Radiation Therapy for Anal Squamous Cell Carcinoma: A Retrospective Multicenter Study

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Abstract. *Aim: To analyze the treatment outcomes, patterns of failures and prognostic factors for patients with anal cancer treated with radiotherapy (RT). Materials and Methods: Between January 2000 and December 2015, 83 patients with anal squamous cell carcinoma were treated with definitive RT. The median RT dose applied to the primary carcinoma site was 55 (range=45-64) Gy. Seventy-six patients (91.6%) received concurrent chemotherapy, and the most common regimen was 5-fluorouracil plus mitomycin C. Results: The median age of patients was 64 (range=36-86) years, and there were 21 males and 62 females. The overall complete remission rate was 89.2%. The median duration of follow-up was 51 (range=3-173) months. The actuarial 5-year overall, progression-free survival (PFS), locoregional progression-free, and distant metastasis-free survival rates were 85.0%, 70.4%, 78.2%, and 82.6%, respectively. On multivariate analysis, eventual treatment response was the only prognostic factor for overall (p=0.023) and progression-free (p<0.001) survival. Age (p=0.013) and eventual treatment response (p<0.001) were significantly associated with locoregional progression-free survival. Initial treatment response, lymph node involvement and RT technique significantly affected distant metastasis-free survival (p=0.016, 0.048 and 0.002, respectively). Conclusion: RT, mainly with concurrent chemotherapy, showed acceptable treatment outcomes and safe toxicity profiles.*

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Anal cancer is a rare malignancy that comprises only 2.7% of all digestive system malignancies, with about 8,600 cases newly diagnosed in the United States annually (1). In Korea, anal cancer comprises only 0.1% of all malignancies (2).

Historically, the treatment of choice for anal cancer has been abdominoperineal resection. However, since its introduction by Nigro *et al.* (3), concurrent chemoradiotherapy (CCRT) has been a standard therapy for anal squamous cell carcinoma, with radical surgery reserved for salvage treatment in the event of recurrence (4). Despite the low incidence of anal cancer, six randomized phase III trials have successfully established a key treatment for anal cancer. Firstly, CCRT *versus* radiotherapy (RT) alone was examined, with CCRT proving to be superior to RT alone regarding local or locoregional control and anal cancer-specific survival (5, 6). As a chemotherapy regimen for CCRT, a 5-fluorouracil (5-FU) plus mitomycin C (FM) regimen proved to be more beneficial for local control, colostomy-free survival and disease-free survival than 5-FU alone (7). Moreover, an FM regimen achieved better progression-free survival (PFS) and overall survival (OS) than induction chemotherapy consisting of 5-FU and cisplatin followed by CCRT with the same chemotherapy

regimen (8). Lastly, the addition of induction or maintenance chemotherapy to CCRT failed to show any benefit (9, 10). Therefore, the current treatment of choice for anal cancer is CCRT with an FM regimen. However, many questions remain concerning the best RT protocol, especially concerning optimal dose and field (4).

In this study, we aimed to evaluate the treatment outcomes, patterns of failures, and prognostic factors for patients with anal cancer treated with RT at eight Institutions in Korea. The impact of RT dose and field were also analyzed.

Patients and Methods

Patient population. The medical records of 86 patients who underwent definitive RT for anal cancer between January 2000 and December 2015 at eight institutions in Korea were retrospectively reviewed. Three patients that had received neoadjuvant chemotherapy before RT were excluded, leaving 83 patients in the final analysis. The Institutional Review Boards of each participating institution approved the study.

All patients had the diagnosis of anal squamous cell carcinoma confirmed by endoscopic biopsy. For the staging workup, abdominopelvic computed tomography (CT) was performed in 81 patients (97.6%), pelvic magnetic resonance imaging in 38 (45.9%) and positron emission tomography-CT in 42 (50.6%).

Treatment. All patients underwent RT with curative intent. The RT target volume encompassed the primary site, pelvic lymph node (LN) area and inguinal LN area. All patients received RT to the primary site, with a median RT dose of 55 (range=45-64) Gy. Every patient except one received elective RT to the uninvolved pelvic LN area, with a median RT dose of 45 (range=30.6-54) Gy. In patients with pelvic LN involvement (N=22), the median RT dose to the involved pelvic LN was 54 (range=45-60) Gy. Elective RT to the uninvolved inguinal LN area was performed in 70 patients, with a median RT dose of 45 (range=30.6-51) Gy. Patients with inguinal LN involvement (N=22) received a median RT dose to the involved inguinal LN of 50.4 (range=41.4-66) Gy. According to the RT technique, two-dimensional RT (2D-RT) was performed in 29 patients (34.9%), three-dimensional conformal RT (3D-CRT) in 36 (43.4%) and intensity-modulated RT (IMRT) in 18 (21.7%).

Seventy-six patients (91.6%) received concurrent chemotherapy, while seven patients (8.4%) did not. The reasons for the omission of concurrent chemotherapy was that six patients were older than 70 years of age and one patient had an early stage cancer which their physician opted to treat without concurrent chemotherapy. Concurrent chemotherapy regimens consisted of FM in 63 patients (75.9%), 5-FU and cisplatin (FP) in nine patients (10.8%) and 5-FU alone in four patients (4.8%). FM regimen was applied as 1,000 mg/m^2/day 5-FU intravenously from day 1 to day 4 and 10 mg/m^2 mitomycin (as intravenous bolus on day 1 with repeat in weeks 1 and 5. FP regimen was made up of the same dose of 5-FU and 25 mg/m^2/day cisplatin intravenously from day 1 to day 4 in the same weeks as FM regimen. Only eight patients received additional chemotherapy after the completion of CCRT: FM in two patients, 5 FP in two patients, and fluoropyrimidine (5-FU, 900 mg/m^2/day doxifluridine or 300 mg/m^2/day tegafur-uracil) in four patients.

Table I. *Patient and tumor characteristics.*

Characteristic	N (%)
Age, years	
Median (range)	64 (36-86)
Gender	
Female	62 (74.7)
Male	21 (25.3)
ECOG PS	
0-1	61 (73.5)
2	12 (14.5)
N/A	10 (12.0)
Tumor size	
≤4 cm	49 (59.0)
>4 cm	23 (27.7)
N/A	11 (13.3)
T Stage	
T1	15 (18.1)
T2	45 (54.2)
T3	16 (19.3)
T4	7 (8.4)
N Stage	
N0	48 (57.8)
N1a	32 (38.6)
N1b	0 (0.0)
N1c	3 (3.6)
Internal iliac or mesorectal LN	
Negative	61 (73.5)
Positive	22 (26.5)
External iliac LN	
Negative	80 (96.4)
Positive	3 (3.6)
Inguinal LN	
Negative	61 (73.5)
Positive	22 (26.5)
Stage by AJCC 8th edition	
I	13 (15.7)
II	32 (38.6)
III	38 (45.8)

ECOG PS: Eastern Cooperative Oncology Group performance status; N/A: not available; AJCC: American Joint Committee on Cancer; LN: lymph node.

Statistical analysis. All outcomes were calculated from the start date of RT. Treatment response was defined as complete remission (CR) for disappearance of disease, partial remission for at least a 30% decrease, and progressive disease for at least a 20% increase in main disease. OS, PFS, locoregional PFS and distant metastasis-free survival (DMFS) were defined as the interval from the start date of RT to death, the date of relapse, the date of locoregional progression and the date of distant metastasis or the last follow-up, respectively. Toxicity was evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events ver. 4.0 (11). The Kaplan–Meier method was used to calculate the actuarial rates of OS, PFS, locoregional PFS and DMFS. For comparisons between groups, two-sided log-rank tests were performed. Multivariate analysis was carried out using the Cox proportional hazards model with prognostic factors with a *p*-value of less than 0.2 on univariate
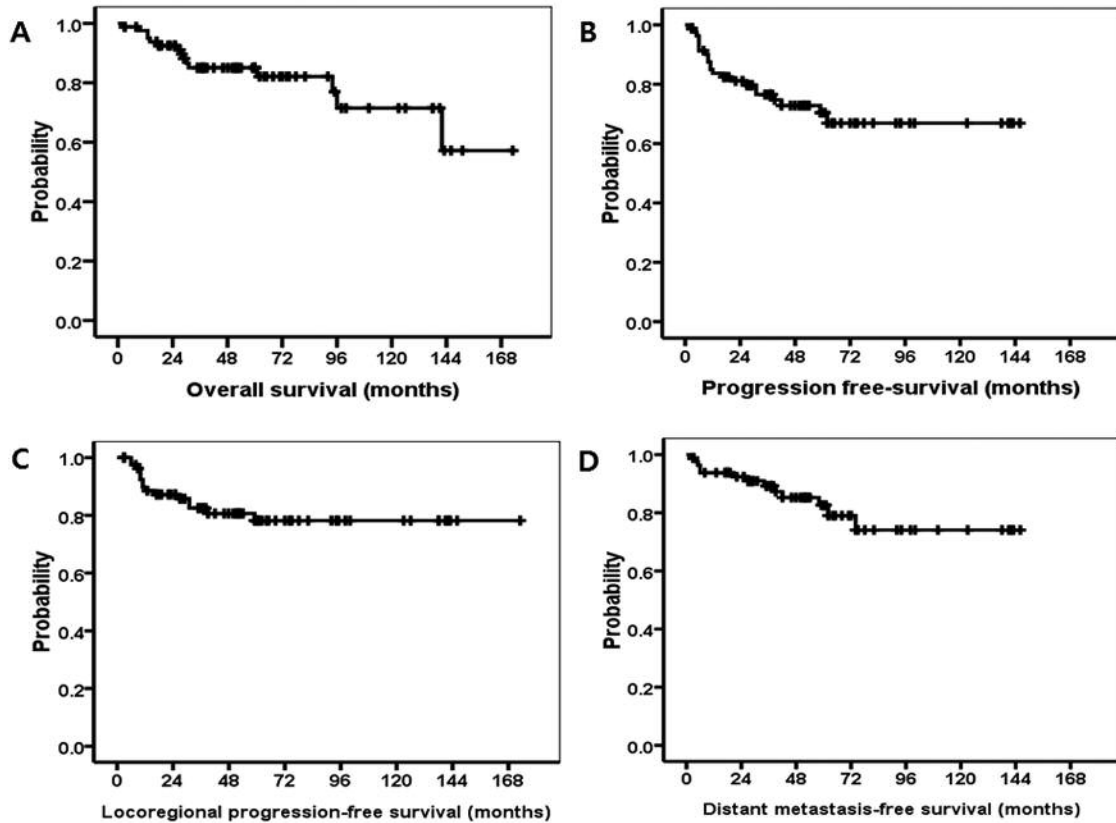
Figure 1. *Kaplan–Meier curves for overall (A), progression-free (B), locoregional progression-free (C) and distant metastasis-free (D) survival.*

analysis. All tests were bilateral and statistical significance was determined when the *p*-value was less than 0.05. All statistical analyses were performed using SPSS version 18.0 (SPSS, Inc., Chicago, IL, USA).

Results

Patient characteristics. Table I summarizes patient and tumor characteristics. The median age of patients overall was 64 (range=36-86) years. Gender distribution was female-dominant (female:male=62:21). Sixty-one patients (73.5%) had an Eastern Cooperative Oncology Group performance status of zero or one. Forty-nine patients (59.0%) had a tumor size of ≤4 cm. The T stage, according to the 8th edition of the classification of the American Joint Committee on Cancer (12), was T1-2 in 60 patients (72.3%) and T3-4 in 23 (27.7%). Thirty-five patients (42.2%) had nodal involvement. Overall, the clinical stage was I in 13 patients (15.7%), II in 32 (38.6%), and III in 38 (45.8%).

Response and patterns of failure. The median duration of follow-up was 51 (range=3-173) months. After the completion of RT, the initial treatment response was evaluated at a median follow-up of 1 month. Forty-nine patients (59.0%) had CR, 33 (39.8%) had partial remission and one (1.2%) had progressive disease. Among the patients with partial remission, 25 attained CR with follow-up. Therefore, a total of 74 patients (89.2%) were found to have CR at a median follow-up of 2 months.

Five patients (22.7%) had isolated local recurrence, four (18.2%) had isolated regional recurrence, seven (31.8%) had isolated distant metastasis and six (27.3%) had regional recurrence plus distant metastasis. The specific sites of regional LN recurrence were as follows: inguinal (N=3), internal iliac (N=1), external iliac (N=1), mesorectal (N=1) and multiple sites (N=4). Thirteen patients did not receive elective RT to the inguinal LN area. Among these patients, only one (7.7%) experienced bilateral inguinal LN recurrences. Among 70 patients treated with elective RT to uninvolved inguinal LN area, only one patient (1.4%) had an inguinal LN recurrence. Thirteen patients experienced distant metastasis at 17 sites: distant LN (N=6), liver (N=4), lung (N=4), bone (N=2) and skin (N=1).

Table II. *Univariate analysis for 5-year overall (OS), progression-free (PFS), locoregional progression-free (LPFS) and distant metastasis-free (DMFS) survival.*

	N	OS (%)	p-Value*	PFS (%)	p-Value*	LPFS (%)	p-Value*	DMFS (%)	p-Value*
Age									
≤64 Years	45	79.9	0.377	59.3	0.153	66.4	0.033	75.6	0.430
>64 Years	38	91.2		82.6		91.2		88.5	
Gender									
Female	62	83.6	0.981	64.1	0.130	74.5	0.234	80.2	0.329
Male	21	89.4		88.7		88.7		90.9	
ECOG PS†									
0-1	61	85.4	0.907	73.9	0.848	80.2	0.862	82.6	0.912
2	12	90.0		71.3		80.0		78.6	
Tumor size†									
≤4 cm	49	88.4	0.145	71.4	0.243	78.4	0.554	84.1	0.187
>4 cm	23	76.0		57.9		70.0		68.7	
T Stage									
T1-2	60	90.7	0.123	73.1	0.452	80.6	0.497	85.2	0.384
T3-4	23	70.3		62.4		70.9		73.5	
LN									
Negative	48	87.7	0.986	87.7	0.136	82.2	0.369	91.6	0.074
Positive	35	81.7		62.4		73.0		69.8	
Stage									
I	13	85.7	0.799	85.7	0.147	87.5	0.395	100.0	0.271
II	32	84.3		73.9		82.2		87.1	
III	38	80.5		63.0		72.9		72.1	
RT technique									
2D	29	81.1	0.425	63.8	0.270	74.5	0.707	71.1	0.022
3D-CRT/IMRT	54	87.7		75.2		82.0		90.5	
RT technique									
2D/3D-CRT	65	84.9	0.996	68.4	0.493	75.2	0.204	83.8	0.420
IMRT	18	88.9		82.1		94.1		82.1	
Treatment period									
≤2007	39	83.5	0.976	65.2	0.334	76.1	0.775	75.2	0.086
>2007	44	86.9		78.7		83.1		92.8	
Total dose									
≤54.0 Gy	40	80.3	0.182	73.3	0.918	75.4	0.257	88.1	0.308
>54.0 Gy	43	89.1		69.7		82.4		79.6	
Concurrent CTx‡									
FM	63	86.1	0.373	72.0	0.680	80.6	0.193	79.5	0.098
Other	13	82.1		64.8		64.8		100.0	
Initial treatment response									
CR	49	90.9	0.252	76.3	0.039	82.9	0.162	89.6	0.007
Non-CR	34	75.8		63.0		72.1		71.1	
Eventual treatment response									
CR	74	89.1	0.037	75.9	<0.001	83.3	<0.001	87.4	<0.001
Non-CR	9	53.3		25.4		37.5		38.1	

ECOG PS: Eastern Cooperative Oncology Group performance status; LN: lymph node; RT: radiotherapy; 2D: Two-dimensional radiotherapy; 3D-CRT: three-dimensional conformal radiotherapy; IMRT: intensity modulated radiotherapy; CTx: chemotherapy; FM: 5-fluorouracil plus mitomycin C; CR: complete remission. *Log-rank test; †Analysis with available data; ‡Patients with no chemotherapy were not included.

Survival and prognostic factors. The actuarial 5-year OS, PFS, locoregional PFS and DMFS were 85.0%, 70.4%, 78.2% and 82.6%, respectively (Figure 1). Table II shows prognostic factors in univariate analysis for 5-year OS, PFS, locoregional PFS and DMFS. Univariate analysis indicated that eventual treatment response (89.1% for CR *vs.* 53.3% for non-CR; *p*=0.037) was the only significant risk factor for OS. As for PFS, initial treatment response (76.3% for CR *vs.* 63.0% for non-CR; *p*=0.039) and eventual treatment response (75.9% for CR *vs.* 25.4% for non-CR; *p*<0.001) were significant risk factors. Younger age (66.4% for ≤64 years *vs.* 91.2% for >64 years; *p*=0.033) and eventual non-
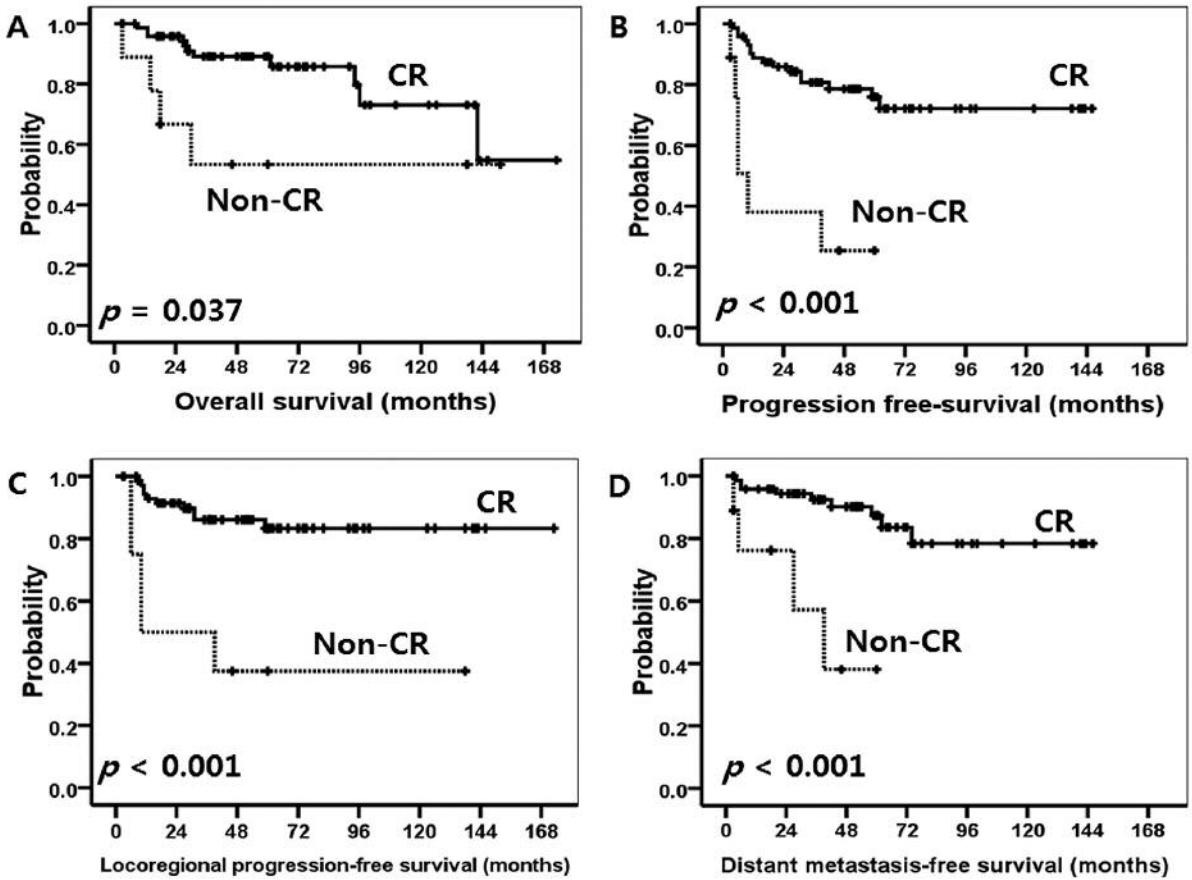
Figure 2. *Kaplan–Meier curves for overall (A), progression-free (B), locoregional progression-free (C) and distant metastasis-free (D) survival according to eventual treatment response. CR: Complete remission.*

CR treatment response (83.3% for CR *vs.* 37.5% for non-CR; *p*<0.001) were associated with worse locoregional PFS. 3D-CRT or IMRT technique (71.1% for 2D-RT *vs.* 90.5% for 3D-CRT or IMRT; *p*=0.022), initial CR treatment response (89.6% for CR *vs.* 71.1% for non-CR; *p*=0.007) and eventual CR treatment response (87.4% for CR *vs.* 38.1% for non-CR; *p*<0.001) were correlated with better DMFS (Figure 2).

Multivariate analysis showed that eventual treatment response was the only significant prognosticator for OS (*p*=0.023) and PFS (*p*<0.001). Younger age (*p*=0.013) and eventual non-CR treatment response (*p*<0.001) were significant risk factors for worse locoregional PFS. Initial non-CR treatment response, LN involvement and 2D-RT technique were significantly associated with worse DMFS (*p*=0.016, 0.048 and 0.002, respectively).

Toxicity. Table III reports toxicity profiles. Each event was counted regardless of other events, and the highest grade of observed complications was recorded. Hematological toxicity occurred mainly in the acute phase. The most common non-hematological toxicity was dermatitis. Only one grade 3 toxicity event occurred in the late phase.

Table III. *Complications of grade 3 or more by the Common Terminology Criteria for Adverse Events 4.0 according to radiotherapy modality.*

	Acute, n (%)			Late, n (%)*
Complication	2D	3D-CRT	IMRT	IMRT
Hematological				
Anemia	2 (6.9)	1 (2.8)		
Leukopenia	6 (20.7)	5 (13.9)	3 (16.7)	
Thrombocytopenia	3 (10.3)	3 (8.3)	2 (11.1)	
Non-hematological				
Skin	4 (13.8)	1 (2.8)	1 (5.6)	
Gastrointestinal		1 (2.8)		
Genitourinary				1 (2.8)

2D: Two-dimensional radiotherapy; 3D-CRT: three-dimensional conformal radiotherapy; IMRT: intensity modulated radiotherapy. *No other late grade 3 or more complications were recorded.

Discussion

In the present study, we performed a multicenter, retrospective analysis of anal cancer treated with definitive RT. Most patients received the current standard treatment, that is, CCRT with an FM regimen, and the outcomes were comparable to previous reports. Locoregional progression was the dominant failure pattern, and eventual treatment response evaluated at a median of 2 months after the completion of RT was a prognostic factor predicting all outcomes except DMFS on multivariate analysis. In addition, initial treatment response and RT technique were significantly associated with DMFS.

The optimal timing of treatment-response evaluation is a critical yet debated factor in the treatment of anal cancer. In the initial randomized trials, it was recommended that patients with a poor response at 6 weeks after the completion of RT should have salvage surgery (5, 6). The current National Comprehensive Cancer Network guidelines recommend an evaluation at 8-12 weeks (13). However, in the ACT II phase III trial, clinical response was assessed prospectively at 11, 18 and 26 weeks after CCRT. Patients with CR at 18 and 26 weeks after CCRT had superior 5-year OS and PFS compared to those without CR, suggesting that deciding on CR can be delayed until 6 months after CCRT if the disease is not progressive (14). In a retrospective study in Korea, Kim *et al*. assessed clinical response at 4 weeks and 6 months after RT and demonstrated that the 6-month response was a marginally significant prognosticator for PFS (p=0.090), based on univariate analysis (15). In our study, we evaluated both initial and eventual responses as risk factors and the eventual response was an independent prognosticator affecting OS, PFS and locoregional PFS. The initial response affected DMFS. Some discrepancy between the ACT II trial and the current study may be explained in part by the observation that 89.2% of our patients attained CR at a median follow-up of 2 months, which was much higher than in the ACT II trial, where patients attained a CR rate of only 64% at 11 weeks after CCRT. Although the ACT II trial prospectively evaluated the treatment response while our study did not, the higher RT dose used in our study (median 55 Gy *vs*. 50.4 Gy in ACT II trial) might have contributed to the higher CR rate at the earlier time.

Regarding the RT technique, we observed that 2D-RT was associated with an inferior DMFS. A similar observation was reported in nasopharyngeal cancer: 3D-CRT or IMRT led to superior 5-year OS than did 2D-RT (16), and IMRT achieved superior DMFS than 2D-RT with borderline significance (17). Anal cancer is a representative case where IMRT is preferred for the complex target coverage (18). Two Radiation Therapy Oncology Group studies were compared indirectly regarding the toxicity of IMRT *versus* 2D-RT, and it was found that IMRT toxicity profiles were better (19). Recently, a study using the National Cancer Database

revealed that IMRT was superior to 3D-CRT in terms of OS (p=0.0036). On multivariate analysis, IMRT retained its significance for death with a hazard ratio of 0.85 (p=0.0049) (20). In the current study, we showed that all of the outcomes, including OS, PFS, locoregional PFS and DFMS, were inferior in patients treated with 2D-RT, although the difference was significant only for DMFS. Thus, advances in RT technique might potentially reduce treatment-related toxicities as well as improve treatment outcomes.

The optimal RT field has not yet been established despite RT being the mainstay of anal cancer treatment. The role of elective RT to the inguinal LN area has been particularly controversial. In the present study, among the 13 patients who did not receive RT to uninvolved inguinal LN area, only one patient (7.7%) had an inguinal failure. Moreover, among 70 patients who underwent elective inguinal RT, only one patient (1.4%) had an inguinal recurrence. Kim *et al*. proposed the omission of prophylactic inguinal RT because they observed no inguinal failure in their retrospective study of 33 patients who received no prophylactic inguinal RT (21). On the other hand, Thompson *et al*. examined the feasibility of inguinal observation in a retrospective chart review of 51 patients. Because they observed no inguinal failure in the elective inguinal RT group compared with a 23% inguinal failure rate in the observation group (p=0.009), the authors recommended treating every patient with elective inguinal RT (22). Many researchers have been trying to determine which patients do not need elective inguinal RT, and patients with T1-2N0 disease are generally considered suitable (23). In the current study, 10 patients (76.9%) with T1-2 and nine patients (69.2%) with N0 disease were among the 13 patients without elective inguinal RT. Although the crude inguinal failure rate was higher in the group that received no elective inguinal RT, we were unable to make any definitive conclusion because of the small number of events.

The optimal RT dose is another source of controversy. In randomized trials, the prescribed dose to the primary tumor was usually 45-50.4 Gy (5-7, 9). The ACCORD-3 trial compared a standard dose of 15 Gy with a high dose of 20-25 Gy boost after 45 Gy in 25 fractions. The 5-year colostomy-free survival was 73.7% for the standard-boost group *versus* 77.8% for the high-boost group (p=0.067) (10). In a retrospective study by Ferrigno *et al*., a dose of more than 50 Gy to the primary tumor achieved better local control (24). In the current study, most patients received an RT dose ≥50 Gy, with a dose of 54 Gy having no impact on any of the outcomes. The PALTO trial in the United Kingdom is underway to test dose escalation for high-risk and dose de-escalation for low- to intermediate-risk patients (25).

Limitations of the current study include that we cannot exclude selection bias, and we might have underestimated the rate of late complications due to the retrospective nature of the study. However, we collected a relatively large number

of patients who received the current standard therapy, and these data might provide the opportunity to compare the outcomes from randomized trials and those from real-world practice, especially from Asia.

In conclusion, this study shows that for anal squamous cell carcinoma, RT mainly combined with concurrent chemotherapy achieved CR in most patients without serious complications. Eventual treatment response is an important predictor for outcomes, and therefore further optimization regarding RT dose and field is needed to improve treatment responses.

Conflicts of Interest

There was no conflict of interest related to this article.

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