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FULL PAPER

Post-operative radiation therapy with or without chemotherapy for anal squamous cell carcinoma incidentally discovered after local excision: a propensity score matched analysis of retrospective multicenter study

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Objective: To evaluate the results of post-operative radiation therapy (RT) for anal squamous cell carcinoma (ASCC) incidentally detected after excision, and compare these outcomes with those of definitive RT without excision for exploring the possibility of treatment de-intensification

Methods and materials: A total of 25 patients with T1-2N0-1 ASCC who underwent RT following incidental tumor resection were selected from multicenter retrospective database. And, we selected one-to-one matched 25 patients receiving definitive RT from the same database using propensity score matching method, and the outcomes were compared.

Results: Median age was 60 years (range, 30–76), and 18 patients (72%) were female. 19 patients (76%) had T0/1 tumors and four patients (16%) had regional lymph node metastases. Hemorrhoidectomy was performed in eight patients (32%) and the others underwent local excision. 12 patients (48%) had microscopic or gross residual diseases. Median RT dose to the primary lesion

was 50.4 Gy (range, 40–60). Concurrent chemotherapy was delivered to 23 patients (92%). Median follow-up period was 71 months (range, 4.5–203.1 months). None of the patients showed recurrence during follow-up. However, one patient died after 6 months due to the chemotherapy-related hematologic toxicity. When compared with those patients receiving definitive RT, clinicopathological variables were well-balanced between the two groups. While matched paired patients treated with definitive RT received a higher median RT dose of 54 Gy (range, 45–61.2) and concurrent chemotherapy was given to 22 patients (88%), overall survival was not significantly different ($p = 0.262$).

Conclusion: Patients treated with RT for early stage ASCC after local excision showed favorable treatment outcomes. Further study is warranted to justify the de-intensification of the treatment for these patients.

Advances in knowledge: Post-operative RT can achieve favorable treatment outcomes in incidental ASCC with residual diseases after local excision.

INTRODUCTION

Anal squamous cell carcinoma (ASCC) is a rare type of cancer comprising only 0.3% of all malignancy.¹ Concurrent

chemoradiation (CCRT) with 5-fluorouracil (5-FU) plus mitomycin-C (FM) has been a standard therapy for ASCC.² However, optimal treatment strategy for Stage I patients

remains uncertain, because randomized trials leading to the current treatment for ASCC included mainly patients with Stage II or III disease. Moreover, there have been several reports on the feasibility of local excision alone for early stage ASCC.^{3–5}

Clinicians often encounter patients after complete or incomplete resection of a lesion that had been turned out to be a T1–2N0 ASCC. After excision biopsy or hemorrhoidectomy, ASCC is often diagnosed by pathologic examination. Currently, there are no definitive recommendations concerning risk assessment and optimal post-operative treatment strategies in this setting. Because margin status could not be assessed clearly in unplanned surgery, post-operative RT or CCRT has usually been offered to these patients. National Comprehensive Cancer Network guidelines recommend re-excision or radiation therapy (RT) ± chemotherapy after local excision for T1N0 perianal cancer with inadequate margins.⁶

However, considering the high toxicity profile of CCRT with FM regimen, deintensified treatment regimen such as RT alone, lower dose of RT and/or omitting elective nodal irradiation might be considered in selected patients. Therefore, it is meaningful to compare the treatment results of these patients with those of patients who did not undergo excision but definitive RT.

In this study, we compared the results of post-operative RT for ASCC incidentally detected after local excision with those patients treated with definitive RT at eight institutions in Korea.

METHODS AND MATERIALS

Patient population

A total of 25 patients (Surgery + RT group) with T1–2N0–1 ASCC who underwent RT following incidental tumor resection were selected from multicenter retrospective database between January 2000 and December 2015 at eight institutions in Korea. Treatment result of the ASCC patients treated with definitive RT ($n = 83$) from the same cohort was reported recently.⁷ Surgery + RT group ($n = 25$) were matched to definitive RT group ($n = 83$) using propensity score matching method. Detailed information of definitive RT group ($n = 83$) was described in the recently published study.⁷ Clinicopathological variables including gender, age, Eastern Cooperative Oncology Group performance status, T stage, N stage and histologic differentiation were matched. One-to-one matching with nearest neighbor method was conducted. After matching, Surgery + RT ($n = 25$) group were compared to the matched definitive RT ($n = 25$) group. This study was approved by the institutional review board (approval no. 2017-06-008-002), and the requirement for obtaining informed consent was waived owing to its retrospective design.

Staging

Staging according to the AJCC eighth edition was performed by proctologic examination, rectoscopy with endosonography of the anal canal, CT or MRI of the pelvis and/or positron emission tomography-CT (PET/CT). Except for the T staging of the Surgery + RT group, which was pathologic staging using the pathologic examination of the resected specimen, other staging was clinical staging. N staging was assessed using CT, MRI or

PET/CT images. MRI and PET/CT was performed in 6 (24%) and 10 (20%) patients in the Surgery + RT group, and 12 (24%) and 12 (24%) patients in the definitive RT group.

Treatment

For all 25 patients in the Surgery + RT group, local excision or hemorrhoidectomy was performed with or without pre-surgical acknowledge of squamous cell carcinoma. RT was delivered to the primary tumor bed with a 1.5–3 cm margin for all patients. Elective lymph nodes (LN) were irradiated in most cases, usually perirectal, pre-sacral, iliac, and inguinal LN. RT was delivered with megavoltage photon beam, five fractions per week. RT techniques varied from two-dimensional RT (2D-RT), three-dimensional conformal RT (3D-CRT) and intensity-modulated RT (IMRT). Most patients received CCRT with different chemotherapy regimen. The most common regimen was FM which was applied as 1000 mg/m²/day 5-FU (intravenously from day 1 to day 4) and 10 mg/m² mitomycin C (intravenous bolus on day 1) with repeat in weeks 1 and 5. A few patients received 5-FU and cisplatin (FP) regimen which consisted of same dose of 5-FU and 25 mg/m²/day cisplatin intravenously from day 1 to day 4 in the same weeks as FM regimen.

Statistical analysis

Overall survival (OS) was defined as the time from the start day of RT to the death from any cause. Progression-free survival (PFS), locoregional progression-free survival (LRPFS) and distant metastasis-free survival (DMFS) were defined as the interval from the start date of RT to the date of relapse, the date of locoregional progression and the date of distant metastasis or the last follow-up, respectively. Kaplan-Meier analysis was conducted to estimate OS and log-rank test was used to compare survival differences between two groups. Toxicity was evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events v. 4.0. Propensity score matching method was analyzed using software R 3.5.2 and survival analysis was performed using SPSS v. 20.0 (SPSS, Inc., Chicago, IL).

RESULTS

Patient and treatment characteristics

Table 1 summarizes patient and tumor characteristics between the two groups. Clinical variables including age, sex, Eastern Cooperative Oncology Group performance status, T stage, N stage and histologic differentiation were well balanced between the two groups. 6 (24%) and 10 (40%) patients were T2 stage and 4 (16%) and 6 (24%) patients had LN metastasis in the Surgery + RT group and definitive RT group, respectively. Hemorrhoidectomy was performed in eight patients (32%) and the others underwent local excision in the Surgery + RT group (Table 2). 7 patients (28%) had R0 status after surgery and 12 patients (48%) had R1 or R2 status. HIV status was assessed in 40 patients (80%), and all of them were confirmed as HIV-negative. None of the other patients had clinically suspected HIV infection.

In the Surgery + RT group, all patients received RT to the primary site, with a median RT dose of 50.4 Gy (range, 40–60). Every patient except one received elective RT to the uninvolved pelvic LN area, with a median dose of 45 Gy (range, 36–50.4).

Table 1. Patient characteristics of matched population

Variables	Surgery + RT (N = 25)	Definitive RT (N = 25)	p-value
Age (yr)			1.000
≤70	23	23	
>70	2	2	
Sex			0.747
Male	7	6	
Female	18	19	
ECOG performance status			0.229
0	6	2	
1	16	15	
2	1	3	
Unknown	2	5	
T stage ^a			0.321
Tis	1	0	
T1	18	15	
T2	6	10	
N stage ^b			0.350
N0	21	19	
N1a	3	6	
N1b	0	0	
N1c	1	0	
Histologic differentiation			0.568
W/D	1	1	
M/D	9	10	
P/D	4	1	
Unknown	11	13	

ECOG, Eastern Cooperative Oncology Group; M/D, moderately differentiated; P/D, poorly differentiated; RT, radiation therapy; W/D, well differentiated.

^aT stage of the Surgery + RT group is pathologic stage, and T stage of the definitive RT group is the clinical stage.

^bN stage is the clinical stage in both groups.

Elective RT to the uninvolved inguinal LN area was performed in 19 (76%) patients, with a median dose of 45 Gy (range, 36–48.6). In node-positive patients ($n = 4$), 45–55.8 Gy was delivered to the involved LN.

In the definitive RT group, primary site were irradiated with a median dose of 54 Gy (range, 45–61.2). 24 patients (96%) received elective RT to the uninvolved pelvic LN area, with a median dose of 45 Gy (range, 36–50.4). Elective RT to the uninvolved inguinal LN area was performed in 22 (88%) patients, with a median RT dose of 41.4 Gy (range, 33–50.4). Involved LN was irradiated with a median dose of 49.4 Gy (range, 41.4–50.4).

According to the RT technique, 2D-RT was performed in 6 patients (24%) and 10 patients (40%), 3D-CRT in 16 (64%) and 12 (48%) patients, and IMRT in 3 (9%) and 3 (9%) patients in the Surgery + RT group and definitive RT group,

respectively. CCRT was delivered to 23 patients (92%) and 22 patients (88%) in the Surgery + RT group and definitive RT group, respectively, and majority of the patients received FM regimen.

Treatment outcome and survival

The median follow-up time was 61.6 months (range, 2.7–203.1 months) without differences between the Surgery + RT and definitive RT groups (median, 71.4 vs 60.0 months, $p = 0.24$). In the Surgery + RT group, none of the patients showed recurrence during follow-up. However, one patient died at 6.4 months due to the chemotherapy-related hematologic toxicity. In the definitive RT group, four patients experienced locoregional recurrences, one of whom was accompanied by distant metastasis. There was a statistically significant difference in PFS and LRPFS between the two groups ($p = 0.043$) (Figure 1).

Table 2. Treatment characteristics of matched population

Variables	Surgery + RT (N = 25)	Definitive RT (N = 25)	p-value
Type of surgery			
Hemorrhoidectomy	8	NA	
Excision	17	NA	
Resection status			
R0	7	NA	
R1/2	12	NA	
Unknown	6	NA	
RT dose to primary			0.778
<54 Gy	14	12	
≥54 Gy	11	13	
Concurrent chemotherapy			0.315
RT alone	2	3	
FM	21	16	
FP	2	4	
5-FU	0	2	

RT, radiation therapy; NA, not applicable; FM, 5-fluorouracil plus mitomycin-C; FP, 5-fluorouracil plus cisplatin; 5-FU, 5-fluorouracil

Toxicity

The toxicity profiles are summarized in Table 3. Regarding acute toxicity, hematologic toxicity was mainly leukopenia and non-hematologic toxicity was usually lower gastrointestinal and skin toxicity. There was no statistically significant difference in the toxicity profile between the two groups. For late toxicity, one

patient died due to mitomycin C-induced hemolytic-uremic syndrome at 6.4 months in the Surgery + RT group. Two patients treated with salvage surgery after local recurrence in the definitive RT group had colostomy.

DISCUSSION

The purpose of this study was to evaluate the treatment outcome of RT following incidental tumor resection for ASCC. Patients treated with incidental surgery plus RT for early stage ASCC showed promising results compared to propensity score matched cohort treated with definitive RT.

Regarding RT dose, RTOG 98–11 protocol stated that for all T3, T4, and node-positive patients or T2 patients with residual disease after 45 Gy, additional 10–14 Gy shall be delivered to the primary lesion.⁸ In the current study, majority of the patients received reduced boost dose without compromising treatment outcome. 13 patients (52%) received RT dose below 50.4 Gy to the primary lesion whereas 6 patients (24%) received more than 59 Gy. The efficacy of reduced RT dose in the post-operative treatment of T1–2N0 ASCC has been supported in a few retrospective series.^{5,9,10} Hatfield et al reported the efficacy of the low-dose (30 Gy), involved-field RT for early stage ASCC of 21 patients. Among 17 patients whose tumor was resected, no local recurrence was reported during a median follow-up of 42 months.⁹ Berger et al reported that post-operative CCRT with a reduced RT dose compared to definitive CCRT (median dose 54 vs 59 Gy) showed promising results.⁵

Moreover, even surgery alone for early stage ASCC has been supported in a few studies. Charkrabati et al reported the safety and effectiveness of local excision alone for selected group

Figure 1. Kaplan-Meier curves for overall survival (a), progression-free survival (b), locoregional progression-free survival (c) and distant metastasis-free survival (d) between the patients of the anal squamous cell carcinoma treated with surgery plus RT and definitive RT. RT, radiation therapy.

Table 3. Toxicity profiles

Variables	Surgery + RT (N = 25)		Definitive RT (N = 25)		p-value
	Grade 2	≥Grade 3	Grade 2	≥Grade 3	
Acute toxicity					
Hematologic toxicity	7 (28%)	5 (20%)	5 (20%)	6 (24%)	0.778
Non-hematologic toxicity					
Skin	11 (44%)	5 (20%)	12 (48%)	0 (0%)	0.099
Gastrointestinal	3 (12%)	1 (4%)	6 (24%)	0 (0%)	0.491
Genitourinary	1 (4%)	0 (0%)	1 (4%)	0 (0%)	1.000
Late toxicity					
Hematologic toxicity	1 (4%)	2 (8%)	0 (0%)	0 (0%)	0.074
Non-hematologic toxicity					
Skin	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1.000
Gastrointestinal	0 (0%)	0 (0%)	1 (4%)	0 (0%)	0.492
Genitourinary	1 (4%)	0 (0%)	0 (0%)	0 (0%)	0.368
Colostomy	0 (0%)		2 (8%)		0.149

RT, radiation therapy

of Stage I ASCC.³ With a median follow-up duration of 106 months, 2 of 13 patients had disease recurrence at 21 and 97 months which were effectively salvaged. However, Leon et al reported a high locoregional recurrence rate in T1-2N0 ASCC treated with surgery alone compared to surgery plus CCRT (65% vs 9%), suggesting that surgery alone is insufficient.⁴ A clinical trial is underway to answer the optimal treatment for early stage and/or post-operative ASCC. ACT3 trial is a non-randomized Phase II trial for patients with early, small tumors who have undergone surgery (local excision).¹¹ The aim of this study is to determine whether a treatment strategy of surgery alone, *i.e.* no further treatment, for patients with margins >1 mm, and highly selective low-dose RT with chemotherapy for patients with close margins ≤1 mm.

Regarding prophylactic inguinal nodal irradiation for early stage node-negative diseases, there has been a controversy. Although many studies including RTOG 98-11 advocate elective inguinal RT,^{8,12-14} some reports suggest the omission of inguinal RT for early stage disease.^{9,15-19} Crowley et al reported the treatment results of 30 patient with T3 or less and clinically node-negative disease. They were treated with CCRT using reduced RT field without delivering inguinal nodal irradiation. Among four patients relapsed, one relapsed in the inguinal nodes.¹⁶ Zilli et al also suggested the omission of elective inguinal RT in T2N0 ASCC because inguinal relapse rate remains relatively low in their retrospective study of 116 patients.¹⁷ On the other hand, Matthews et al suggested that elective inguinal RT should be performed in all patients unless more effective staging is introduced.^{12,14} In the present study, six patients without LN involvement omitted inguinal nodal irradiation. Although omitting elective inguinal RT may be discussed in patients with node-negative and early T stage ASCC, thorough LN staging should be accompanied.

The benefits of CCRT on the local control and colostomy-free survival have been demonstrated in randomized trials for locally advanced tumors.²⁰⁻²² However, large retrospective studies have shown that a high local control rate can be achieved for early stage ASCC with RT alone.^{19,23-25} In the current study, CCRT was delivered to 23 patients (92%) causing one severe treatment-related death. Considering substantial treatment toxicity accompanied by CCRT, RT alone might be considered for resected ASCC patients without other risk factors.

The human papillomavirus (HPV) positivity is known to be a favorable prognostic factor in oropharyngeal cancers, and there is an attempt to apply treatment deintensification for these patients.²⁶ In case of ASCC, recent data suggested that HPV- and/or p16-positivity are favorable prognostic factors for OS.^{27,28} Unfortunately, we could not assess the HPV status of the patients in the current study. Further study is needed to explore the possibility of treatment de-intensification for HPV-positive ASCC.

Some limitations of this study need to be addressed. First, this analysis was conducted in a retrospective, multicentric, and non-randomized manner. Despite the small number of population, we tried to compare treatment outcomes of resected ASCC patients with those of the propensity score matched population treated with definitive RT. Second, central pathology review was not assessed, and the resection status was based on the original reports from the surgeon and pathologist. Since the exact tumor margin status after surgery is important for the treatment decision, accurate central pathologic review is recommended in the future studies.

In conclusion, majority of the patients with ASCC after incidental local excision showed excellent local control with post-operative RT. Hence, RT alone or reduced field RT might be

considered after thorough LN staging for the reduced toxicity without compromising treatment result. An ongoing clinical trial will give the answer to the justification of deintensified treatment of this population.

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ETHICAL APPROVAL

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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