

Low dose preoperative and selective high dose postoperative radiation therapy for rectal cancer

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Abstract

Twenty six patients with adenocarcinoma of the rectum were entered in a program of adjuvant “sandwich irradiation” at Pramongkutkla hospital. All patients were given a single dose of preoperative radiation 500 cGy one day before surgery. After surgical staging, the patients who had diseases beyond stage B1 (modified Astler-Coller staging) would receive postoperative

radiation 4500-5400 cGy. Twenty one patients received full course of this treatment regimen, but only 16 patients could be followed up after completion of treatment. The mean follow up time was 35 months. The 2-year and 4-year Kaplan-Meier actuarial survival were 74% and 44% respectively. No severe treatment-related complication has been observed.

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การฉายรังสีปริมาณน้อยก่อนการผ่าตัดและการฉายรังสีหลังการผ่าตัด เมื่อมีข้อบ่งชี้ในมะเร็งลำไส้ใหญ่ส่วนปลาย

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บทคัดย่อ

ผู้ป่วยมะเร็งลำไส้ใหญ่ส่วนปลายจำนวน 26 ราย ได้รับการรักษาโดยการผ่าตัดร่วมกับฉายรังสีแบบ sandwich technique ที่โรงพยาบาลพระมงกุฎเกล้า ผู้ป่วยทุกรายได้รับการฉายแสง 500 cGy ใน 1 fraction หนึ่งวันก่อนผ่าตัด หลังจากทราบระยะของโรคจากการผ่าตัดแล้วผู้ป่วยที่มีระยะของโรคมากกว่าระยะ B1 (ตาม modified Astler - Coller staging) จะได้รับการฉายรังสีหลังผ่าตัด 4,500-5,400 cGy ผู้ป่วย 21 รายได้รับการรักษาตามแผนการรักษา แต่สามารถติดตามผู้ป่วยได้ 16 ราย หลังการรักษา ระยะเวลาเฉลี่ยในการติดตามผู้ป่วยประมาณ 35 เดือน อัตราการรอดชีวิตของผู้ป่วยที่ 2 และ 4 ปี (ตาม Kaplan-Meier survival) เป็น 74% และ 44% ตามลำดับ โดยไม่พบผลแทรกซ้อนที่รุนแรงจากการรักษา

Introduction

For rectal carcinoma, surgical resection is accepted as the initial treatment of choice for most patients(1). The objective is removal of the tumor and primary nodal drainage with as wide a margin around both as feasible. Adjuvant radiation therapy is becoming widely accepted as an effective therapeutic modality. The objective of adjuvant radiation therapy is to prevent the growth of cancer cells not removed at the time of surgery. Preoperative radiation treatment can inhibit the proliferation of such cells whether they remain local or spread outside the pelvis after therapy. Postoperative radiation treatment can effect only those cancer cells that remain within the volume exposed to radiation. By combining pre and postoperative irradiation (so-called "sandwich" technique), one could achieve the theoretical advantages of both. (1) The use of combined low dose preoperative (500 cGy) and selective high dose postoperative radiation treatment (4500-5400 cGy) has been utilized in the management of rectal cancer at Pramongkutkla hospital since 1987. This report presents the results of the "sandwich" irradiation technique in rectal cancer patients at our institution.

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Materials and Methods

The eligibility criteria were as follows: histologically proven adenocarcinoma of the rectum in operable stage, medically fit for surgery either by A-P resection (APR) or low anterior resection only (LAR) , ECOG performance status of 0,1 or 2, no evidence of liver metastasis on liver ultrasound, normal LFT and chest x-rays.

All patients who have met the above criteria would be treated by the schedule in Fig. 1.

From September 1987 to November 1993, a total of 26 patients with adenocarcinoma of the rectum were entered in a program of adjuvant "sandwich irradiation". All patients received a single dose of preoperative irradiation 500 cGy one day before surgery. After surgical staging, two patients who had stage A and B1 disease received no postoperative irradiation. Five patients who had stage more than B1 but did not receive postoperative irradiation or received only partial course of postoperative irradiation were excluded from the program. As a result, only 21 patients received full course of treatment and were included for final analysis. The characteristics of those 21 patients were shown in Table 2.

Irradiation technique

The preoperative irradiation was administered using parallel AP/PA treatment fields including whole pelvis (about 15x15 cm), 500 cGy single fraction, 24 hours before surgery.

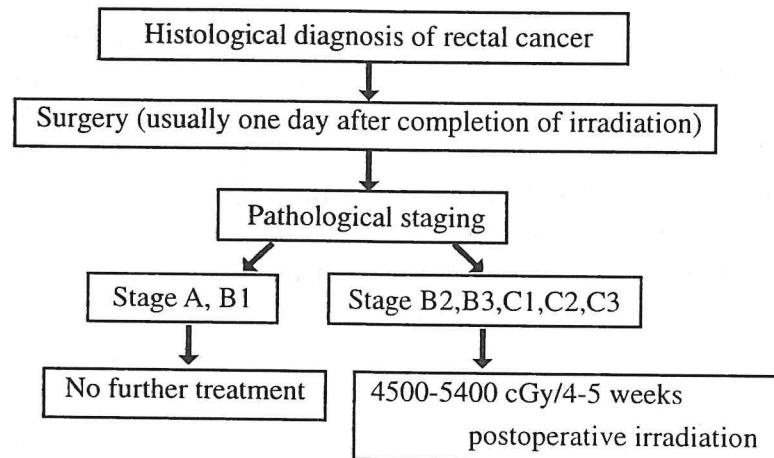
All postoperative irradiation treatments were started within 3-4 weeks

following surgery, using parallel AP/PA technique. (with colostomy block). The dose was 180-200 cGy / fraction, 5 days per week, for a total dose of 4500-5400 cGy depending on the decision of radiation oncologist. Megavoltage equipment with photon energy of 10 MV was used.

Results

Among the 21 patients, 6 cases were lost to follow up after completion of post-operative irradiation and was excluded from final analysis. The remaining 16 patients who came back for a follow up visit after completion of radiation treatment also received chemotherapy (5-FU) at the surgical department. The follow up period ranged from a minimum of 4 months to a maximum of 7 years after completion of postoperative irradiation. (mean follow up of 35 months) No severe radiation or surgical complication was detected.

According to the follow up record, 5 patients died. Two patients with stage C2 died from unknown cause. Residual tumor was noted in one case of stage D and the patient died at 1.5 year after surgery was done. Two patients with stage C2 had metastatic disease, one with bony metastasis died at 4 years, the other one with lung metastasis and recurrence at the primary site died at 1.5 year. The remaining 11 patients were alive without evidence of disease. The mean follow up time in this group was 2.5 years. The survival was calculated from the day of surgery. The 2-year and 4-year Kaplan-Meier actuarial survival were 74% and 44% respectively.

Fig.1 Scheme of Adjuvant “Sandwich irradiation” for rectal cancer**Table 1 Modified Astler - Coller staging**

A	Nodes negative; limited to mucosa
B1	Nodes negative; penetration into submucosa but not through muscularis propria
B2	Nodes negative; penetration through muscularis propria.
B3	Nodes negative; penetration through muscularis propria with adherence to or invasion of surrounding organs or structures.
C1	Stage B1 with nodes positive
C2	Stage B2 with nodes positive,
C3	Stage B3 with nodes positive.
D	Distant metastasis

Table 2 Patient Characteristics

Sex	Male : Female	12:9
Age (yr)		41-85 (mean = 55.12)
Tumor level (cm)	0-6	6 cases
	6	12 cases
	not specified	3 cases
Type of surgery	APR	17 cases
	LAR	2 cases
	Loop colostomy	2 cases
Stage	A	1 case
	B1	1 case
	B2	5 cases
	C1	1 case
	C2	9 cases
	C3	1 case
	D	2 cases
	Unknown	1 case

Discussion

The major reasons(2) given for preoperative radiation therapy have been the intent to reduce both the rate of extrapelvic metastases and pelvic recurrence from cancer cell released during resection; reduction the size of the primary tumor and regional node metastasis before resection; the lower likelihood of late radiation enteritis because the small bowel is less likely to be adherent in the pelvis; and the greater radiation responsiveness of normally oxygenated cancer cells relative to possible hypoxic cells in tissue in which vascularity has been altered by recent surgery.

For patients who have undergone incomplete tumor resection or apparently complete resection and have been found to have tumor extending into entire bowel wall, perirectal tissue or regional lymph node metastasis are those usually selected for postoperative adjuvant radiation treatment to prevent local recurrence of tumor.(2)

A program of "sandwich" adjuvant irradiation has been favored by those who wish to realize the theoretical benefits of low-dose preoperative radiation and to select those at higher risk by histopathologic stage for postoperative radiation treatment. (2)

In 1967, Nias suggested that low dose preoperative irradiation was the most advantageous procedure.(3) Although only a moderate degree of cell sterilization was obtained before operation, there was negligible disturbance of the surgical field and wound healing was not delayed. Immediate operation was possible and high dose radiation treatment could still be given

postoperatively if indicated. The lowest dose that would sterilize a useful proportion of cells was 500 cGy in a single fraction. (resulted in a 90-99% depopulation of oxygenated cells, 50% depopulation of anoxic cells, assuming that the cells disseminated at the time of operation were oxygenated). With such low dosage, there was no advantage to be gained by fractionation, and immediate surgery was desirable before there would be time for repopulation. Cells disseminated immediately after irradiation would possess the minimum reproductive capacity and there was another reason why it was so important to have a minimum delay between irradiation and operation.

In a randomized series of rectal cancer patients, Rider et al (4) found a statistical improvement in survival in patients with involved nodes who received 500 cGy in a single dose prior to surgery versus those treated with operation alone.

In 1975, the MRC trial protocol was designed to assess the effectiveness of low dose radiotherapy given before definite excision of operable carcinoma of the rectum. (5) There were 824 patients randomized to receive surgery alone, surgery plus a single fraction of 500 cGy and surgery plus 2000 cGy in 10 fraction over 2 weeks. They reported no evidence of an increased morbidity or mortality following irradiation. The 5 year survival, the local recurrence free survival and metastasis free rates did not show any significant difference among these 3 groups. (6) However, the authors still suggested that the patients with fixed or partially fixed cancer might benefit from preoperative

radiotherapy and survival of patients beyond five years in these patients would continue to be followed up. Anyhow, this study did not mention about postoperative irradiation which the patients would have gained a benefit in terms of reduction in the local recurrence and increase in survival.

In 1983, Gunderson et al, (7) reported the results of low dose preoperative irradiation 500 cGy in a single fraction and 1000cGy in 5 fractions and elective postoperative radiation treatment 4500-5000 cGy in 5 to 6 weeks in selected cases for resectable carcinoma of the rectum in 36 patients. Fifteen patients who had indications for postoperative irradiation had 4-year survival rate of 79%, with 4 patients subsequently relapsed. This regimen of treatment was well tolerated.

In 1990, Sause et al, reported the results of RTOG 81-15, ECOG 83-23 testing the efficacy of sandwich irradiation in rectal carcinoma. (8) The study compared between preoperative irradiation 500 cGy, 24 hours prior to surgery and no irradiation. Those patients with stage B2,B3 or C carcinoma underwent postoperative radiation treatment. The 304 analyzable cases were obtained and there appeared to be a trend towards improvement in locoregional control for patients in the stage B2-C3 group undergoing preoperative irradiation, but no difference in distant metastasis and survival was observed.

Lingareddy et al from Thomas Jefferson University Hospital reported long term result of "selective sandwich" adjunctive radiotherapy for cancer of the rectum in 1990. (9) One hundred and twenty patients with adenocarcinoma of the rectum were given a single dose of preoperative radia-

tion treatment 500 cGy and postoperative radiation treatment 4,500 cGy in 5 weeks for patients with stage B2 or C cancer. The treatment was well tolerated. The results for patients with stage B2 and C in terms of 5-year survival and local recurrence rates in the combined pre and postoperative irradiation group were better than those treated with either low dose preoperative radiation alone or postoperative radiation only.

Recent report about long term results of "selective sandwich" adjuvant radiotherapy for cancer of the rectum was shown by Mohiuddin et al in 1994. (10) They used a single dose of preoperative irradiation 500 cGy on the day of surgery or one day before surgery and postoperative irradiation 4500 cGy in 5 weeks for patients with stage B2 or C cancer in 54 patients. Local recurrence and 5 year survival were 9% and 72% respectively. Four percents of patients had major small bowel complications.

Summarizing from those reports, the benefit of low dose preoperative irradiation 500 cGy combined with selective postoperative irradiation was still controversial. Due to limited number of patients in our study, we could not interpret the true beneficial effect of the sandwich irradiation. Anyhow, we demonstrated that there was no severe complication from this combined modality treatment. Therefore, this regimen could be used safely to the patients who had the indication for combined treatment in rectal carcinoma. Strict patient selection criteria should be defined, preferably in a prospective randomized trial, to optimize the actual benefit of preoperative and postoperative radiation therapy.

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