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Original Research Article

Metastatic Status and Dissection Effect of Regional/Extraregional Lymph Nodes in Japanese Patients with Squamous Cell Carcinoma of the Anal Canal: A Multicenter Retrospective Cohort Study

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Abstract

Objectives: Squamous cell carcinoma of the anal canal (SCCA) is a rare condition. Standard treatment includes chemoradiotherapy, with surgical treatment reserved for limited cases. In the future, the decrease in surgical frequency makes it more difficult to pathologically assess the depth of tumor invasion and lymph node status; therefore, those studies based on relatively recent surgical cases may offer valuable insights into diagnosing and treating SCCA.

Methods: This multicenter, retrospective cohort study evaluated 435 patients with SCCA in Japan, of which 84 underwent surgical lymph node dissection. The correlation of regional/extraregional lymph node metastasis with T-primary tumor category/depth of tumor invasion, and the index of estimated benefit from lymph node dissection (IEBLD) was evaluated histopathologically.

Results: Primary tumor progression was associated with metastasis and recurrence of the inguinal node and further inferior mesenteric trunk/root node metastasis, an extraregional lymph node. The IEBLD for the inferior mesenteric trunk/root node was 6.9, which was higher than 4.0 IEBLD of the lateral lymph nodes classified as the regional lymph nodes.

Conclusions: The assessment of the primary tumor involvement can predict metastases of the inguinal node and inferior mesenteric trunk/root node and recurrence of the inguinal node. Although the UICC TNM Classification considered the inferior mesenteric trunk/root nodes as extraregional lymph nodes, actively targeting them with the treatment can improve the prognosis.

Keywords

anal canal cancer, squamous cell carcinoma, surgical treatment, extraregional lymph node, index of estimated benefit from lymph node dissection

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Introduction

Anal canal cancer (ACC) is a relatively rare malignant disease, accounting for approximately 2.8% of all digestive system cancers[1]. Because of the histological specificity of the anal canal, ACC encompasses various histological types,

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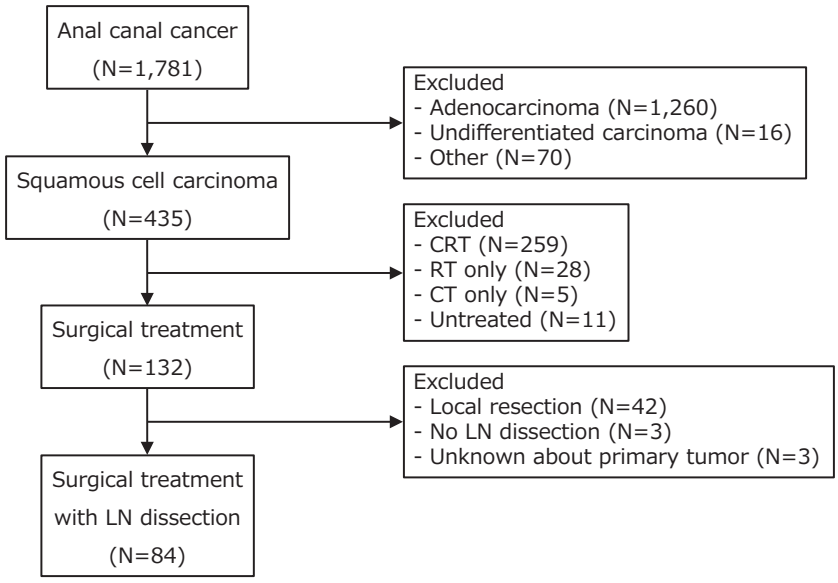

Figure 1. Flowchart showing the patient selection process in this study.
CRT, chemoradiotherapy; RT, radiotherapy; CT, chemotherapy

including squamous cell carcinoma (SCC), adenocarcinoma, small cell carcinoma, undifferentiated cancer, and melanoma[2]. In the United States, 74.5%-84.6% of ACC is described as SCC[3,4], whereas in Japan, adenocarcinoma is the predominant form, comprising 70.7% and SCC comprising 24.0%[5].

Risk factors for squamous cell carcinoma of the anal canal (SCCA) development include human papillomavirus (HPV) infection; a history of receptive anal intercourse or sexually transmitted diseases; a history of cervical, vulvar, or vaginal cancer; immunosuppression following solid organ transplantation or human immunodeficiency virus infection; long-term use of corticosteroids; and smoking[6-10]. Therefore, the HPV vaccine, which reduces the risk of SCCA, has been approved worldwide[11]. In Japan, the HPV positivity rate, a well-known risk factor for SCCA, is also high (approximately 85%), and HPV-16 is frequently observed among HPV genotypes[12].

No clinical trials have directly compared the surgical treatment and chemoradiotherapy (CRT) for SCCA; however, CRT replaced surgery as the primary treatment regimen according to Nigro et al. in 1974, who reported that three patients achieved a complete response with CRT for SCCA[13]. Several randomized controlled trials reported that the combination of 5-FU and mitomycin C (MMC) is currently considered the standard regimen for CRT[14-18]. According to the National Comprehensive Cancer Network (NCCN) guidelines for Anal Carcinoma (version 2. 2023), surgical treatment is limited to patients with local perianal cancer (T1, N0, well or moderately differentiated, or selected T2, N0) and salvage abdominoperineal resection (APR) for locally recurrent and persistent disease[19].

During the initial treatment of SCCA, surgical treatment is usually not performed, making a pathological diagnosis of depth of primary tumor and lymph node status challenging. Magnetic resonance imaging (MRI) and ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) play critical roles in the assessment of primary tumor and lymph node involvement; however, they present several limitations[20-22], thus, the true depth of tumor invasion and lymph node condition may not be accurately assessed. Pathological analysis of these patients and the exploration of new treatment strategies were conducted in relatively recent surgical cases collected from multiple institutions.

Methods

1. Patient selection and data sources

Clinical data of 1,781 patients diagnosed with ACC between 1991 and 2015 and registered at 47 affiliated medical institutions in the Japanese Society for Cancer of the Colon and Rectum (JSCCR) were included for analysis. Of these, 435 patients (24.4%) were diagnosed with SCCA, including seven adenosquamous cell carcinomas. One hundred thirty-two (30.3%) patients with SCCA underwent surgical treatment, and 292 (67.1%) treated with CRT, radiotherapy (RT) and chemotherapy (CT). A total of 84 patients who underwent surgical treatment with regional/extraregional lymph node dissection were included in this study (Figure 1). Three patients with unknown maximum tumor size and depth of tumor invasion were excluded from the analysis.

The UICC TNM Classification of Malignant Tumors 8th

edition/the Japanese Classification of Colorectal, Appendiceal, and Anal Carcinoma; JCCRC, 3rd English edition identified the following clinicopathological data: age, sex, tumor markers in the peripheral blood (SCC antigen and carcinoembryonic antigen), tumor location, macroscopic type, histopathological type, T-primary tumor category, depth of tumor invasion, pathological status of lymph node metastasis, clinical distant metastasis, TNM stage, degree of lymph node dissection, survival outcomes, date of last survival confirmation, recurrent outcomes, and recurrence site.

The depth of tumor invasion was classified and defined based on JCCRC (3rd English edition) as follows: ≤SM, tumor is confined to the mucosa or submucosa and does not invade the internal sphincter; MP, tumor extends to the internal sphincter, but not the conjoined longitudinal muscle; A, tumor has invaded beyond the conjoined longitudinal muscle; and AI, tumor has invaded the levator ani muscles or adjacent organs or structures. The extent of lymph node dissection was classified into four types: D1, complete perirectal lymph node dissection; D2, complete perirectal and inferior mesenteric trunk node dissection; D3, perirectal, inferior mesenteric trunk/root node dissection; and LD, lateral lymph node (internal iliac/obturator node, external iliac node) dissection.

2. Statistical analysis

Cochran-Armitage tests for trend were performed to examine the relevance between the primary tumor stage/depth of tumor invasion and lymph node metastasis/recurrent outcomes, and site of recurrence. The lymph nodes included regional lymph nodes (inguinal, mesorectal, and lateral lymph nodes) and extraregional lymph nodes (inferior mesenteric trunk nodes and inferior mesenteric root nodes). Patients with missing values were excluded from the analysis. The Kaplan-Meier method was used to estimate survival curves, and statistical significance was evaluated using the log-rank test for each cohort. The data were analyzed using EZR software, a graphical user interface for R (the R Foundation for Statistical Computing, Vienna, Austria, version 4.1.2)[23], and a *P*-value of <0.05 was considered statistically significant. To assess the therapeutic value of lymph node dissection, the index of estimated benefit from lymph node dissection (IEBLD) was calculated by multiplying the frequency of lymph node metastasis by the 5-year overall survival (OS) rate, as described by Sasako et al.[24].

This retrospective multi-institutional cohort study was approved by the JSCCR Ethics Review Committee (Registration No.: 88-5) and the Ethics Review Board of the University of Occupational and Environmental Health (Registration No.: UOEHCRB21-185). Informed consent was obtained using the opt-out method with the approval of the JSCCR Ethics Review Committee. This study was performed in compliance with the Declaration of Helsinki.

Results

1. Patient characteristics

The clinicopathological data of 84 patients who underwent surgical treatment with regional/extraregional lymph node dissection are summarized in Table 1. Among 84 patients, 18 (21.4%) were men and 66 (78.6%) were women, and the median age was 69 (range, 37-92) years. For the macroscopic type, the most common was type 2, an ulcerated type with a clear margin (40.5%), followed by type 3, an ulcerated type with infiltration (17.9%). The most frequent histopathological type was moderately differentiated SCC (32.1%). Concerning surgical procedures, APR and total pelvic exenteration were performed in approximately 98% of patients, whereas anal preservation surgery was performed in only 2%. Surgical procedures with D1, D2, D3, and LD were performed in 10.7%, 25.0%, 64.3%, and 47.6% of 84 patients, respectively. T2 (35.7% of patients) was most frequent in the pathological T-primary tumor category, whereas A, tumor has invaded beyond the conjoined longitudinal muscle (46.4%), in depth of tumor invasion.

2. Relationship between the primary tumor and lymph node metastasis

Histopathological examination using Cochran-Armitage tests was performed to determine the trends between the progression of primary tumor (T-primary tumor category/depth of tumor invasion) and the frequency of lymph node metastasis and recurrence (Table 2). The frequency of regional/extraregional lymph node (inferior mesenteric trunk/root node) metastasis was as follows: mesorectal lymph nodes, 38.1%; lateral lymph nodes, 11.9%; inguinal nodes, 17.9%; and extraregional lymph nodes, 13.1%. With primary T-stage progression, based on TNM classification, no statistically significant differences were found; however, inguinal node metastasis tended to occur (*P*=0.067). In contrast, the progression of the depth of tumor invasion was statistically correlated with inguinal node metastasis (*P*=0.048), and no statistical significance was observed, but there was a tendency for extraregional lymph node metastasis to occur (*P*=0.064). Furthermore, there was a significant correlation between the progression of the primary T-stage/depth of tumor invasion and recurrence, particularly of the inguinal node.

3. OS rates of patients undergoing D2/D3 lymph node dissection with stage II-IV

A JSCCR retrospective multi-institutional study reported that the difference in 5-year OS rates by stage between CRT and surgical treatment in SCCA was not statistically significant[12]. Similarly, among patients diagnosed with stage IV due to extraregional lymph node (inferior mesenteric trunk/root node) metastasis, no significant difference in 5-year OS

Table 1. Characteristics of 84 Patients with Squamous Cell Carcinoma of the Anal Canal Who Underwent Surgical Treatment with Lymph Node Dissection in Japan.

Age (years)	Median (range)	68.5 (37–92)
Gender	Male	18 (21.4%)
	Female	66 (78.6%)
SCC (ng/mL)	≤1.5	18 (21.4%)
	>1.5	41 (48.8%)
	Unknown	25 (29.8%)
CEA (ng/mL)	≤5.0	60 (71.4%)
	>5.0	19 (22.6%)
	Unknown	5 (6.0%)
Tumor location	P	81 (96.4%)
	E	3 (3.6%)
Tumor size (mm)	Median (range)	40.0 (2–200)
Macroscopic type	Type 0	2 (2.4%)
	Type 1	12 (14.3%)
	Type 2	34 (40.5%)
	Type 3	15 (17.9%)
	Type 4	1 (1.2%)
	Type 5	14 (16.7%)
	Unknown	6 (7.1%)
Histology	Well differentiated	16 (19.0%)
	Moderately differentiated	27 (32.1%)
	Poorly differentiated	10 (11.9%)
	Differentiation unknown	21 (25.0%)
	Basaloid cell carcinoma	7 (8.3%)
	Adenosquamous cell carcinoma	3 (3.6%)
Type of surgery	Intersphincteric resection	2 (2.4%)
	Abdominoperineal resection	76 (90.5%)
	Total pelvic exenteration	6 (7.1%)
Extent of lymph node dissection	Perirectal lymph nodes: D1	9 (10.7%)
	Inferior mesenteric trunk nodes: D2	21 (25.0%)
	Inferior mesenteric root nodes: D3	54 (64.3%)
Lateral node dissection	NO	44 (52.4%)
	YES	40 (47.6%)
Primary tumor	≤T1	12 (14.3%)
	T2	30 (35.7%)
	T3	12 (14.3%)
	T4	23 (27.4%)
	TX	7 (8.3%)
Depth of tumor invasion	≤SM	8 (9.5%)
	MP	13 (15.5%)
	A	39 (46.4%)
	AI	23 (27.4%)
	Unknown	1 (1.2%)
Regional LNs	N0	23 (27.4%)
	N1	45 (53.6%)
	NX	16 (19.0%)
Stage	≤I	4 (4.8%)
	II	12 (14.3%)
	III	35 (41.7%)
	IV	14 (16.7%)
	Unknown	19 (22.6%)

P: surgical anal canal; E: perianal skin defined as hair-bearing skin within 5 cm of the anal verge.

TNM stage according to the UICC TNM Classification of Malignant Tumors, 8th edition.

Depth of tumor invasion according to the Japanese Classification of Colorectal, Appendiceal, and Anal Carcinoma, 3rd English edition.

Table 2. The Relationship between the Progression of T-Primary Tumor Category, Wall Invasion Depth, and the Frequency of Regional/Extraregional Lymph Node Metastasis and Recurrence.

Metastasis of lymph nodes/ Type of recurrence	T-primary tumor category				*P*-value	Depth of tumor invasion				*P*-value
	≤T1	T2	T3	T4		≤SM	MP	A	AI	
Inguinal nodes	12.5%	15.0%	25.0%	40.0%	0.067	0%	11.1%	28.6%	40.0%	0.048
Perirectal lymph nodes	25.0%	46.7%	50.0%	31.8%	0.935	0%	53.8%	46.2%	31.8%	0.492
Lateral lymph nodes	0%	14.3%	28.6%	21.1%	0.216	0%	0%	21.4%	21.1%	0.155
Internal iliac/Obturator lymph nodes	0%	9.5%	28.6%	15.0%	0.279	0%	0%	17.9%	15.0%	0.273
External iliac lymph nodes	0%	5.0%	0%	5.9%	0.659	0%	0%	3.6%	5.9%	0.413
Inferior mesenteric trunk/root nodes	8.3%	10.3%	8.3%	25.0%	0.147	0%	8.3%	13.2%	25.0%	0.064
Inguinal node recurrence	0%	26.1%	30.0%	43.8%	0.022	0%	20.0%	28.1%	43.8%	0.027
Local recurrence	10.0%	18.2%	20.0%	25.0%	0.359	0%	10.0%	22.6%	25.0%	0.113
Distant metastasis recurrence	10.0%	4.3%	20.0%	12.5%	0.479	14.3%	20.0%	9.4%	12.5%	0.671

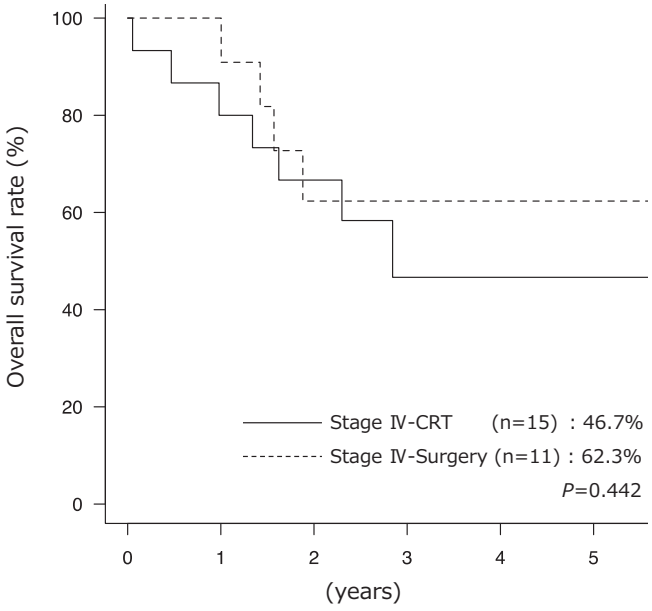

Figure 2. Overall survival rates of patients with stage IV resulting from extraregional lymph node metastasis compared with surgical treatment and CRT/CT only. Stage IV (CRT), stage IV resulting from extraregional lymph node metastasis, with CRT/CT only; Stage IV (Surgery), those with surgical treatment.

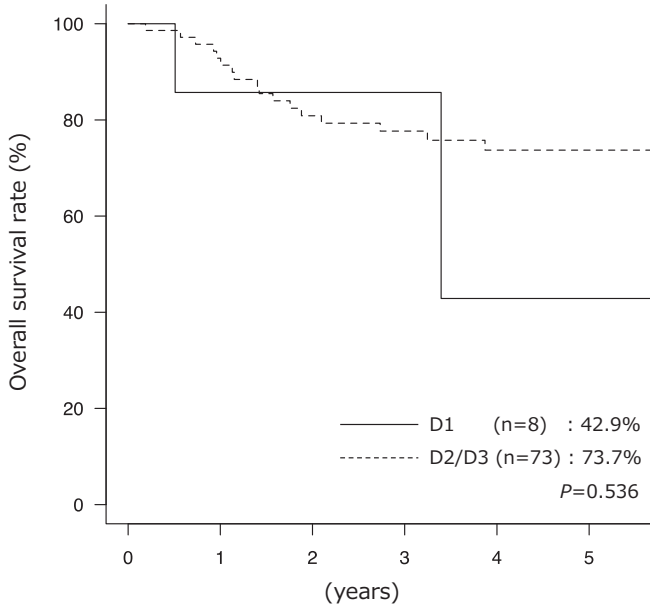

Figure 3. Overall survival rates of patients with surgical treatment in stage II-IV compared with D1 lymph node dissection and D2/D3 lymph node dissection. D1, surgical treatment with D1 lymph node dissection; D2/D3, surgical treatment with D2/D3 lymph node dissection.

rates was observed between patients who received CRT/CT only (46.7%) and those who underwent surgical treatment (62.3%) (*P*=0.442) (Figure 2).

Surgical procedures with D2/D3 lymph node dissection, i.e., extraregional lymph node (inferior mesenteric trunk/root node) dissection, were performed in 75 of 84 patients (89.3%). To assess the effectiveness of surgical procedures with D2/D3 lymph node dissection in patients with stage II-IV, the 5-year OS rates were compared between D1 lymph node dissection and D2/D3 lymph node dissection (Figure 3), i.e., 42.9% and 73.7%, respectively, but no statistically significant difference (*P*=0.536).

4 Therapeutic value of lymph node dissection in SCCA

The therapeutic value of regional/extraregional lymph node dissection in SCCA was examined using IEBLD. Among the regional lymph nodes, the perirectal and inguinal lymph nodes exhibited high IEBLD values of 19.0 and 9.4, respectively. The frequency extraregional lymph node metastasis (inferior mesenteric trunk/root node), the 5-year OS rate of metastasis-positive patients, and IEBLD were 13.1%, 53.0%, and 6.9, respectively. IEBLD for the inferior mesenteric trunk/root node was higher than that of 4.0 for the regional lymph node, specifically the lateral lymph node (in-

Table 3. Frequency of Lymph Node Metastasis, 5-Year OS Rate, and IEBLD for Each Type of Lymph Node.

Type of lymph nodes	Number of patients with metastasis (%)	5-years OS rate of patients with metastasis	IEBLD
Inguinal nodes	15 (17.9)	52.5%	9.4
Perirectal lymph nodes	32 (38.1)	49.9%	19.0
Lateral lymph nodes	10 (11.9)	33.8%	4.0
Internal iliac/Obturator lymph nodes	8 (9.5)	29.2%	2.8
External iliac lymph nodes	2 (2.4)	50.0%	1.2
Inferior mesenteric trunk/root nodes	11 (13.1)	53.0%	6.9

OS, overall survival; IEBLD, the index of estimated benefit from lymph node dissection

ternal iliac/obturator node, external iliac node) (Table 3).

Discussion

In Japan, adenocarcinoma is the predominant histological type of ACC, and SCC is relatively rare[5]. The JCCRC and JSCCR guidelines separately tallied tumors in the anal canal and those in the colorectum. For this reason, the classification of SCCA follows the UICC TNM Classification of Malignant Tumors, and treatment guidelines are based on the NCCN guidelines for Anal Carcinoma. In a JSCCR retrospective multi-institutional study of 435 patients with SCCA, surgical treatment accounted for 93.8%, whereas CRT, RT, or CT were administered in only 6.3% of the patients, from 1991 to 1995. However, from 2001 to 2005, an equal ratio of CRT, RT, or CT to surgical treatment was reported. From 2011 to 2015, surgical treatment was only administered to 14.7% of patients, whereas CRT, RT, or CT was preferred in 84.3% of patients, indicating that NCCN guideline-based treatment approaches are followed in Japan. Furthermore, through a single-arm confirmatory study (JCOG0903) in Japan, S-1/MMC CRT has become one of the primary treatment options for stage II/III SCCA[25].

Surgical treatment for SCCA is limited to the excision of certain localized perianal cancers and salvage APR, and multimodality therapy, including salvage APR, may increase the chances of achieving pelvic control[26]. However, salvage APR for persistent disease was recently reported not to improve the prognosis, which was not the case for disease recurrence[27]. This means that there will be fewer opportunities for pathological examination in the future because of further limitation of surgical treatment. MRI and ^{18}F-FDG PET/CT may be useful in enhancing the diagnostic accuracy of primary tumors/nodal staging in ACC; however, they present several limitations compared to pathological examination[20-22]. Therefore, examining the pathological relationship between tumor depth and lymph node metastasis may provide beneficial information in SCCA. The study results, obtained through Cochran-Armitage tests for the trend, revealed a tendency for inguinal node and extraregional lymph node metastases to occur with the tumor invasion progression. Furthermore, a significant correlation was observed between the progression of the primary T-stage/depth of tumor invasion and recurrence, particularly the recurrence of the inguinal node. Recently, the tumor depth was reported as a predictive factor for local recurrence following local excision of early-stage SCCA[28]. Accurate tumor depth diagnosis, in addition to primary T-stage, is important for determining the treatment regimen and may serve as a predictive factor for inguinal and extraregional lymph node metastasis and inguinal node recurrence.

Inferior mesenteric trunk/root nodes are classified as extraregional lymph nodes, and their metastases correspond to stage IV in the UICC TNM Classification, 8th edition, of SCCA. Among the 435 patients with SCCA in the present study, the frequency of node metastasis was 5.5% but 13.1% in surgical patients, a relatively high result. In patients with stage IV, characterized by extraregional lymph node metastasis, the outcomes for surgical treatment and CRT/CT alone were equivalent. This may be influenced by the fact that D2/D3 lymph node dissection was performed in approximately 90% of surgical patients. The prognosis of patients with D2/D3 lymph node dissection in stage II-IV tended to be better than that of those with D1 lymph node dissection; however, this difference was not statistically significant. Due to the limited sample size of the present study, further accumulation of cases is required to thoroughly examine the impact of the extent of lymph node dissection on prognosis. To assess the therapeutic effectiveness of regional/extraregional lymph node dissection, an evaluation using IEBLD, as described by Sasako et al.[24], was conducted. In Japanese patients with adenocarcinoma of the anal canal, the effectiveness of inferior mesenteric trunk/root node dissection was reported to be similarly low compared with that of lateral lymph node dissection, whereas that of inguinal lymph node dissection was higher[29]. In contrast, in Japanese patients with SCCA, the therapeutic effectiveness of inferior mesenteric trunk/root node (extraregional lymph node) dissection was higher than that of lateral lymph node (regional lymph node) dissection. The 9th edition of the American Joint Committee on Cancer (AJCC) staging system for anal cancer indicated the definition of N1a in the AJCC TNM staging system includes the superior rectal node[30,31]. This definition of the AJCC adequately explains the high effectiveness of

inferior mesenteric trunk/root node dissection in our histopathological examination. Therefore, surgical treatment involving D2/D3 lymph node (inferior mesenteric trunk/root node) dissection is also warranted in salvage APR and may be considered a treatment option for frail CRT-intolerant patients or those with a history of RT in stage IV with extraregional lymph node metastasis. The inferior mesenteric trunk/root nodes could be considered potential treatment targets for surgical treatment, and the same might apply to CRT/RT. Yamada et al. have also reported the need to determine whether inferior mesenteric trunk/inferior mesenteric root node metastases should be classified as stage IV[5].

This retrospective observational study has limitations due to its short follow-up period and some missing data values. Moreover, as this study focused on surgical treatment of SCCA, which is a rare histological type in Japan compared to Western countries, the sample size was small. Consequently, the findings may be specific to the Japanese population. The indication for surgical treatment, including the extent of lymph node dissection, was determined based on the proprietary criteria of each institution; therefore, the potential for selection bias cannot be excluded. However, this study was a multicenter, retrospective cohort study conducted across 47 affiliated medical institutions within the JSCCR. The data obtained from this study are considered highly reliable and broadly applicable. In the future, the establishment of registries and large-scale international prospective cohort studies on ACC is crucial for elucidating the comprehensive characteristics of this disease. Ultimately, these efforts will play a pivotal role in reducing the incidence and improving the prognosis of ACC.

In conclusion, the depth of tumor invasion in SCCA may serve as a predictive factor for metastases of the inguinal node and inferior mesenteric trunk/root node, as well as recurrence of the inguinal node. In addition, inferior mesenteric trunk/root nodes are classified as extraregional lymph nodes; however, proactive treatment approaches directed at these nodes, including both surgical treatment and CRT, may contribute to improved prognosis. In order to validate these treatment approaches, further investigation is anticipated, including prospective clinical trials and randomized controlled trials.

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Conflicts of Interest

There are no conflicts of interest.

Author Contributions

Takayuki Torigoe: Conceptualization, Methodology, Formal analysis, Writing - Original Draft. Keiji Hirata: Conceptualization, Methodology, Writing - Review & Editing. Kazutaka Yamada: Writing - Review & Editing, Project administration. Yoichi Ajioka: Writing - Review & Editing, Project administration. Kenichi Sugihara: Writing - Review & Editing, Project administration.

Ethical Approval and Informed Consent

This retrospective multi-institutional cohort study was approved by the Japanese Society for Cancer of the Colon and Rectum Ethics Review Committee (Registration No.: 88-5) and the Ethics Review Board of the University of Occupational and Environmental Health (Registration No.: UOEHCRB21-185). Informed consent was obtained using the opt-out method with the approval of the Japanese Society for Cancer of the Colon and Rectum Ethics Review Committee.

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