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Result of Postoperative Radiotherapy of the Rectal Cancer

Moon June Cho, M.D., Sung Whan Ha, M.D., Charn Il Park, M.D.
Kuk Jin Choe, M.D.* and Jin Pok Kim, M.D.*

*Department of Therapeutic Radiology, Department of Surgery,**
College of Medicine, Seoul National University

To assess the effect of postoperative radiotherapy on tumor recurrence and patient survival, 133 patients who received adjuvant postoperative radiotherapy for adenocarcinoma of the rectum were retrospectively analyzed. Sixty-one percent of the patients were in stage C_2 by Astler-Coller staging system. A significant statistical difference was noticed in failure rates for lymph node negative vs lymph node positive patients; 26% (9/35) vs 50% (49/98). The incidence of local failure was found to be strongly dependent on the pathologic stages; with 9% (3/35) of recurrence in stage B and 21% (21/98) in stage C. Distant metastasis has occurred in 29% (38/133) of the patients; 2% (7/35) in stage B and 32% (31/98) in stage C. The actuarial survival at 3 years for patients in stage B_2, stage C_1, and stage C_2 were 78%, 47%, and 38%, respectively. In conclusion, the postoperative adjuvant radiotherapy for rectal carcinoma appears to reduce local recurrence significantly.

Key Words: Rectal cancer, Post-op radiotherapy.

INTRODUCTION

Adenocarcinoma of the rectum represents the seventh most common malignant tumor in Korea (3.5%). The majority of the lesions are found in the rectum[1]. The lower two-thirds of the rectum is surrounded by periadiopose tissues, and is a relatively fixed organ. In cases of penetration of the bowel wall, lymph node involvement, or venous invasion by tumors, the incidence of local recurrence is very high even after radical surgery[2].

A thirty to fifty percent of local recurrence rate after curative resection has been reported in rectal cancers penetrating through the bowel wall, with or without regional lymph node[2,3]. However, it has been suggested by various authors that postoperative adjuvant radiation therapy can dramatically reduce the risk of local recurrence[3,4]. As a consequence of sterilizing the residual microscopic tumors by radiation, it is hoped that the improved survival would ultimately be realized. This paper presents the results of postoperative radiotherapy in 133 patients treated at the Department of Therapeutic Radiology, Seoul National University Hospital during the 5-year period from March, 1979 to April, 1984. Part of the patients has been included in previous report[5].

MATERIALS AND METHODS

One hundred forty four patients with rectal cancer were referred for postoperative adjuvant radiotherapy after radical surgery during the 5-years from March, 1979 to April, 1984. Of these, 11 patients were excluded from this analysis because of incomplete treatment. As of May, 1986, all but 8 patients have been followed for more than 2-years or to the time of death.

The patients were classified postoperatively according to the modified Astler-Coller (AC) staging system[2].

The patients consisted of 78 males and 55 females. Their age ranged from 26-years to 75-years, with a median of 49. Of the 133 patients, 21 received low anterior resection, 105, abdominoperineal resection (Miles' operation), and 7, pull-through operation. According to the AC staging system, 81 patients were stage C_2; 17, C_1; 29, B_2; and 6, B_1, respectively (Table 1).

The histopathologic diagnosis was adenocarcinoma in all cases, and most of them were well-differentiated. Six patients with AC stage B_1 were treated postoperatively because of narrow distal resection margin or small number of dissected lymph nodes. All of these patients are clinically without evidence of disease (NED) until the time of analysis. These six patients are not dicussed further in this report except in the evaluation of treatment toxicity. In the remaining 127 patients, tumors penetrated through the bowel wall and/or lymph nodes were involved. In failure pattern analysis, B_2 and C_2 were subclassified; B_2 into B_2, and B_3, C_2 into C_2 and C_3, respectively[2].

The radiation therapy was started 3 to 4 weeks after curative resection, using 10 MV photon beam from a linear accelerator or gamma ray from Co-60 teletherapy unit. Radiation was given through AP and PA parallel opposed portals or AP, PA, and both lateral 4 portals.

Table 1. Patient Characteristics (N=133)

Characteristics	No. of patients	Percentage
Sex		
Male	78	59
Female	55	41
Age (years)		
Range	26 – 75	
Median	49	
Resection		
APR#	105	79
LAR##	21	16
Pull-through	7	5
Stage		
B_1	6	4
B_2	29	22
C_1	17	13
C_2	81	61

\# APR : Abdominoperineal resection
\## LAR : Low anterior resection

The superior border of the radiation field was mid L5. The inferior margin was determined by the tumor site and the surgical technique: after low anterior resection, the inferior border was determined with the intent of a minimum 3 to 5 cm margin below the anastomosis site, and after abdominoperineal resection (APR), the entire perineum was included. The lateral border of AP and PA portals was 1 to 1.5 cm lateral to the greater sciatic notch. Lateral fields sparing small bowell and bladder anteriorly and soft tissue and muscles posteriorly were also used. Five thousand rad was applied to this field over 5 to 6 weeks, 5 times a week. After APR for tumors located within 6 to 8 cm from anal verge, additional 800 to 1,000 rad was given in 4 to 5 fractions through direct perineal field[5].

Follow-up evaluation was done every 3 months. When histologic or cytologic evidence was not avaliable, evidences on chest X-ray, skeletal X-rays, pelvic CT, or liver scan and/or elevation of serum CEA were accepted as a proof of tumor recurrence. Perineal pain was also accepted as a evidence of recurrent disease if the pain had been preceded by a pain-free interval.

Survival was counted from the day of operation. Life-table method was used to calculate the survival rate[6]. Log rank test was used for comparision of pairs of survival rate[7].

RESULTS

Recurrence of rectal cancer was detected in 58

Table 2. Failure Pattern by Stage

Stage	No. of pts	LF (%)*	LF + DM (%)	DM (%) **	Total failure (%)	
B_2	26	2 (7.7)	1 (3.8)	6 (23.1)	9/26 (34.6)	9/29 (31.0)
B_3	3	–	–	–	0/3	
C_1	17	1 (5.9)	–	3 (17.6)	4/17 (23.5)	45/81 (55.6)
C_2	64	13 (20.3)	1 (1.6)	22 (34.3)	36/64 (56.3)	
C_3	17	4 (23.5)	2 (11.8)	3 (17.6)	9/17 (52.9)	
Total (%)	127	20/127 (15.7)	4/127 (3.1)	34/127 (26.8)	58/127 (45.7)	

* LF : Local failure
** DM : Distant metastasis

patients out of the 127 patients (46%). Of the 58 patients, 20 had local recurrences, 4 had local and distant recurrences, and 34 had distant metastases only as the first sign of recurrence (Table 2).

The overall failure rate was 31.0% for stage B_2 ($+B_3$), 23.5% for C_1, and 55.6% for stage C_2 ($+C_3$). The incidence of local failure was 10.3% for stage B_2 ($+B_3$), 5.9% for stage C_1, and 24.7% for stage C_2 ($+C_3$) (Table 2). The most common extra-abdomical site of recurrence was lung, followed by bone, supraclavicular lymph node (Table 3). These, compared to the previously reported data from our hospital, indicate increase of local control with postoperative adjuvant radiotherapy in advanced lesions (Table 4)[8~10].

Table 3. Initial Recurrence Pattern

Site of faliure	Stage B_2		Stage C	
Pelvis	3		21	
Intraabdominal	4		10	
Liver		3		7
Peritoneal seeding		1		3
Extraabdominal	6		28	
Lung		2		6
Bone		1		4
Lymph node #		2		4
Pericardium		0		2
Abdominal wall		0		2
Pleura		0		1
Kidney		0		1
Brain		0		1
Unspecified ##		1		7
Total	9/29*		49/98**	

* Two patients had concurrent failure in 2 sites.
** Eight patients had concurrent failure in 2 or more sites.
\# Supraclavicular, inguinal ## Elevated CEA

Acute or chronic reaction during or after postoperative radiotherapy was minimal; most of the reactions were mild or moderate and were easily controlled with conservative treatment. Of the 133 patients, only 7 needed a surgical intervention for small bowel obstruction.

The patient survival was strongly dependent on surgical stage: the actuarial 3-year survival was 78 % for stage B_2, 47% for stage C_1, and 39% for stage C_2. And the actuarial 3-year disease free survival was 68% for stage B_2, 51% for stage C_1, and 31% for stage C_2. The 3-year overall survival and disease free survival for the 127 patients of all stages were 50% and 43%, respectively (Fig. 1 and 2).

DISCUSSION

The rectum is a fixed structure anatomically surrounded by a fibrofatty networks in the lower two thirds and visceral organs in the upper and mid portions. It is located within the bony pelvis which limits the extent of possible resection. Once a lesion extends through the entire bowel wall, the surrounding tissues or structures are easily infiltrated and the extent becomes difficult to diagnose, and complete surgical removal becomes less achievable. As the number and the size of involved lymph nodes increase, a tumor extension through the nodal capsule into adjacent tissues is more probable and the complete operative removal becomes less likely. Recent studies have demonstrated local recurrence rates to be around 30% to 50% in such patients after curative resection[3,4]. In a series of studies that have analysed the cause of death after the curative resection, 50% to 60% of patients died of local recurrence[11]. The high incidence of local recurrence in rectal cancer after curative surgery may

Table 4. Comparison of Local Failure Rate by Treatment Modality

Stage	Surgery alone		Surgery + Radiotherapy	
	SNUH (%) #	MGH (%) ##	SNUH (%)	MGH (%) ###
$B_2 + B_3$	5/ 69 (7)	18/ 59 (31)	3/ 29 (10)	2/36 (6)
C	22/ 38 (58)	22/ 44 (50)	21/ 78 (21)	7/59 (12)
Total	27/107 (25)	40/103 (39)	24/127 (18)	9/95 (19)

\# From SW Kim, et al, 1985
\## From Gunderson LL, et al, 1983
\### From Gunderson LL, et al. 1985

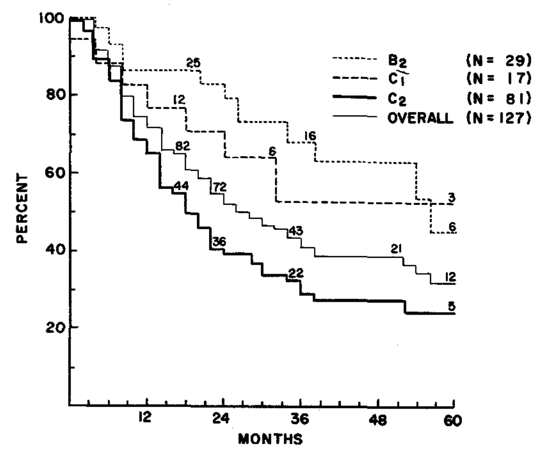

Fig. 1. Actuarial disease free survival by stage.

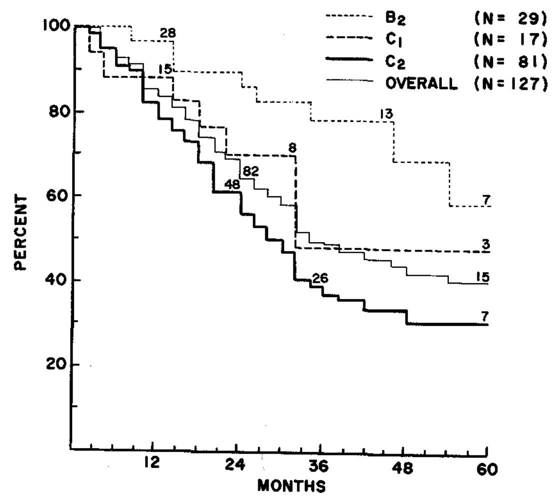

Fig. 2. Actuarial overall survival by stage.

be explained as follows: (1) the possibility of viable tumor cells remaining in local lymphatic channels, (2) tumor cells found in regional vascular channels, (3) cells liberated from the primary tumor during resection may be implanted into local tissues and serve as a nidus for recurrence[12].

The following factors are considered to influence the prognosis: the lymph node involvement, the number of involved lymph nodes, the depth of penetration of the bowel wall, the histologic grading, the location of the primary tumor, the involvement of adjacent organs or structures, preoperative carcinoembryonic antigen (CEA) levels, obstruction, perforation of bowel, and venous invasion[8,12]. Of these, the presence or absence of lymph node involvement and the depth of penetration of the bowel wall are considered to be the most important prognostic factors. AC staging system is based on these two factors, which is now widely accepted[2,13].

In the hope that, by inactivating subclinical disease in tumor bed or lymphatic tissue, the prevention of local recurrence and the prolongation of life would be achieved, adjuvant radiotherapy has been used for rectal cancers with surgery. This adjuvant radiotherapy can be given either preoperatively, postoperatively, or both. The possible advantages of preoperative radiotherapy are the followings: (1) there is no delay in administering the radiation as it might occur for postoperative patients due to wound healing, (2) following surgery, the small bowel may be at a greater risk, (3) hypoxic cells may be present after surgery, (4) there is no increase in surgical morbidity, (5) the delay of surgery does not compromise the patient's chance for cure, (6) there is a reduction of positive lymph nodes found at surgery, (7) there may be a reduction of viable malignant cells, (8) resectability may be increased, and (9) there is a possible reduction of local recurrence[14]. The main disadvantage of preoperative radiation is that a certain number of patients receive the treatment when they do not need it, since the pathologic stage can not be known before surgery. The delay in surgery is frequently pointed out as a problem, and chemotherapeutic agents can be tried to minimize the adverse effect of delay[15]. The possible reasons for using postoperative radiotherapy are as follows: (1) a small tumor volume is left behind, (2) an accurate staging is possible at surgery, thus those patients who need radiation therapy can be selected, (3) surgery is not delayed, (4) there are no radiation changes which might complicate certain surgical procedures[14]. On the other hand, the disadvantages of postoperative radiatherapy are: (1) possible spread of tumor at the time of surgery by manipulation, (2) possible interference with the blood supply by surgical procedure renders remaining cancer cells hypoxic, and (3) possible interference with small bowel mobility renders this organ more susceptible to damage by radiation[15]. Five thousand rad in 5 weeks, 5 days a week, is considered adequate to eradicate more than 90 percent of subclinical aggregates of cancer cells, though most of the data comes from clinical experiences with head and neck cancers and breast cancers[16,17]. In those patients with B_3 or C_3 stages, an additional 540 to 720 rad in 3 to 4 fractions through a reduced boost field to the tumor bed would be needed if small bowel can be excluded (a total of 5580-5760 rad in 6 to 6.5 weeks). This is because the number of remaining tumor cells can be bigger in these cases[9].

The incidence of perineal recurrence ranges from approximately 10% to 30% in surgical series[18,19]. The decision whether to include the perineum in radiation field is not easy to make. Most radiotherapist agree to radiate perineum when the tumor is located within 5 cm from anus, but there is controversy in radiating perineum in patients with tumors at higher location[20,21]. And a dose of 4,500 rad can be delivered to the perineal tissues with acceptable acute morbidity and no chronic morbidity[22]. Surgeons are now using sphincter sparing procedures with increasing frequency for patients whose lesions have an inferior extent within 5 to 8 cm of the anal verge. Some of the resulting anastomoses are at or near the anorectal junction, and the use of an inferior radiation margin 2 to 3 cm below the anastomosis can result in inclusion of the perineum even in patients with low anterior resection.

The incidence of severe actue or chronic toxicity of postoperative adjuvant radiation therpy is usually minimal. Most of the reaction is mild or moderate and can be easily controlled with conservative management. With doses in the range of 4,500 to 5,000 rad in 5 to 6 weeks, a small bowel adhesion requiring operative intervention has been reported to occur in approximately 5 to 10% of the patients. And this is not higher than the incidence of 2 to 15% in the patients having sugery alone[8,9,12,14]. In the present study, 5% of patients showed small bowel obstruction requiring operative intervention. Both the surgeons and the radiation therapists have to be somewhat innovative if small bowel radiation enteritis is to be avoided or minimized. To keep the small bowel out of the pelvis, retroperitionealization often combined with retroversion of retained uterus or the use of an omental flap to fill the pelvis occasionally eliminates small bowel radiation damages. Leaving clips within the pelvis, particularly at the high risk are, allows radiation fields to be shaped. A dose of 4,000 rad is usually well tolerated by small bowel, but from the adjuvant treatment point of view, the tumor bed itself should be treated with at least 4, 500 rad and preferably 5,000 rad. If the highest risk area is appropriately marked by the surgeon, the radiation therapist can reduce the field size dramatically for boosting purposes. The use of carefully shaped fields in pelvis with patient in prone position and often with distended bladder will reduce the small bowel radiation even further. Small bowel barium study can be done on patients at the time of simulation to define the mobility and position of the small bowel[23].

Adjuvant preoperative and postoperative radiation therapy (the sandwitch technique) was attempted to combine the best features of of pre- and postoperative radiation therapy and hopefully minimize the disadvantages of each therapy. A large single dose of radiation (500 rad) is given preoperatively either on the day of or the day before the surgery in an attempt to sterilize well oxygenated tumor cells that might either be implanted locally at the time of surgery or be dislodged to distant sites. A single dose of this type of radiation given in such close proximity to surgery is not expected to alter the histologic findings, thus the surgical staging would be unchanged. The high-risk patients may be selected for full dose (4,500 rad) radiation postoperatively[15].

In Thomas Jefferson University Hospital, 31 patients received the sandwitch approach with a total treatment failure rate of only 20%, compared to 83% for the concurrently treated surgery controls, and 59% for the group that received postoperative radiation therapy only. Only two patients (7%) sustained a local recurrence, the actuarial five-year survival was 78% compared to 10% for the surgery only group. The incidence of complication was not high; 7% of small bowel obstruction compared to 5% for the surgery alone patients[24]. These results seem somewhat better than the results of postoperative radiation therapy alone from the same institution. Since the number of patients treated with the sandwitch technique is small, it is hard to make a meaningful comparison. Randomized trials requiring multi-institutional participation is undoubtedly necessary to resolve this issue.

Recently combined chemotherapy and radiotherapy was studied by the Gastrointestinal Tumor Study Group. The chemotherapy and radiotherapy group have shown a statistically significant longer disease-free interval than did the surgery only group. But, considerable toxicity (35%) developed in the group receiving combined radiotherapy and chemotherapy[25]. A large group of patients receiving combined radiotherapy and chemotherapy as postoperative adjuvants with a longer follow-up period and comparison with a control group is needed to establish whether this approach significantly improves the disease-free interval with an acceptable degree of toxicity. At present, well-deviced combinations of surgery and radiation offer the best hope of cure in patients with the rectal cancers with extension through the bowel wall and/or nodal involvement.

CONCLUSION

A retrospective analysis was done for 133 patients who were referred for radiotherapy after curative srugery of adenocarcinoma of the rectum during the period of March, 1979 to April, 1984. They were given postoperative adjuvant radiotherapy at the Department of Therapeutic Radiology, Seoul National University Hospital.

The results are as follows:

1) The incidences of local failure were 10% for stage B_2+B_3, 6% for stage C_1, and 25% for stage C_2+C_3.

2) Three-year disease free survival rates were 68% for stage B_2+B_3, 51% for stage C_1, and 31% for stage C_2+C_3.

3) Actuarial 3-year survival rates were 78% for stage B_2+B_3, 47% for stage C_1, and 39% for stage C_2+C_3.

4) In 7 (5%) out of 133 patients, a surgical intervention was required for small bowel obstruction.

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＝국문초록＝

직장암의 수술후 방사선치료 성적

서울대학교 의과대학 치료방사선과학교실

조문준 · 하성환 · 박찬일

외 과 학 교 실

최 국 진 · 김 진 복

직장암은 한국인에서 발생하는 악성종양 중 7번째로 빈번한 종양이며, 그 해부학적 구조상 근치적 절제술이 비교적 어려운 것으로 되어 있어 수술후 상당수에서 국소적인 재발이 발생한다.

수술후 방사선치료를 병용하여 국소재발율이 현저히 저하되는 것으로 알려졌으며 나아가서 생존률의 향상을 기대하고 있다.

저자들은 1979년 3월부터 1984년 4월까지 서울대학병원 치료방사선과에서 직장암으로 근치적 수술후 방사선치료를 받은 133명의 환자들을 대상으로 다음과 같은 성적을 얻었다.

1) 국소재발율은 B_2+B_3가 10%, C_1이 6%, C_2+C_3가 25%였다.
2) 3년 무병 생존율은 B_2+B_3가 68%, C_1이 51%, C_2+C_3가 25%였다.
3) Life-table 방식에 의한 3년 생존율은 B_2+B_3가 78%, C_1이 47%, C_2+C_3가 39%였다.
4) 133명중 7명에서 수술이 필요한 정도의 장폐쇄 증상이 있었다.