy was performed.

The 5 year survival rate for pN_0 patients (Fig. 2) was 7% (5 year specific survival rate in this group was 100%, as 4 patients died from non-oncologic causes: car accidents, suicides, thoracic aorta aneurysm).

For pN_1 and pN_2 patients, the 2 year survival rate and the 5 year survival rate was 56.9% and 50.6%, respectively. In the pN_1N_2 group, 9 patients died: 7 during the first postoperative year (1 due to pulmonary metastasis, 1 due to diffuse hepatic metastases, 4 due to peritoneal carcinomatosis and 1 due to local anastomotic recurrence) and 2 during the second postoperative year (1 case of hepatic metastasis and 1 due to local recurrence in one of the patients who underwent a non-curative resection).

DISCUSSION

To date, more than 10,000 patients have been treated all over the world with IORT. The main technical discussion remaining today concerns using IORT alone (the method undertaken by Japanese and German teams) or as a boost in adjunction with postoperative external complementary irradiation (as undertaken by American and French teams). Concerning the radiobiological efficacy of irradiation, we think that IORT must be used as a boost on the tumoral bed after curative surgery in order to prevent local failures.

From a technical point of view, some differences exist between different teams (such as size and type of collimation cones, docking systems for collimation cones,...); however, all teams agree now on the use of electrons rather than X-rays for IORT– the good homogeneity of electron doses and the rapid decrement of the electron dose behind the target make electron beams ideal for IORT.[7]

All the feasability studies performed throughout the world clearly demonstrated that IORT does not increase the mortality and morbidity rates of gastric surgery.[8-12] No anesthetic accidents have been reported in the literature[13] and immunological and biological studies on patients after IORT never delineated any important consequences.[6,14] Main problems could be late complications as reported in some series: the one we observed in a pT_1N_0 patient with gastric adenocarcinoma who died four months postoperatively from a sudden and massive upper GI hemorrhage led

Table I. pTNM stages of the 51 patients included in the IORT protocol for gastric adenocarcinoma

	N_0	N_1	N_2	N+
T_1	5	1	0	6
T_2	7	2	5	14
T_3	8	3	19	30
T_4	0	0	1	1
Total	20	6	25	51

Table II. 5 year survival rate of gastric adenocarcinoma: randomized study of 211 patients (IORT of 28 to 35 Grays without external postoperative complementary irradiation). Adapted from Takahashi and Abe.[5,16]

	Surgery and IORT	Surgery alone
Stage I	87.2%	93.0%
Stage II	83.5%	61.8%
Stage III	62.3%	36.8%
Stage IV	14.7%	0%

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us to smoothly decrease our IORT doses.[15] Radiobiological experimentations have shown that a single IORT dose achieved a 3 times equivalent dose when compared with fractionated doses; we now use 12 to 13 Grays in IORT for gastric adenocarcinoma, even if a response of late complications to IORT is not strongly demonstrated.

As far as clinical results are concerned, the first randomized study reported in the literature was that of M. Abe.[5,16] Two-hundred eleven patients with gastric adenocarcinoma were randomized into 2 groups; surgery alone or surgery and IORT (30 Grays without external postoperative complementary irradiation); results strongly demonstrated the advantage of IORT, as an improvement of 20-25% was achieved for 5 year survival rates in stage II and III gastric carcinoma (Table II). Unfortunately, this series suffered some methodological mistakes (such as randomization according to the operation date of the patient), therefore the results obtained were not as encouraging as first believed.

Pilot studies undertaken in USA and Europe with IORT in gastric adenocarcinoma revealed promising results in patients with lymph node involvement.[17]

In our experience, historical control series were found to be scientifically incomparable with our's: however, we must emphasize that a 50.6% 5 year survival rate in pN_1N_2 gastric adenocarcinoma is a very encouraging result. The study we performed regarding causes of death in our IORT series showed that only 2 pN_1N_2 patients died from a local failure while the others died from distant metastases, on which local IORT is not able to achieve any control.

In Europe, 2 multi-institutional studies[18,19] are currently being carried out: one by the French Group of IORT (randomization surgery alone versus surgery, IORT and external postoperative complementary irradiation), and one by the Munchen University in Germany (randomization surgery alone versus surgery and IORT).

Finally, the main problem of IORT concerns its infrastructure: in order to perform IORT, it is necessary to have an irradiation room and an operative theatre located nearby one another, and to have experimental multi-disciplinary teams including radiotherapists, surgeons, radiophysicists, anesthesiologists and operative room nurses. The cost of IORT is heavy; a solution could be the Lyon Intraoperative System where an IORT installation is built in the city center and open to all surgical teams of the city.[7] In the near future, another solution could be the Mobetron, which is a mobile linear accelerator which could be used for IORT in a nonspecific operative theatre; this machine is actually undergoing a trial study in San Francisco.[20]

In conclusion, every new medical experience obtained in the field of oncology has shown that intensification of the irradiation doses within tolerance limits has always improved the local control of tumors; IORT probably follows the same rule and has its own place in the multi-disciplinary approaches of local and regional tumor treatment. Preliminary results observed with IORT in gastric adenocarcinoma demonstrate that improvements in local and regional control are possible; therefore we must further evaluate this particular approach for treating digestive tract cancers.

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