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Oncologic benefit of adjuvant chemotherapy for locally advanced rectal cancer after neoadjuvant chemoradiotherapy and curative surgery with selective lateral pelvic lymph node dissection: An international retrospective cohort study

Yudai Fukui [a], Koya Hida [a, *], Nobuaki Hoshino [a], Seung Ho Song [b], Soo Yeun Park [b], Gyu-Seog Choi [b], Yusuke Maeda [c], Shuichiro Matoba [c], Hiroya Kuroyanagi [c], Sung Uk Bae [d], Woon Kyung Jeong [d], Seong Kyu Baek [d], Yoshiharu Sakai [a]

[a] Department of Surgery, Graduate School of Medicine, Kyoto University, Kyoto, Japan
[b] Colorectal Cancer Center, Kyungpook National University Medical Center, Department of Surgery, School of Medicine, Kyungpook National University, Daegu, South Korea
[c] Department of Gastroenterological Surgery, Toranomon Hospital, Tokyo, Japan
[d] Division of Colorectal Surgery, Department of Surgery, School of Medicine, Keimyung University and Dongsan Medical Center, Daegu, South Korea

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ABSTRACT

Introduction: Intensive local treatment comprising total mesorectal excision (TME) with selective lateral pelvic lymph node dissection (LPND) after neoadjuvant chemoradiotherapy (CRT) for locally advanced rectal cancer (LARC) has received attention among clinicians treating rectal cancer. It remains unclear whether adjuvant chemotherapy (ACT) after intensive local treatment is beneficial for these patients. We evaluated the oncologic benefit of ACT for patients with LARC who received intensive local treatment.
Materials and methods: This international multicentre retrospective cohort study included 737 patients treated in Japan and Korea between 2010 and 2017. The effectiveness of ACT on recurrence-free survival (RFS) was evaluated using univariable and multivariable Cox proportional hazards models, with subgroup analyses to identify subpopulations potentially benefiting from ACT.
Results: The median follow-up was 49 months; the 5-year RFS and local recurrence rates for the entire cohort were 72.1% and 4.9%, respectively; 514 patients (69.7%) received adjuvant chemotherapy, without an oncologic benefit (hazard ratio, 1.14; 95% confidence interval [CI]: 0.79–1.68) demonstrated in the multivariable Cox regression analysis. In subgroup analyses, the distributions of the 95% CI in patients aged ≥70 years and those with ypStage 0 tended to place a disproportionate emphasis that favoured the non-ACT treatment strategy.
Conclusion: Despite achieving good local control with intensive local treatment strategy, the effectiveness of ACT for the LARC patients with CRT followed by TME with selective LPND was not proved. Elderly patients and those with ypStage0 may not receive benefit from ACT after CRT and TME ± LPND.

1. Introduction

The treatment for locally advanced rectal cancer (LARC) mainly comprises neoadjuvant chemoradiotherapy (CRT), total mesorectal excision (TME) with or without lateral pelvic lymph node dissection (LPND), and adjuvant chemotherapy (ACT) [1–3]. CRT and TME are performed to reduce local recurrence in LARC [4,5], whereas ACT is administered to prevent distant metastases by eliminating circulating tumour cells and micrometastases [6].

Local treatment strategies for rectal cancer differ between Asian and Western countries; for instance, LPND is performed in Asian countries, whereas preoperative CRT is undertaken in Western countries [1–3]. Recently, a combined local treatment strategy of

* Corresponding author. Department of Surgery, Graduate School of Medicine, Kyoto University, Kyoto, 606-8507, Japan.
E-mail address: hidakoya@kuhp.kyoto-u.ac.jp (K. Hida).

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Abbreviations

LARC	locally advanced rectal cancer
CRT	chemoradiotherapy
TME	total mesorectal excision
LPND	lateral pelvic lymph node dissection
ACT	adjuvant chemotherapy
RFS	recurrence-free survival
LR	local recurrence
LLR	lateral local recurrence
DR	distant recurrence
CT	computed tomography
HR	hazard ratios
CI	confidence intervals
ASA-PS	American Society of Anesthesiologists Physical Status
RCTs	randomized controlled trials
CR	complete response

CRT followed by TME and selective LPND has been employed in some leading Japanese and Korean hospitals to ensure better local control and prognosis [7–9] because a single local therapy – either neoadjuvant CRT or LPND – may be insufficient to prevent local recurrence [10–15].

ACT is commonly used in both Asian and Western countries, although the effectiveness of ACT for rectal cancer remains unclear. ACT is administered for rectal cancer based on the evidence that was reported from studies of the effectiveness of ACT for colon cancer. To date, however, no study has investigated the effectiveness of ACT for patients with LARC who have received both CRT and radical surgery, including selective LPND.

In this study, we aimed to investigate the effectiveness of ACT on the recurrence-free survival (RFS) and recurrence, local recurrence (LR), lateral local recurrence (LLR), and distant recurrence (DR) rates of patients with LARC in a new era of intensive local treatment, that is, CRT followed by TME and selective LPND.

2. Material and methods

2.1. Ethics

This study was approved by the Ethics Committee of Kyoto University (approval number: R1614) and by the Ethics Committees of all other participating institutions. Based on the opt-out procedure, we posted information about this study on the website and gave participants the opportunity to decline study participation.

2.2. Study design and setting

This international retrospective study was conducted collaboratively at four leading hospitals that specialized in colorectal cancer surgery over a 7-year study period: Kyoto University Hospital and Toranomon Hospital in Japan and Kyungpook National University Medical Center and Keimyung University Dongsan Hospital in Korea.

2.3. Eligibility

Adult patients (aged ≥18 years) who received CRT followed by curative TME for histologically confirmed LARC between April 2010 and March 2017 were eligible for this study. Patients with distant metastases or those who received preoperative systemic chemotherapy (i.e., induction or consolidation chemotherapy) in addition to CRT were excluded.

2.4. Treatment strategy

The indications of CRT for LARC were based on each institutional criterion, such as the status of the circumferential resection margin and radiologically suspected metastatic regional lymph nodes when the inferior border of the tumour was located below the peritoneal reflection (Supplementary Table S1). The CRT regimen consisted of 5-fluorouracil-based chemotherapy and 45 or 50.4 Gy of radiation to the posterior pelvis, including the primary tumour, regional lymph nodes, and the lateral pelvic area. TME was performed in all patients at 6–8 weeks after the completion of CRT. In addition to TME, LPND was performed only when indicated in patients suspected to have lateral lymph node metastasis based on the findings from pre-treatment imaging investigations (selective LPND). The indication of bilateral or unilateral pelvic lymph node dissection was based on the laterality of the possible lymph node metastasis suspected based on pre-treatment imaging [9]. ACT was considered for all patients who received CRT regardless of ypStage following the NCCN guidelines, and the final decision to administer ACT was individually customized based on discussions between clinicians and patients. The addition of Oxaliplatin was considered for limited patients such as relatively younger patients with ypStage II or III in this study period.

2.5. Outcome measures

The primary outcome of this study was RFS, which was defined as the time from surgery to any recurrence or death, whichever occurred first, or to the end of follow-up. The secondary outcomes included the 5-year recurrence, LR, LLR, and DR rates. Postoperative follow-up was performed according to each of the locally applicable follow-up protocols. In Japan, postoperative follow-up was conducted according to the recommendations of the Japanese Society for Cancer of the Colon and Rectum guidelines [3]. Investigation of serum carcinoembryonic antigen levels and computed tomography (CT) of the chest, abdomen, and pelvis were undertaken during the 5-year postoperative follow-up period. A similar follow-up strategy was undertaken in Korea.

2.6. Statistical analysis

Survival curves and recurrence rates were estimated using the Kaplan–Meier method and compared using the log-rank test. ACT effectiveness on RFS was evaluated using univariable and multivariable Cox proportional hazards models to obtain hazard ratios (HR) with 95% confidence intervals (CI). In the multivariable analysis, we adjusted for clinically relevant factors (age, sex, American Society of Anesthesiologists Physical Status [ASA-PS], and ypStage). Subgroup analyses were conducted based on the relevant clinical factors for the induction of ACT. Complete case analysis was performed in all analyses. *P*-values <0.05 were considered statistically significant. All analyses were performed using JMP statistical software (version 14; SAS Institute, Cary, NC, USA).

3. Results

3.1. Patient characteristics

A total of 737 patients met the inclusion criteria for this study. ACT was administered to 514 (69.7%) patients. The baseline characteristics of patients who did (ACT group) and did not receive ACT

Table 1
Patient characteristics.

Characteristic	ACT (n = 514)		Non-ACT (n = 223)	
	n	%	n	%
Age (years)				
<70	394	76.7	151	67.7
≥70	120	23.4	72	32.3
Sex				
Female	154	30.0	77	34.5
Male	360	70.0	146	65.5
ASA-PS				
1	285	55.5	129	57.9
2	213	41.4	84	37.7
3	16	3.1	10	4.5
Distance from AV (cm)				
>5	239	46.7	73	32.7
≤5	273	53.3	150	67.3
cT				
1	3	0.6	2	0.9
2	19	3.7	13	5.8
3	409	79.6	178	79.8
4	83	16.2	30	13.5
cN				
Negative	108	21.0	68	30.5
Positive	406	79.0	155	69.5
cStage				
1	3	0.6	6	2.7
2	105	20.4	62	27.8
3	406	79.0	155	69.5
Surgical procedure				
Sphincter preserving	471	91.6	196	87.9
– LAR	312	60.7	118	52.9
– ISR	159	30.9	78	35.0
Non-sphincter preserving	43	8.4	27	12.1
– APR	40	7.8	23	10.3
– Hartmann	2	0.4	3	1.4
– Pelvic exenteration	1	0.2	1	0.5
Stoma				
None	157	30.5	52	23.3
Yes	357	69.5	171	76.7
– Transient	314	61.1	144	64.6
– Permanent	43	8.4	27	12.1
LPND				
No	421	81.9	180	80.7
Yes	93	18.1	43	19.3
ypT				
0	36	7.0	76	34.1
1	15	2.9	13	5.8
2	107	20.8	53	23.8
3	335	65.2	71	31.8
4	21	4.1	10	4.5
ypN				
0	319	62.1	191	85.7
1	140	27.2	21	9.4
2	55	10.7	11	4.9
ypStage				
0	30	5.8	75	33.6
1	97	18.9	63	28.3
2	192	37.4	53	23.8
3	195	37.9	32	14.4
Differentiation				
Differentiated	481	94.3	206	94.5
Undifferentiated	29	5.7	12	5.5
Lymphatic invasion				
Absent	427	84.4	189	88.3
Present	79	15.6	25	11.7
Venous invasion				
Absent	430	85.2	172	80.4
Present	75	14.9	42	19.6

Abbreviations: ACT, adjuvant chemotherapy; APR, abdominoperineal resection; ASA-PS, American Society of Anesthesiologists physical status; AV, anal verge; ISR, intersphincteric resection; LAR, low anterior resection; LPND, lateral pelvic lymph node dissection.

(non-ACT group) are shown in Table 1. Patients who were younger and those with advanced disease were more likely to receive ACT. The surgical procedure (sphincter preservation, presence of stoma, and LPND) and pathological findings (tumour differentiation, lymphatic invasion, and venous invasion) were balanced between the ACT and non-ACT groups.

3.2. Details of ACT

A detailed description of the ACT in this study is presented in Supplementary Table S2. The mean (standard deviation) administration period was 3.1 (1.8) months, and oxaliplatin was used in 13.0% of the patients in the ACT group.

3.3. Survival and recurrence rates

With a median follow-up of 49 months, the 5-year RFS rate for the entire cohort was 72.1%. The 5-year LR, LLR, and DR rates for the entire cohort were 4.9%, 2.3%, and 22.6%, respectively (Supplementary Fig. S1).

Fig. 1 shows the survival curves for the ACT group. The ACT group had significantly worse 5-year RFS (68.3% *vs.* 81.2%, $P = 0.001$) and 5-year recurrence (14.8% *vs.* 30.2%, $P < 0.001$), LR (1.9% *vs.* 6.1%, $P = 0.036$), and DR (13.8% *vs.* 26.2%, $P < 0.001$) rates compared to the non-ACT group. There was no significant between-group difference in the 5-year LLR rate (1.4% *vs.* 2.6%, $P = 0.484$).

3.4. Risk factors for RFS

In univariable analyses, ASA-PS, ypStage, tumour differentiation, lymphatic invasion, venous invasion, and ACT were significantly associated with RFS (Table 2). After adjustment for clinically relevant confounding factors in multivariable analysis, ACT did not significantly improve RFS (HR, 1.14; 95% CI: 0.79–1.68) ($P = 0.504$).

Fig. 2 shows the effectiveness of ACT in the subgroup analyses according to age and ypStage. ACT was not significantly effective for patients with LARC in all subgroup analyses. The distributions of the 95% CIs in the subgroups of patients aged ≥70 years and those with ypStage 0 tended to place a disproportionate emphasis that favoured the non-ACT treatment strategy.

4. Discussion

In this study, ACT did not significantly improve RFS in patients with LARC who received CRT followed by TME, including selective LPND. Instead, ACT may even be unfavourable for elderly patients and those with ypStage 0 disease.

To date, the survival benefit of ACT for patients with LARC, after CRT and radical surgery, has been controversial. Four randomized controlled trials (RCTs) have been conducted to assess the efficacy of ACT for patients with LARC; however, none of the studies showed ACT efficacy for patients with LARC [16–19]. Moreover, a systematic review of the four RCTs did not reach a definitive conclusion regarding ACT efficacy for patients with LARC [6].

The National Comprehensive Cancer Network guidelines recommend ACT for all patients with LARC who have received CRT regardless of ypStage [2]. The European Society for Medical Oncology clinical practice guidelines state that it is reasonable to administer ACT only for ypStage III and high-risk ypStage II LARC patients who have received CRT [1]. In Japan, where TME plus LPND without CRT is the standard treatment for LARC, ACT is often administered to patients with LARC, after curative surgery, based on

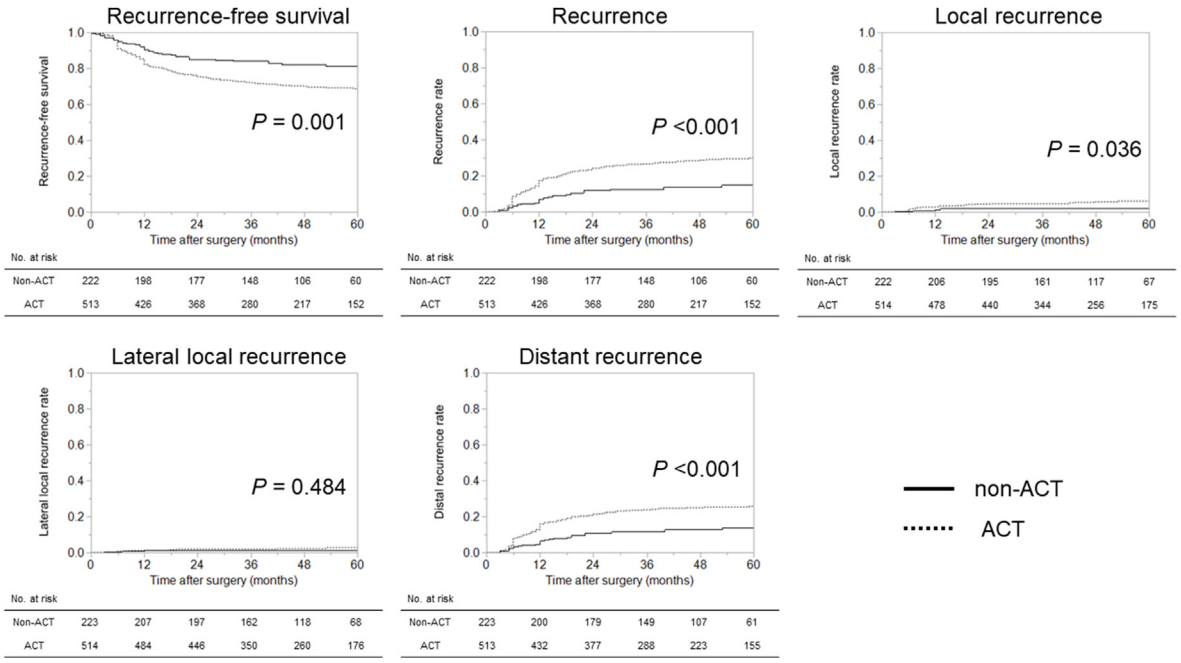

Fig. 1. Kaplan–Meier curves for rates of recurrence-free survival, recurrence, local recurrence, lateral local recurrence, and distant recurrence based on the administration of adjuvant chemotherapy (ACT).

Table 2
Univariable and multivariable analyses of risk factors for recurrence-free survival.

Factor	Univariable analysis			Multivariable analysis		
	Unadjusted HR	95% CI	*P* value	Adjusted HR	95% CI	*P* value
Age (years)						
<70	1			1		
≥70	1.26	(0.92–1.72)	0.151	1.26	(0.91–1.73)	0.168
Sex						
Female	1			1		
Male	1.37	(1.00–1.92)	0.050	1.40	(1.01–1.96)	**0.041**
ASA-PS						
≤2	1			1		
3	2.38	(1.32–3.95)	**0.006**	2.21	(1.22–3.70)	**0.011**
Surgical Procedure						
Sphincter preserving	1			–		
Non-sphincter preserving	1.53	(0.98–2.29)	0.059	–		
LPND						
No	1			–		
Yes	1.13	(0.78–1.60)	0.503	–		
ypStage						
0	0.29	(0.13–0.54)	**<0.001**	0.31	(0.14–0.61)	**<0.001**
1	0.48	(0.29–0.75)		0.49	(0.30–0.78)	
2	1			1		
3	1.69	(1.23–2.32)		1.68	(1.22–2.32)	
Differentiation						
Differentiated	1			–		
Undifferentiated	2.78	(1.72–4.28)	**<0.001**	–		
Lymphatic invasion						
Absent	1			–		
Present	2.00	(1.41–2.79)	**<0.001**	–		
Venous invasion						
Absent	1			–		
Present	1.54	(1.08–2.16)	**0.017**	–		
Adjuvant chemotherapy						
No	1			1		
Yes	1.78	(1.27–2.57)	**<0.001**	1.14	(0.79–1.68)	0.504

Abbreviations: ASA-PS, American Society of Anesthesiologists physical status; CI, confidence interval; HR, hazard ratio; LPND, lateral pelvic lymph node dissection.

the results of an RCT that demonstrated survival benefits of ACT for patients with LARC who underwent TME plus LPND without CRT [20].

Thus far, however, no study has assessed ACT effectiveness for patients with LARC who underwent intensive local treatment, that is, CRT followed by TME and selective LPND. The 5-year LR and LLR

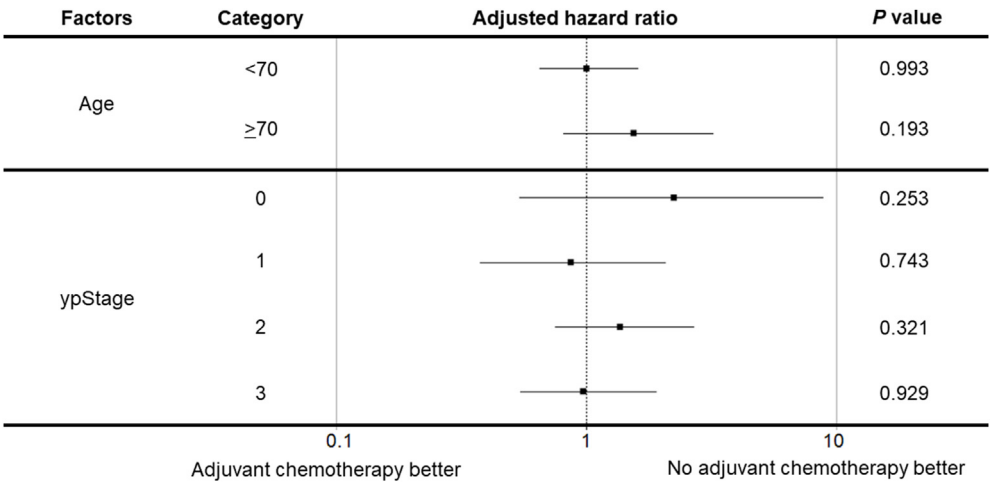

Fig. 2. Forest plot displaying hazard ratios with 95% confidence intervals for recurrence-free survival that were derived from the comparison of patients treated with and without adjuvant chemotherapy in each subgroup.

rates of patients who received CRT and TME without LPND were reported to be approximately 7–10% and 5%, respectively [10,11,21]. In this study, our intensive treatment strategy of CRT followed by TME and selective LPND achieved 5-year LR and LLR rates of 4.9% and 2.3%, respectively, which were better than the standard treatment outcomes reported previously. Conversely, the 5-year DR rate was high, and further reduction of systemic disease recurrence and improved survival were needed. We hypothesized that ACT would be more effective under conditions where local recurrence was well controlled by a combination of CRT and selective LPND. However, the effectiveness of ACT was not proved in this study. The survival curve of the ACT group was worse in Fig. 1. This is due to confounding factors such as age, sex, performance status, and ypStage. To adjust confounders, we performed a multivariable analysis in Table 2 and found that ACT was not independently associated with RFS. The reasons for ACT ineffectiveness in this study may include an insufficient dose of 5-fluorouracil or the small proportion of doublet chemotherapy that included oxaliplatin (Supplementary Table S2). ACT short duration may be related to tolerability to chemo agents and timing of stoma closure. The benefit of the addition of oxaliplatin to fluorouracil-based chemotherapy for rectal cancer was demonstrated by the ADORE and CAO/ARO/AIO-04 trials [22,23]. This study's small proportion of oxaliplatin may be due to the study period. Oxaliplatin was considered for limited patients, such as relatively younger patients with ypStage II or III in the later era of this study period because national guidelines did not strongly recommend the addition of oxaliplatin in the early era of this study period.

Furthermore, we assumed that there were specific patient characteristics that indicate those who could have a greater benefit from ACT. Some studies retrospectively assessed indications of ACT in patients with LARC after CRT. Collette et al. [24] reported that only down-staged (ypT0–2) patients seemed to benefit from ACT, whereas Park et al. [25] reported that post-CRT ACT did not improve the RFS of patients with down-staged rectal cancer. Focusing on patients with a complete response for CRT (ypCR), two large national cohort studies showed that ACT was associated with improved overall survival in LARC patients with ypCR after CRT [26,27], whereas other retrospective studies that assessed survival and recurrence concluded that patients with ypCR may not benefit from ACT [28–30]. There is no consensus on which patients could gain a greater survival benefit from ACT. In this study, we focused on patient age and ypStage. We considered that ACT might be unfavourable for elderly patients and those with ypStage 0 (Fig. 2). Patients achieving ypStage 0 had a low recurrence rate under our intensive local treatment strategy (Supplementary Fig. S2), and ACT benefit would be small in this study. Elderly patients may not be able to tolerate ACT (Supplementary Fig. S3) and therefore may not have sufficient dose intensity. Especially, half of the patients aged ≥70 who treated with Oxaliplatin had a dose reduction due to adverse events in this study. Thus, ACT may have had a negative impact rather than an oncological benefit in the elderly after intensive local treatment.

The strengths of this study include its high generalizability due to the international multicentre study design and the inclusion of many patients who were managed with the intensive local treatment strategy of CRT followed by TME and selected LPND. Moreover, the quality of surgery was highly maintained in these leading Japanese and Korean hospitals. In this study, the incidence of positive surgical margin was less than 1.0%, which is quite low compared to the incidence reported in previous studies (Supplementary Table S3) [31]. The low incidence of positive surgical margins enabled an exact evaluation of the effectiveness of ACT for distant control in this study. Furthermore, we adjusted for as many relevant confounders as possible to minimize the possibility of selection bias. However, this study has several limitations. Several potential confounding factors, such as pathological tumour regression grade and socioeconomic status, were not assessed. Additionally, the indications of CRT and LPND depended on each institutional treatment policy, which may have led to heterogeneity in the treatment strategy across hospitals. RCTs that verify the noninferiority of the non-ACT approach are warranted to resolve these limitations; however, it may be difficult to obtain a large sample size.

In conclusion, the effectiveness of ACT for patients with LARC who received CRT followed by TME and selective LPND was not proved in this study. Elderly patients and those with ypStage 0 are less likely to benefit from ACT after receiving CRT and TME including selective LPND.

Data accessibility statement

Our study protocol does not permit secondary use of the data by other researchers.

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None.

CRediT authorship contribution statement

Yudai Fukui: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft. **Koya Hida:** Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Writing – review & editing. **Nobuaki Hoshino:** Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – review & editing. **Seung Ho Song:** Data curation, Resources, Writing – review & editing. **Soo Yeun Park:** Data curation, Resources, Writing – review & editing. **Gyu-Seog Choi:** Resources, Supervision, Writing – review & editing. **Yusuke Maeda:** Data curation, Resources, Writing – review & editing. **Shuichiro Matoba:** Resources, Writing – review & editing. **Hiroya Kuroyanagi:** Resources, Supervision, Writing – review & editing. **Sung Uk Bae:** Data curation, Resources, Writing – review & editing. **Woon Kyung Jeong:** Resources, Writing – review & editing. **Seong Kyu Baek:** Resources, Writing – review & editing. **Yoshiharu Sakai:** Project administration, Resources, Supervision, Writing – review & editing.

Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2022.01.030.

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