

The Role of Radiation Therapy on Local Recurrence of Rectal Cancer

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Ninety five patients of rectal cancer treated with surgery with or without adjuvant radiation therapy since January 1982 to December 1990 at the Chonnam University Hospital were analysed retrospectively regarding local failure. Of these 95 patients 72 patients were treated with surgery alone and remaining 23 patients received postoperative radiation therapy to pelvis. There were 45 men and 50 women with 53 years of median age. Minimum follow-up period was 19 months and median was 47 months (range, 19-125 months). Kaplan-Meier method was used to calculate actuarial risk of local recurrence and survival rate. Comparison between two groups was evaluated by Log rank test.

Of total 95 patients twenty seven patients (28.4%) developed local recurrence and 13 patients (17.3%) developed local and distant metastasis concomitantly. Eighty nine percent (24/27) of patients developed local recurrence within 24 months. Pelvic organ adjacent to the primary tumor area was the most common site of initial local recurrence.

Of 72 patients treated with surgery alone local recurrence developed in 24 patients. Of 17 patients with stage A and B1 (Gunderson-Sosin modification of Dukes' staging system) 6 patients experienced local recurrence (31.2%). The local recurrence rate of B2 and B3 group was 29.9% (7/33) and that of C2 and C3 was 54.7% (11/19), respectively. There was statistically significant difference between two groups ($p < 0.05$). Of 23 patients treated with definitive surgery and radiation therapy 10% (1/10) recurred in B2 and B3 patients. This was slightly lower than C2 and C3 patients (22.2%, 2/10) of similar policy, but revealed no statistically significant difference ($p > 0.05$). In the patients of B2+3 local failure rate decreased when radiation therapy was added (29.9% vs 10%, $p > 0.05$) and also similar results in C2+3 group (34.7% vs 22.2%, $p < 0.05$). The local failure rate in relation to distance from the anal verge had no statistically significant difference.

Key Words: Rectal cancer, Radiation therapy, Local control

1982 and December 1990.

INTRODUCTION

Recently many series have shown that surgery alone may be inadequate treatment for rectal and rectosigmoid cancers that extend through the entire bowel wall with or without involvement of lymph node¹⁻⁶. Because of the known high incidence of local failure in patients with Stage B2 and C rectal tumors, a number of groups have shown an interest in evaluating adjuvant radiation therapy combined with surgical correction⁷.

To evaluate the relative role of the postoperative pelvic radiation therapy on local control, a study was performed retrospectively to a group of 95 patients with carcinomas of the rectum and rectosigmoid who were treated with surgery alone or surgery with postoperative radiation therapy at the Chonnam University Hospital between January

MATERIALS AND METHODS

During the 9 years period since January 1982 to December 1990 one hundred and thirty one patients of rectal cancer had been treated with surgery alone or surgery and postoperative adjuvant radiation therapy at the Chonnam University Hospital. Those with palliative surgery (30 patients) or metastatic lesions found at surgery (6 patients) were excluded in this analysis, and 95 patients with curative surgery including 23 patients who received adjuvant radiation therapy to pelvis were analysed. All patients except one who received local tumor excision with stage A disease had radical surgery. Abdominoperineal resection was performed in 50 patients (52.6%), low anterior resection in 34 patients (35.8%) and anterior resection in 10 patients

(10.5%). There were 45 men (47.4%) and 50 women (52.6%). Median age of patients was 53 years and most common in sixth decade (range, 19-75 years). Most of patients (92.6%) revealed adenocarcinoma in their histologic type. The Stage of rectal cancer was reevaluated by Gunderson-Sosin modification of the Dukes' staging system⁸⁾ based on surgical pathologic findings. Patients with Stage B disease had negative lymph node with Stage B1 disease limited to the bowel wall, B2 with extension through the bowel wall into the preirectal fat, and Stage B3 having tumor adherence or fixation to adjacent structure.

Postoperative adjuvant radiation therapy was performed in 23 patients staged above B2. Radiation therapy began after surgical wound healed and median time interval was 33 days ranging from 17 to 301 days. Lesions of 45 patients (47.4%) located in the rectum within 5 cm from the anal verge, those of

42 patients from 6 to 11 cm and remaining 8 patients above 12 cm (Table 1). All patients were treated with 6 MV or 10 MV X-ray produced by linear accelerator. Whole pelvis was irradiated by anterior and posterior portals in 19 patients, by four fields "box" technique in 3 patients and by 3 portals with prone position in 1 patient. The superior border of the whole pelvis field was at upper border of fifth lumbar vertebral body and lateral margin was within 2 cm from pelvic brim laterally. The inferior margin was usually designed to cover the obturator foramen and was extended in order to include perineum fully in patients who received abdominoperineal resection. When using the lateral portal anterior border was designed to cover obturator lymph node, and posterior border covered sacrum fully. The radiation dose to whole pelvis was prescribed at mid-plane in anterior-posterior portals and box technique up to 5040 cGy in 20 patients with daily 180 cGy and five times per week. Five patients of abdominoperineal resection received additional 900 cGy to perineum by 6 MV photon or electron beam.

This analysis was performed on August 1992. The base of follow up was on the date of operation. Minimum follow up period was 19 months and median was 47 months (range, 19-125 months). Seventy five (78.9%) patients were completely followed up more than 19 months or died of disease from the date of operation. Kaplan-Meier method was used to calculate actuarial local recurrence rate and survival rate. Log-rank test was used to compare survival data between two groups.

RESULTS

Of 72 patients treated with surgery alone 24 developed local recurrence, 31.2% (6/17) in stage A and B1, 29.9% (7/33) in B2 and B3, 54.7% (11/19) in C2 and C3 respectively and there was statistically significant difference ($p < 0.05$) on local recurrence between the group of B2+3 and C2+3. All recurrence developed within 24 months except three who recurred at 25, 28, 39 months respectively. Of 23 patients treated with definitive surgery and postoperative adjuvant radiotherapy 10% (1/10) recurred in B2+3 and 22.2% (2/10) in patients of C2+3, but revealed no statistical significance (Table 2)(Fig. 1). In the patients of B2+3 local failure rate was decreased to 10% when radiation therapy was added ($p > 0.05$) and also in the patients of C2+3 local failure rate was decreased

Table 1. Patient Characteristics

Characteristics	No. of Patients (%)
Sex	
Male	45 (47.4)
Female	50 (52.6)
Age	
Range	19-75
Median	53
Histology	
Adenocarcinoma	88 (92.6)
well differentiated	46
moderately differentiated	15
poorly differentiated	4
not specified	23
Mucinous	5
Signet ring	1
Adenosquamous	1
Stage*	
A+B1	17
B2+3	43
C1	6
C2+C3	29
Operation	
Abdominoperineal resection	50 (52.6)
Low anterior resection	34 (35.8)
Anterior resection	10 (10.5)
Local excision	1 (1.0)
Tumor location (cm)*	
-5	45
6-11	42
12-	8

*Gunderson-Sosin modification of Dukes' staging system

*Distal margin of tumor from anal verge.

Table 2. Local Failure by Stage

Stage	No. of Patients (%)	
	S	S+R
A+B1	6/17 (31.2)	
B2+3	7/33 (29.9)	1/10 (10.0)
C1	0/ 3 (0.0)	0/ 3(0.0)
C2+3	11/19 (54.7)	2/10 (22.2)

S: surgery, S+R: surgery plus radiation

when the radiation therapy was followed postoperatively ($p < 0.05$). Overall local failure rate of B2+3 and C2+3 was 33.2% in surgery alone group and decreased to 24.3% in patients with post operative radiation therapy ($p > 0.05$). We calculated 3 year actuarial disease free survival rate. In the patients of B2+3 disease free survival rate was 74.9% (26/33) with surgery alone and 64% (7/10) when using the

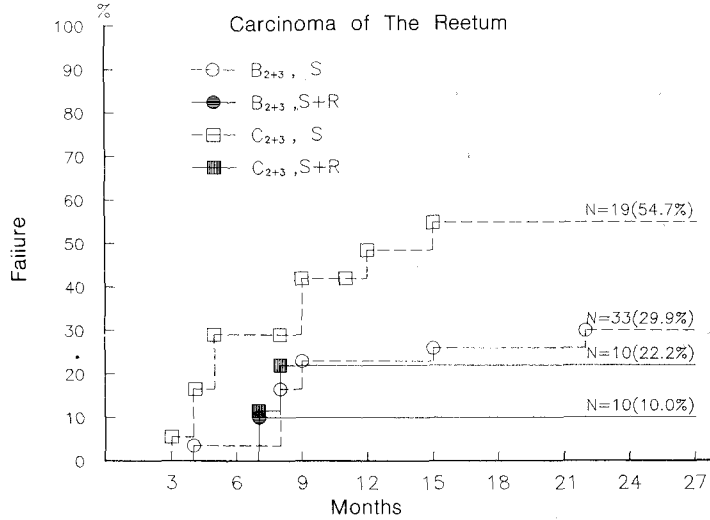


Fig. 1. Actuarial 2 year local failure rate (S; Surgery, S+R; Surgery plus radiation)

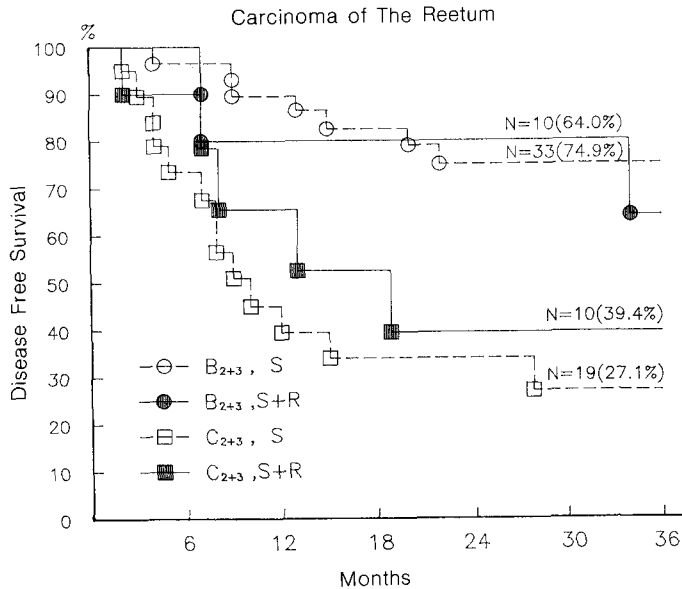


Fig. 2. Actuarial 3 year disease free survival rate (S; Surgery, S+R; Surgery plus radiation).

postoperative radiation therapy ($p > 0.05$). In the patients of C2+3 disease free survival rate was 27.1% (6/19) with surgery alone and 39.4% (5/10) with surgery and radiation ($p > 0.05$)(Fig. 2). We analysed the local failure rate in relation to location of rectal lesion. Of 45 patients with lesions within 5 cm from anal verge 15 patients (37.5%) experienced local recurrence, and 11 (26.2%) of 42 patients with lesions 6 to 11 cm and 1 of 8 (12.5%) patients with lesions more than 12 cm developed local recurrence (Table 3). There was no statisti-

Table 3. Local Failure by Tumor Location

Tumor Location	No. of Patients	
	S	S+R
- 5	14/33	1/12
6-11	9/32	2/10
12-	1/ 7	0/ 1

Table 4. Site of Locoregional Recurrence

Sites	Number of Patients	
	S	S+R
Perineum	7	0
Pelvic organ	13	2
pelvic lymph node	1	1
Anastomosis	3	0

cally significant difference on local recurrence according to the distance of lesion from anal verge. Thirteen patients experienced local and distant recurrence concomitantly.

Actuarial survival rate at 3 years was calculated by Kaplan-Meier method and resulted that 71.1% in A+B1, 72% in B2+3 and 66.9% in C2+3 respectively in surgery alone group. Three year survival rate was 60%, 47.6% in B2+B3 and C2+C3 respectively in pateints with adjuvant radiation therapy ($p > 0.05$)(Fig. 3).

Locoregional recurrence occurred most frequently in pelvic organ (15/95) and secondly in perineum (7/95). Three patients developed local recurrence in anastomotic site and 2 patients in pelvic lymph node (Table 4). In our series distant metastases occurred more frequently in C2+3 patients and in surgery alone group (Table 5). And also distant metastases developed most frequently

Table 5. Distant Metastases by Stage

Stage	No. of Patients	
	S	S+R
A+B1	2/17	
B2+3	2/33	2/10
C1	0/ 3	1/ 3
C2+3	11/19	4/10

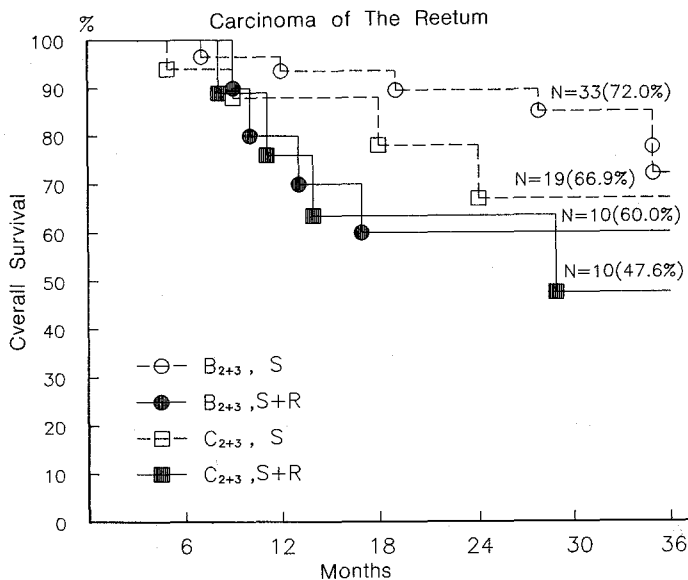


Fig. 3. Actuarial 3 year overall survival rate (S; Surgery, S+R; Surgery plus radiation).

Table 6. Site of Distant Metastases

Sites	No. of Patients		Total
	S	S+R	
Distant lymph node	7	3	10
Liver	2	5	7
Abdomen	3	2	5
Peritoneum	0	4	4
Lung	2	1	3
Bone	0	1	1

in distant lymph node (Table 6).

DISCUSSION

In rectal cancer local failure rate have ranged between 20% and 70% for patients undergoing surgical resection alone for tumors extending through the entire bowel wall and/or pelvic lymph node^{6,8-11}). Gunderson et al⁸) have reported on the failure patterns in the reoperation series from the University of Minnesota. There were 17 patients with Stage C1 disease with 4 local failure (24%). Of 40 patients with Stage C2 and C3 disease, 33 (83%) had local failure. Interestingly 44% of patients with tumor recurrence had local failure as the only site of failure, whereas only 1 patient had distant metastases. Gilbert⁹) from the Maine Medical Center has analyzed patient morbidity from tumor recurrence after surgery alone. Sixty-eight percent of the patients who failed had symptoms related almost entirely to the pelvic recurrence, and additional 1% of patients had symptoms from both local and distant metastases, and 20% of patients had symptoms primarily from metastases. Thus, pelvic recurrence is the major cause of morbidity in patients treated only with Surgery for rectal cancer, and a decrease in the incidence would be of great value.

Improvement in local control when resection was combined with radiotherapy with or without chemotherapy has been reported in many series^{5-7,12,13}). Many reports deal with the value of postoperative adjuvant radiotherapy. Data published from UT M.D. Anderson Hospital^{4,14}) and Latter Day Saints Hospital¹⁵) demonstrated that local recurrence decreased from expected 37~48% with the Surgery alone, to 6~8% in patients receiving adjuvant radiotherapy for the Stages B2, B3, C1, C2 and C3. Hoskins et al⁶) reported that for Stage B2 with gross tumor extension through the entire bowel wall and Stage B3 a decrease of local recurrence rate from 34% with surgery alone to 3%

for combined treatment. For Stage C1, C2 and C3 he reported a rate of 50% after surgery alone to 12% with addition of radiation. Tepper et al⁷) compared the treatment results of patients from the MGH with rectal cancer treated with surgery alone previously with that of the addition of postoperative radiation therapy and resulted that there was a substantial decrease in the incidence of local failure. Local control was improved in Stage B2 patients from 77% with surgery alone to 91% with surgery plus radiation therapy. In patients with Stage C2 disease, local control was improved from 53% to 79% with the addition of adjuvant irradiation. This was associated with an improvement in survival with 5 year NED rate improving from 47% to 76% in patients with Stage B2 disease and from 27% to 34% in patients with Stage C2 tumor. It is of note that this improvement in local control and survival was produced with no detectable increase in late severe complication. Tepper and associates' series⁷) reported local failure rate as 9% (5/53) in B2 patients and was similar to 10% (1/10) in B2 plus B3 of this study. According to Schild et al¹⁶) 6(18%) of 33 recurred locally and explained this different result would be due to irradiation. In Tepper et al series⁷) the perineum was routinely included in the irradiation fields after CAPR and only 1 (2%) of these 60 patients had local failure in the perineum. In Schild et al's report¹⁶) 3 of 6 local failure of Mac B2 patients occurred in the perineum after CAPR with inadequate perineal coverage. In our study 1 of 10 (10%) local recurrence was noted in B2+3 group with adjuvant radiation therapy and 7 of 33(21.2%) patients recurred with surgery alone group of B2+3. 3 of 7 recurrence developed in perineum after abdominoperineal resection, 2 of 7 recurred in pelvic organ (1 after APR, 1 after LAR), 1 of 7 recurred in pelvic lymph node after LAR and 1 in anastomosis after LAR. Overall the local failure incidence in node positive patients (C1, C2, C3) was 22% in Schild et al's series¹⁶), 21% in Tepper et al's series⁷). In this series actuarial local failure rate of Stage C2+3 with surgery alone group was 54.7% at 2 years and 22.2% in patients treated with adjuvant radiation therapy. There was actual decrease in local failure after postoperative adjuvant radiation therapy. This result was similar to Schild et al's series. Among 6 patients of C1 group (3; surgery alone, 3; surgery plus radiation) no one experienced local recurrence. Among 8 patients of C3 (4; surgery alone, 4; surgery plus radiation) 1 recurrence was noted in perineum after abdominoperineal resection without radiation. 4

patients who received all abdominoperineal resection and adjuvant radiation therapy had no local failure.

In the GITSG randomized study⁵⁾, surgery alone was compared to adjuvant XRT +/- chemotherapy, the incidence of local failure in the pelvis was 20% (10/50) while local failure was decreased to only 11% for those with combined modality treatment (XRT+5 FU and Methyl CCNU). In the GITSG study, 81% (77/96) received radiotherapy dose below 46 Gy. The local failure rate for patients treated with dose below 46 Gy was 14.3% (11 of 77) and 21.1% (4 of 19) failed when slightly higher doses were used. Schild et al¹⁷⁾ reported that if only initial sites of failure are counted 22 (16%) of the 139 patients would be considered to have had local failures. In that series patients were in high risk of local recurrence (Stage B2, B3, C1, C2, C3) and treated with complete surgical resection followed by radiation and chemotherapy. In the Mayo-NCTG trial¹²⁾ both initial and subsequent sites of failure were reported. Local failure occurred in 20% of those treated with adjuvant radiotherapy and in 11% of those treated with adjuvant irradiation and chemotherapy ($p < 0.05$). It is possible that uncontrolled selection factor resulted in a failure of the analysis to detect a significant association between the use of chemotherapy and improved local control. In our study most of patients were treated with chemotherapy at least one cycle of ACNU plus 5FU regimen. Because of irregular number of chemotherapy schedules and variable regimens we could not analyze its effect on local control in this time. In the future further evaluation is needed about the impact of chemotherapy.

Rich et al¹⁰⁾ demonstrated that the incidence of local failure after surgery alone is strongly dependent on pathology staging; 17% of patients without lymph node metastases but with microinvasive extension through the bowel wall (MAC-B2m) experienced local recurrence. A larger percentage (54%) had local recurrence when the tumor was adherent to or was invading adjacent organs and structures (MAC B3). Similarly, the risk of pelvic disease recurrence increased from 36% of MAC-C1/C2m to 67% of MAC C-3 when nodes are involved¹⁰⁾. In our series 29.9% of B2+3 patients with surgery alone had recurrence and 54.7% of C2+3 patients. This difference by Stage was statistically significant.

Brizel and Tepperman¹⁸⁾ reported a dose response effect in the adjuvant setting with a significant increase in local control with dose above 45 Gy:

50% of those receiving < 45 Gy had pelvic relapse compared with 10% of those receiving above 45 Gy. In our study 23 patients received postoperative radiation therapy and received 50.4 Gy in 20 patients. So we think that total dose delivered to whole pelvis would not affect local control significantly. 5 patients who received abdominoperineal resection had boost irradiation to perineum additional 900 cGy by 6 MV photon or electron beam. The radiation doses used in this study are higher, in general, than those used in the GITSG study and equivalent to the dose used in most non-randomized studies.

The importance of treating the perineum following APR has been emphasized by Thomas et al¹⁹⁾ and many studies^{2,8,20)} show that such recurrence is a frequent event in the natural history of this tumor. Ciatto et al²⁰⁾ reported a perineal recurrence rate of 36% in 39 of 108 patients treated with abdominoperineal resection or low anterior resection. Furthermore, in 13 of 39 patients, the perineum was the only site of recurrence.

Vigliotti et al¹³⁾ of M.D. Anderson Hospital shows about half the patients with recurrence (7 of 15) received perineal boost where the dose of irradiation at the tumor recurrence was below 50 Gy. If all patients treated with a perineal boost are excluded from analysis of failure then the rate of local recurrence is still unacceptably high at 17% (8 of 48). They no longer use the perineal boost at M.D. Anderson Hospital and all patients are treated to dose above 50 Gy in an attempt to reduce the incidence of local recurrence. They recommend that the perineum be included in the primary treatment volume and in the boost for lesions treated with abdominoperineal resection. The perineal skin and drain site should receive the full irradiation dose in the first course of treatment to 45 Gy but can be excluded from the boost volume. In our study perineal recurrence occurred in 7 patients (7/27, 25.9%) who were treated surgery alone, but no one observed in postoperative radiation group. This would be result of routine inclusion of perineum to radiation port up to 5040 cGy in case of abdominoperineal resection.

SUMMARY

There was decrease on local recurrence with postoperative radiation therapy in rectal cancer Stage B2+3 ($p > 0.05$) and C2+3 ($p < 0.05$). Postoperative radiation therapy increased disease free survival rate at 3 years in B2+3 and C2+3, but had

no statistical significance. Regarding overall survival rate at 3 years more decreased result was observed in radiation group, but had no statistical significance. In the future further study is needed with more longer follow-up period and adequate number of patients included in radiation group.

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≡ 국문초록 ≡

직장암에서 수술후 방사선치료의 역할

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1982년 1월 부터 1990년 12월까지 전남대학교 병원에서 치료를 받은 95 명의 직장암 환자를 대상으로 국소종양제어에 대한 수술후 방사선 치료의 역할을 알아보기 위하여 후향적 분석을 시행하였다. 95 명의 환자중 72 명은 수술만 받았으며 나머지 23 명은 수술후 방사선 치료를 함께 받았다. 환자의 성별 분포는 남자가 45명 여자가 50 명으로 비슷하였으며 연령의 중앙치는 53 세였다. 최소 추적기간은 19 개월(범위 : 19~125)이었으며 중앙치는 47 개월이었다. 종양의 국소재발율과 생존율은 Kaplan-Meier 법으로 계산하였으며 두 군간의 비교는 Log-rank test에 의하였다.

전체 95 명의 환자중 27 명(28.4%)에서 국소 종양의 재발이 관찰되었으며 13 명(17.3%)에서는 원격 전이가 동시에 관찰되었다. 국소 종양 재발이 관찰된 27 명중 24 명(89%)이 수술 후 24 개월이내에 재발되었으며 부위는 원발 병소 주위의 골반강내 조직에 가장 흔하였다.

수술만 받은 72 명의 환자중 24 명에서 국소 재발이 관찰되었다. 병기 A와 B1의 17 명중 6 명에서, B2와 B3 33 명중 7명(29.9%)에서, C2와 C3 19 명중 11 명(54.7%)에서 각각 재발되었으며 병기에 따른 재발율의 차이는 통계학적 의의가 있었다($p < 0.05$). 수술 후 방사선 치료를 받은 23 명의 환자중 병기 B2와 B3 10 명중 1명(10%)에서, 병기 C2와 C3 10 명중 2명(22.2%)에서 재발이 관찰되었으며 두 군간의 차이는 통계학적 의의가 없었다($p > 0.05$). 한편 병기 B2 와 B3 에서 수술 후 방사선 치료를 시행하지 않은 군 보다 시행한 군에서 국소 종양 재발율이 낮았으나 통계학적 의의를 갖지 못하였으며(29.9% vs 10.0%, $p > 0.05$), 병기 C2와 C3의 경우는 수술 후 방사선 치료를 시행한 군에서 종양의 재발이 낮았으며 통계학적 의의가 있었다(34.7% vs 22.2%, $p < 0.05$).