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Long-Term Results of High-Dose Extracorporeal and Endocavitary Radiation Therapy Followed by Abdominoperineal Resection for Distal Rectal Cancer

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Abstract

Purpose. To examine the complications, local effects, survival, and prognostic factors of preoperative high-dose radiation therapy in patients with advanced carcinomas of the distal rectum.

Methods. Forty-one patients with tethered or fixed rectal cancer located a median distance of 3.0 cm from the anal verge were treated with extracorporeal and endocavitary radiation therapy (70 Gy), followed 2 weeks later by abdominoperineal resection (APR).

Results. This combined radiotherapy achieved acceptable results. Postoperative complications developed in 18 patients (43.9%), 10 (24.3%) of which involved perineal dehiscence. Two patients (4.8%) suffered more than grade 3 toxicity. Destructive changes were histologically confirmed in all specimens, and there were four (9.8%) sterile specimens. Recurrence developed in 11 patients and there were 6 cancer-related deaths. Among six cases of local recurrence, three were found just outside of the radiation field. The 5-year survival and disease-free survival rates were 82.9% and 71.8%, respectively. Multivariate analysis revealed that nodal involvement was the sole independent prognostic factor for survival. Sexual function was maintained in the most recent patients who underwent APR with autonomic nerve-preserving surgery.

Conclusion. Although the original aim of our treatment focused on curability, this combination therapy may be an option for selected patients, because of potential prevention of local recurrence, relatively low morbidity, and promising autonomic nerve function.

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Key words Distal rectal cancer · Preoperative radiotherapy · Endocavitary irradiation

Introduction

Locally advanced carcinoma in the distal rectum remains a surgical challenge and is associated with a grim prognosis. The treatment of advanced carcinomas in the distal rectum is made problematic by the facts that lateral nodes are potentially involved in spreading microscopic tumor cells based on the anatomical location of the cancer,[1,2] local recurrence develops after curative surgery,[3] and abdominoperineal resection (APR) of the rectum may be the only surgical option for curative surgery.

Recent surgical advances have led to successful total mesorectal excision with autonomic nerve-preserving surgery,[4,5] and several centers have reported the frequency of local recurrence to be lower than 10%.[6,7] However, the skill and ability of individual surgeons vary greatly, and the frequency of local recurrence after curative resection is still generally accepted as 20% and 30%[8] or even higher in patients with advanced carcinomas of the distal rectum.

In some European countries, the high frequency of locoregional recurrence after surgery for operable rectal carcinoma has led to the inclusion of radiation therapy, especially preoperatively, in the treatment regimen.[9] Several selected series of full-dose (45 Gy) radiation therapy have shown promising survival benefits and local control.[10,11] Furthermore, sphincter-preserving surgery with systemic chemotherapy[12,13] has been attempted for invasive carcinoma of the distal rectum, but the survival and functional results have not been satisfactory.

Endocavitary irradiation is the delivery of low energy X-rays through a special applicator[14,15] and is widely accepted as an important treatment for cervical cancer treatment. Its advantage lies in the fact that it can deliver doses of radiation as high as 180 Gy, sparing most of the adjacent normal tissue from the potentially harmful effects of radiation.[14,15] Few studies have attempted to combine endocavitary irradiation with extracorporeal irradiation to treat rectal cancer, and the indications were mainly confined to small mobile cancers for conservative treatment, followed by a salvage operation.[16] In 1988, we first combined endocavitary irradiation and extracorporeal irradiation up to a tumoricidal dose of 70 Gy for advanced cancer in the distal rectum, followed by curative APR to prevent local recurrence and raise the curability by downstaging the effects. This study is unique because it investigates combined modality of extracorporeal and endocavitary irradiation, with strict eligibility oriented to APR. From 1997 onward, we performed autonomic nerve-preserving surgery to conserve urinary and sexual functions.[6,17] The purpose of this study was to evaluate the efficacy of this treatment and to identify the prognostic factors for survival after radiation therapy for distal rectal cancer.

Patients and Methods

Patients

The eligibility criteria for inclusion in this study were: the tumor was primary and located mainly below the pelvic peritoneal reflection; it was a cT3 or cT4 tumor; there were no distant metastases; the patient had never received pretreatment of chemotherapy, immunotherapy, or radiation therapy to the pelvis; the patient was younger than 80 years old at diagnosis; and there were no pre-existing serious disorders of the heart, lungs, liver, or kidneys. Informed consent to this treatment was given by all patients. Among 138 patients with carcinomas in the distal rectum treated at Nara Medical University Hospital between April 1988 and July 1997, 51 consecutive patients met these criteria. However, 7 refused this treatment because of the long-term hospitalization required and 3 were excluded because distant metastasis was found. Thus, a total of 41 patients were treated by our high-dose radiotherapy prior to surgery.

The pretreatment workup included digital examination, pelvic and abdominal computed tomography (CT), transrectal endoscopic ultrasonography (EUS), chest X-ray, barium enema, colonoscopy with biopsy, and screening for serum carcinoembryonic antigen (CEA). By performing digital examination, we ascertained that all tumors involved the entire rectal wall, which was confirmed by pelvic CT and EUS. Within 1 week after finishing radiotherapy, restaging was done by the same examinations.

Radiation Therapy

After admission, combined radiation therapy was delivered in the following way. First, extracorporeal irradiation was delivered by photon radiation generated by a 10-Mev linear accelerator using the two-opposing-field technique. The radiation field was the true pelvis, which extended from above the top of the promontory of the sacrum to below the anal verge, and laterally to about 3 cm outside the rectal wall bilaterally, delivered to totally include the mesorectum. A dose of 30 Gy was delivered to this field in 15 fractions over 3 weeks. Second, endocavitary irradiation was delivered by the ^{60}Co remote-controlled loading system. A dose of 40 Gy was delivered to a target depth about 1–2 cm from the source using a hand-made applicator in four fractions over 2 weeks. The most recent 14 patients, treated from July 1996 onward, received a modified regimen of 40 Gy extracorporeal irradiation and 30 Gy endocavitary irradiation to improve local control.

Operative Technique

All patients underwent an extended radical operation with lateral node dissection. The operative options were APR or low anterior resection (LAR), but we made it a rule to perform APR in all patients who had received our high-dose radiation therapy because of the risk of severe damage to the rectal wall with consequent anastomotic insufficiency or fistula formation. However, we performed an autonomic nerve-preserving operation (ANP) in ten patients treated after March 1997. Our procedure of ANP was to identify and completely preserve the lumbar splanchnic nerve, the superior hypogastric nerve, the hypogastric nerve, and the bilateral pelvic plexuses during APR. Surgery was performed within 2 weeks after the completion of radiation therapy.

Grading of Histological Change

Histopathological grading of the resected specimens after radiation therapy was done according to the criteria proposed by the Japanese Research Society for Cancer of the Colon and the Rectum,[18] as follows: grade 0, no change; grade 1, slight change; grade 2, necrosis and degeneration in less than one third of the tumor tissue; grade 3, necrosis and degeneration in one third to two thirds of the tumor tissue; grade 4, necrosis and degeneration in more than two thirds of the tumor tissue; and grade 5, no viable cells, being a sterile specimen.

Follow-Up

All patients took 200 mg 5-fluorouracil per day orally for 1 year after their operation and attended regular clinical reviews according to our follow-up schedule. The serum CEA and carbohydrate antigen 19-9 levels were measured every 3 months, and abdominal ultrasonography, chest X-ray, and pelvic CT were done every 6 months for 3 years. The outcome of all patients was well documented. Local recurrence was diagnosed by clinical examination, supplemented by pelvic CT or magnetic resonance imaging (MRI). Patients with elevated levels of either of the tumor markers or any clinical suggestion of local recurrence underwent repeated CT or MRI. We asked all patients about their urinary and sexual functions, before discharge and then again about 6 months later.

Statistical Analysis

Statistical comparison of the clinicopathological variables was made using Student's *t*-test or Fisher's exact probability test. Survivals were analyzed by the Kaplan-Meier procedure, and distribution comparisons were made with the generalized Wilcoxon test and the log-rank test. Multivariate analyses of prognostic factors for survival based on clinicopathological findings were undertaken by a stepwise forward Cox proportional hazard model. In each test a P value of less than 0.05 was considered significant.

Table 1. Clinical features in the 41 patients

Age (years)	Mean	61
	Range	27–74
Gender	M : F	33 : 8
Tumor size[a]	⩽2/3	20
	>2/3 subcircular	15
	circular	6
Distance from anal verge (cm)	Mean	3.4
	Range (CI)	2.9–3.9
Biopsy grade	Well	23
	Moderately	14
	Poorly	3
Radiation effect to primary tumors	Grade 0–2	1
	Grade 3	17
	Grade 4	19
	Grade 5	4
Tumor size	Mean	4
	Range (CI)	3.2–4.8
Tumor stage	⩽pT2	7
	⩾pT3	34
Number of nodes involved	Negative	27
	1–3	8
	⩾4	6
TNM stage	I	7
	II	20
	III	14

CI, 95% confidence interval
[a] Degree of circumference of tumor invasion estimated by endoscopy

Results

The clinical features of the 41 patients are summarized in Table 1. All tumors were mainly located below the peritoneal reflex, a median distance of 3 cm from the anal verge (range 1–6 cm, average 3.4 cm, 95% confidence interval (CI) 2.9–3.9 cm), and involved the anal sphincter complexes or had no distal margin for anastomosis. Histological examination revealed cellular destructive changes in all resected specimens after the radiation therapy. According to the grading criteria, 18 tumors were grade 0–3 (43.9%), 19 were grade 4 (46.3%), and 4 were grade 5 (9.8%). Of the 41 tumors, 7 (15.8%) were confined to the muscularis propria, and downstaged after radiation therapy, based on the histological findings of mucinous degeneration, necrotic tumor tissue, and fibrotic tissue continuous to tumor. Fourteen (34.1%) specimens had nodal involvement and the median number of positive nodes was 3 (average 5.5, range 1–22). Comparing tumor size and nodal status between grade 1–3 tumors and grade 4 tumors, the average size of a grade 4 tumor was significantly less than that of a grade 1–3 tumor (32.7 *vs* 42.4 mm, $P = 0.05$). Furthermore, among the 14 tumors with positive nodes there was a higher percentage of over N2, defined as more than four positive lymph nodes, in the grade 4 tumors (5 of 7, 71.4%) than in the grade 1–3 tumors (1 of 7, 14.3%; $P = 0.05$). The median follow-up period was 79.2 months (95% CI 66.5–91.9 months) and the median hospitalization, including the preoperative radiation therapy, was 86 days (95% CI 74–92 days).

All patients tolerated our radiation therapy regimen, without any severe complications or hematological abnormalities during the course. Only one patient suffered an aggravating diabetic condition, which was resolved by suspending radiation therapy for 1 week. Mild to moderate diarrhea with anal pain developed in 25 patients, which was managed by medication (grade 1 and 2, 61.0%). The anal pain seemed to be exacerbated by inserting the applicator for endocavitary irradiation for a few days. A relapse of herpes zoster occurred in two patients (9.8%). In total, there were 18 nonhematological postoperative complications (43.9%). Perineal dehiscence occurred in 10 (24.3%) patients, 6 (14.4%) of whom still suffered prolonged fistula formation. Three of four patients (9.8%) with small bowel obstruction required surgical treatment, one of whom still had a small bowel vesicocutaneous fistula 6 months after the operation (grade 4 toxicity, 2.4%), and underwent sur-

gery twice. Chronic cystitis was diagnosed by biopsy in two patients, one of whom finally received percutaneous nephrostomy (grade 3 toxicity, 2.4%). Two men needed to perform temporary self-catheterization before ANP was performed. There were no other serious problems within 6 months after surgery. Six of the ten patients who underwent APR with ANP had to be excluded; three because they refused to discuss their sexual function, one who was older than 60 years, one who was impotent before surgery, and one who underwent incomplete ANP. Of the four patients we were able to interview and examine, two reported normal erectile and ejaculative ability, one reported erectile ability, and one became impotent because of a neurogenic bladder.

There were 11 cases of recurrence and 6 cancer-related deaths during the follow-up period. The cumulative 5-year survival and disease-free survival rates were 82.9% and 71.8%, respectively (Fig. 1). Four of the 11 patients with recurrence had distant metastasis (lung 2, liver 1, brain 1), 1 had distant metastasis with local recurrence, and the other 6 had local recurrence. The local recurrence was inside the radiation field in three of these six patients (3 of 41, 7.3%) and just outside the radiation field in the other three patients; being outside the left common iliac artery in two and in the inguinal lymph nodes in one (7.3%). One of two patients with a positive radial margin had lung metastasis. None of the four patients from whom sterile specimens (grade 5) were histologically determined had recurrence. There was no difference in the ratio of local recurrence between the patients who underwent APR with ANP (2 of 10, 20%) and those who underwent APR (4 of 31, 12.9%). Two of the 11 patients with recurrence underwent surgical intervention (18.8%) but recurrence developed again. The other nine were treated with systemic chemotherapy. The most recent five were given a chemotherapy regimen including CPT-11 (irinotecan). Three of the six patients with recurrence after treatment for grade 1–3 tumors are alive with disease.

Univariate analysis revealed that nodal status significantly affected both recurrence and survival (Table 2). Contrary to the degree of radiation effect, the cumulative 5-year survival rate of patients with grade 1–3 tu-

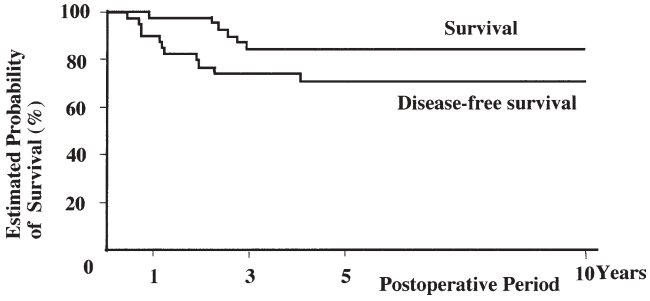

Fig. 1. Kaplan-Meier distribution of percent survival and percent disease-free survival

Table 2. Univariate analysis of prognostic variables for survival and recurrence

Variable	Components	*n*	Survival rate			Disease-free survival rate		
			3-year	5-year	*P*	3-year	5-year	*P*
Age (years)	⩽60	17	83.3	83.3	n.s.	81.2	72.2	n.s.
	>60	24	82.2	82.2		70.9	70.9	
Gender	Male	33	83.3	83.3	n.s.	78.4	74.3	n.s.
	Female	8	82.2	82.2		62.5	62.5	
Tumor size	⩽2/3	20	86.5	86.5	n.s.	76.6	71.8	n.s.
	>2/3	14	76.0	76.0		71.4	71.4	
Biopsy	Well	23	100	100		86.7	86.7	0.15
	Moderately	14	78.9	78.9	n.s.	72.4	66.4	
	Others	3	50.0	50.0		50.0	50.0	
Distance from anal verge (cm)	⩽3	22	83.1	83.1	n.s.	69.8	69.8	n.s.
	>3.1	19	82.7	82.7		85.2	76.2	
Radiation effect	0–3	18	94.1	94.1	0.200	72.2	65.7	n.s.
	4, 5	23	75.7	75.7		77.4	77.4	
Tumor stage	⩽pT2	7	100	100	NA	100	100	NA
	⩾pT3	34	79.2	79.2		69.7	65.8	
Nodal involvement	0	27	91.7	91.7		92.6	92.6	0.001
	1–3	8	85.7	85.7	0.004	50.0	50.0	
	⩾4	6	31.4	0		25.0	0	

NA, not accessed because no event had occurred during follow-up period; n.s., not significant

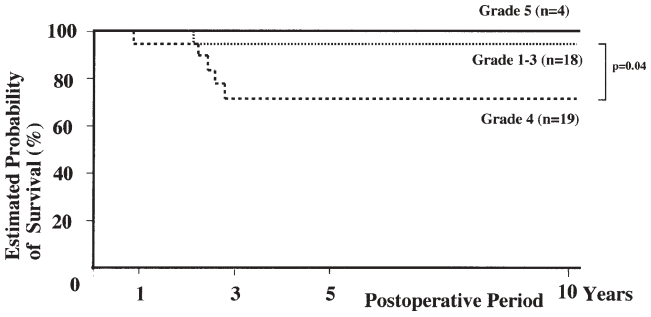

Fig. 2. Kaplan-Meier distribution of survival according to histological grade. Distribution comparisons were made with the generalized Wilcoxon test. A *P* value of less than 0.05 was considered significant

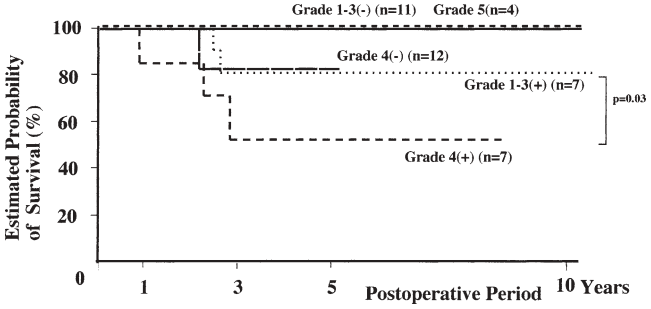

Fig. 3. Kaplan-Meier distribution of survival according to histological grade and nodal status. Distribution comparisons were made with the generalized Wilcoxon test. A *P* value of less than 0.05 was considered significant. *Grade 1–3 (−)*, grade 1–3 specimens without positive nodes; *Grade 1–3 (+)*, grade 1–3 specimens with positive nodes; *Grade 4 (−)*, grade 4 specimens without positive nodes; *Grade 4 (+)*, grade 4 specimens with positive nodes

mors (94.1%) was significantly higher than that of those with grade 4 tumors (71.3%, $P = 0.04$) (Fig. 2). A subset analysis of grading in combination with nodal status revealed that the cumulative 5-year survival rates were 100% in patients with grade 5 tumors and those with grade 1–3 tumors without nodal involvement, and 81.8% in those with grade 4 tumors without nodal involvement. There were no differences in survival rates among these three grades when there was no nodal involvement, but the survival rate of patients with grade 4 tumors was significantly worse than that of those with grade 1–3 tumors (53.6% *vs* 83.3%, $P = 0.03$) (Fig. 3). There was no difference in the cumulative 5-year disease-free survival rate between patients with grade 1–3 tumors (69.1%) and those with grade 4 tumors (72.9%). Finally, nodal involvement was the only independent prognostic factor of survival according to the forward stepwise method in a Cox proportional hazard model (hazard ratio 0.172, regression coefficient −2.010, $P = 0.045$, 95% CI 0.031–0.958).

Discussion

We expected that this direct delivery method would have a remarkable local effect, but only four surgical specimens histologically showed sterile tumor cells (9.8%) without nodal involvement. This rate was equivalent to that reported in recent studies using conventional radiation therapy (10%–15%)[19,20] and endocavitary irradiation alone (10.6%).[21] In general, the rate of tumor cell sterility is thought to be dependent on the tumor stage and the interval between completing radiation therapy and surgery.[22] Therefore it is encouraging that there were four sterile specimens in such a short period, which reflects the tumoricidal radiation effects. If we had waited to perform surgery until maximum tumor regression had occurred after radiotherapy,[17] our rate of tumor cell sterility might have been higher.

Unfortunately, there was a high incidence of postoperative perineal complications. This high incidence of wound infection was criticized in a previous study.[23] Two of three patients excluded from this series who underwent LAR after similar high-dose radiation therapy had fistula formation near the anastomosis and required surgical intervention (66.7%). Compared with the reported incidence of fistula formation, which ranges from 3.1% to 7.1%,[24–26] this high incidence in the patients after LAR suggests the potential hazard of anastomosing damaged rectum. Although a larger number of cases must be examined before a conclusion is drawn about this complication of LAR, we considered it sufficient grounds to justify performing APR following high-dose radiation therapy in our patients.

There are many causes of postoperative sexual dysfunction, including damage to the nervous system or insufficient blood supply as a result of lymphadenectomy during the operation. Extracorporeal radiation therapy can also cause impotence of varying degree, mainly due to the vascular factor, with secondary changes to obliterative arteries affecting the vasa nervosa. Although this series was small, the percentage of patients with impotence after surgery (3 of 4, 75%) was comparable with the results of other studies.[1,5,17] Further examples and longer follow-up are necessary before this modality is fully evaluated on the balance of autonomic functions and local recurrence.

It is difficult to compare the results of radiation therapy because of the nonuniform clinical staging methods, inconsistent patient selection, and differences in preoperative therapy.[12,27] The results of this study are clear in this respect because all of the patients had at least clinical stage T3 tumors which transmurally infiltrated the sphincter complex or had no adequate distal margin from the sphincter complex. By performing digital examination, we judged that all these tumors

Table 3. Past results of preoperative radiation therapy for lower rectal cancer

First author[Ref.]	Year	n	Tumor location (cm)[a] Range	Median	Clinical stage (T stage)	No. (%) of T3 and T4	Dose (Gy)	Chemotherapy	APR (%)	Toxicity[c]	Local rec. (%)	5-year survival (%)	Follow-up (median)
Rouanet[28]	1995	27	3–6	5	T2, T3	12 (44.4%)	60	No	0	NA	6	NA	24
Minsky[20]	1995	31	3–7	4	T2, T3	28 (90%)	50.4	No	0	NA	23	75[d]	43
Marks[10]	1995	52	3.5–6	NA	T2, T3, T4	NA	45–60	No	0	NA	14	85	50
Chari[32]	1995	43	NA	NA	T2, T3	NA	45	5FU-CDDP	82.9	21	5	90	25
Rich[33]	1995	77	NA	5.3	T1, T2, T3	57 (75%)	45	5FU	33	30	4	88[e]	27
Amhad[29]	1997	74	3–15	6–9	T3, T4	74 (100%)	45	No	28	5	20	73	57
Wagman[30]	1998	36	3–7	4	T2, T3	31 (86.1%)	50	No	0	0	17	64	56
Mohiuddin[11]	1998	70	3–5	4–5	T2, T3, T4	34 (48.5%)[b]	40–45	No	0	0	15	82	48
Kaminsky-Forrett[31]	1998	88	0–15	0–6	T3, T4	88 (100%)	40–45	No	75	0	14	54	33
Valentini[34]	1999	83	3–15	6–8	T3, T4	83 (100%)	37.8	5FU-MMC	19.3	10	10	72	NA
Grann[12]	2001	72	1–10	5	T3	72 (100%)	50	5FU-LV	5	28	2	88	22
Rullier[13]	2001	43	2–6	4–5	T3	40 (93%)	50	5FU-LV	0	2.3	2	85	30
This series	2002	41	1–6	3	T3, T4	41 (100%)[b]	70	No	100	0	15	83	80

APR, abdominoperineal resection; rec., recurrence; 5FU, 5-fluorouracil; CDDP, cis-diamine-dichloroplatinum; MMC, mitomycin C; LV, leucovorin
[a] distance from anal verge (cm): anorectal ring was 3 cm proximal to the anal verge
[b] Tethered and fixed
[c] Acute grade 3–4 toxicity
[d] 4-year survival
[e] 3-year survival

were a definite indication for APR (CI 2.9–3.9 cm). Table 3 shows recent representative published results of similar eligibility. These results suggest that our 5-year survival (82.9%) and local recurrence rates (14.6%) were among the best in the series of conventional radiation therapy.[10,28–31] In 1995 Rouanet et al.[28] reported low rates of local recurrence (6%) using high-dose radiation therapy with doses as high as 60 Gy, although their study mainly included patients with T2 disease (T3 44%) and the follow-up period was no more than 24 months. Recent studies on chemoradiation therapy[15,32–34] demonstrated lower rates of local recurrence (2%–10%) and higher 5-year survival rates (72%–90%), but these were inevitably accompanied by severe perioperative morbidity of grade 3+ toxicity (10%–30%) and again, long-term results are unclear because of the short follow-up periods (20–30 months).

All of these investigators, except Chari et al.[32] and Kaminsky-Forrett et al.,[31] attempted sphincter-preserving surgery with radiation therapy for distal cancer, because of the longer median distance from the anal verge and less advanced tumor stage than in our series. Mohiuddin et al.[11] reported good results with a low local recurrence rate (15%) and a high 5-year survival rate (85%) after treating carcinomas of median distance 4–5 cm, but this treatment was not successful for patients with node-positive disease who had a high local recurrence rate (41%) and a low 5-year survival rate (50%). The results of previous challenges suggest the potential hazard of expecting a downstaging effect after radiation therapy for advanced carcinoma in the distal rectum followed by anastomosis, because there have been no pathological discussions on the safe distal margin in irradiated specimens. Moreover, the functional results after low anastomosis following radiation therapy are still uncertain. A Swedish randomized trial demonstrated that preoperative radiation therapy affected long-term bowel function after sphincter–preserving surgery for rectal cancer.[35] Another recent prospective follow-up study found, by multivariate analysis, that patients who underwent APR did not have a poorer quality of life than those who underwent LAR.[36]

Regarding local effect and survival, excluding the patients with grade 5 tumors, there was an inverse relationship between the survival rates of grade 1–3 and grade 4. There are two possible explanations for this. First, the percentage of over N2 disease was higher in the grade 4 tumors than in the grade 1–3 tumors (71.4% *vs* 14.3%; $P = 0.05$) and therefore, patients with grade 4 tumors and positive nodes had a very bad prognosis. Second, the fact that there were three patients with grade 1–3 tumors alive with disease after chemotherapy including CPT-11[37] by the end of the follow-up period is notable in this small series. However, Chari et al.[32] divided the resected specimens into three degrees

according to residual status, and reported that the survival rate improved as the residual volume decreased. Our definition of grades 1–3 and 4 was ambiguous and both grades were macroscopically positive. Nevertheless, with the exclusion of tumors that are highly sensitive to radiation, our results suggest that survival after radiation therapy was affected more by nodal involvement than by the local effect of irradiation. Indeed, multivariate analysis showed that nodal involvement was the sole independent prognostic factor for survival. The poor survival of patients with nodal involvement, especially those with involvement of more than four nodes, affected the overall survival in this study. Conversely, we reconfirmed the finding of previous reports that the postirradiated staging of resected specimens after radiation therapy reflects the prognosis as well as the staging of rectal cancer.[38] Thus, patients found to be node-positive should receive adjuvant chemotherapy.

We think APR is the most appropriate surgical procedure for advanced tumors in the distal rectum located below 3 cm from the anal verge, if the anal sphincter is deficient, or if the sphincter complex is infiltrated by the tumors[39] even after radiation therapy. Originally, the aim of our treatment focused on curability, but it may also assist in the prevention of local recurrence, with low morbidity and promising autonomic nerve function in selected patients.

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