Dosimetric comparison of incidental axillary irradiation between three-dimensional conformal and volumetric modulated arc techniques for breast cancer

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Abstract. Radiotherapy techniques for breast cancer have evolved with efforts to reduce treatment-related side effects. In the present study, we conducted dosimetric analysis of incidental axillary irradiation between volumetric modulated arc therapy (VMAT) and three-dimensional conformal radiotherapy (3D-CRT). A total of 20 patients with early stage left breast cancer who underwent breast-conserving surgery followed by postoperative radiotherapy were analyzed. For VMAT plans, dose-volume constraints were not imposed on the axilla, as with 3D-CRT. We compared the dosimetric parameters of the planning target volumes, organs at risk and axillary level I-III of the two plans. VMAT showed better target coverage and a normal organ-sparing effect compared with 3D-CRT. The incidental axillary irradiation of VMAT was lower; the mean dose and the $V40_{Gy}$ were significantly reduced at all axillary levels, with the exception of no difference in the maximum dose to axillary level I. In conclusion, VMAT decreased incidental axillary irradiation, even in the absence of a dose-volume constraint on the axilla, and can, therefore, decrease the risk of radiotherapy-related lymphedema. However, caution is also required because it is unclear whether this incidental axillary irradiation is beneficial for reducing recurrence on the axilla.

Introduction

Breast cancer treatment has gradually evolved to reduce side effects without compromising treatment outcomes (1,2). Treatment-related side effects negatively affect quality of life, delay treatment, and compromise results. The typical side effects include cardiac toxicity, dermatitis, and lymphedema by multimodal treatments using surgery, adjuvant chemotherapy and radiotherapy (RT) (3-7). Among them, the incidence of breast cancer-related lymphedema (BCRL) after treatment ranges from 14 to 40% (8), caused principally by axillary lymph node dissection (ALND) and adjuvant RT, particularly irradiation of the axillary level I and II (8-10). Sentinel lymph node biopsy has thus become standard treatment for clinically node-negative patients and has become an alternative for complete ALND. RT has also evolved from application of three-dimensional conformal RT (3D-CRT) to intensity-modulated RT (IMRT) or volumetric modulated arc therapy (VMAT) to achieve better conformity with the treatment target and reduce unnecessary irradiation of normal organs (11-22). VMAT has the potential for reduced treatment time compared with IMRT and the clinical use of VMAT is increasing gradually (23). When planning VMAT, dose-volume constraints should be applied to reduce or minimize irradiation of normal tissue. If axillary constraints are imposed in VMAT plan, the axillary dose can be less than that of 3D-CRT. However, it is unclear whether incidental axillary irradiation differs in VMAT without axillary constraint, as with 3D-CRT. In the present study, we investigated the difference in incidental irradiation dose on the axilla and dosimetric characteristics between the two aforementioned plans.

Materials and methods

Ethics approval. This study was approved by The Institutional Review Board of Soonchunhyang University Cheonan Hospital (approval no. SCHCA 2019-11-015-001) (Chungnam, Republic of Korea). Due to the retrospective nature, the requirement to obtain informed consent of the patients was waived by the board. All the procedures in this study were in accordance with the Declaration of Helsinki. Patients who participated in this research had complete clinical data. The signed informed consents were obtained from the patients or the guardians.

Stimulation of radiotherapy. We investigated 20 patients with left breast cancer who received breast-conserving

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surgery followed by postoperative RT in 2015 and 2016. Eighteen patients (90%) were T1 stage and two patients (10%) were Tis stage. There were no axillary metastases in all patients. All patients underwent a free-breathing simulation computed tomography scan using the Philips Brilliance Big Bore (Philips Medical Systems) with 3 mm slice thickness. The patients lay supine on a no-tilting breast board (CIVCO Medical Solutions) without tilting angle, with the arms above the head for appropriate exposure of their breasts and axillae.

Contouring and planning. The clinical target volumes (CTVs) and axillary level I-III were delineated on the basis of the Radiation Therapy Oncology Group contouring guidelines for breast cancer (24). The superior CTV border was the sternal notch or 1 cm above the breast tissue, and the inferior border was 2 cm below the inframammary fold. The medial CTV border was the mid-sternum line and the lateral border was the mid-axillary line or a line 2 cm lateral to breast tissue. To generate the planning target volume (PTV), the CTV was expanded by 1 cm in all directions, and then 3 mm of skin was trimmed from the anterior border of the body surface. Axillary levels I-III were contoured separately, based on the positions of the pectoralis major, pectoralis minor, and intercostal muscles as well as the ribs. The organs at risk (OARs) included the ipsilateral and contralateral lung, heart, and spinal cord. All VMAT and 3D-CRT plans were performed using a radiation treatment planning system (Eclipse ver. 8.9; Varian Medical Systems Inc.) and 6-MV photon. Each 3D-CRT plan consisted of four portals with two optimal tangential angles. The physical wedges in the x- and y-axis were applied once at each portal to improve the dose distribution. Each VMAT plan was performed using the same algorithm with the same energy as for 3D-CRT. The beam arrangement was optimized between 290 and 180 to conform maximally to individual PTVs and afford the OARs the best possible preservation. A ring structure around the PTV was created to obtain the appropriate treatment target conformity. During optimization of VMAT plan, the normal tissue objective was conducted dose-volume constraints for the heart and ipsilateral lung, but not the axilla to set similar conditions between 3D-CRT and VMAT. The prescription dose was 50 Gy in 25 fractions, and the plans were normalized such that ≥95% of the PTV received 100% of the prescription dose.

Statistical analysis. We recorded all doses to the PTVs, OARs and axillary level I-III. Additionally, the integral dose (ID) was reconstructed. The ID was calculated using the simplified formula $ID=V_{body}$ (liters) x $D_{mean\ in\ body,\ outside\ PTV}$ (Gy) (25). Plan data were analyzed using the Mann-Whitney test with the SPSS 18.0 (SPSS, Inc.). P<0.05 was considered to indicate a statistically significant difference.

Results

Patient characteristics. The median age of the patients was 47 years (range: 36-66 years). Invasive ductal carcinoma was confirmed in 17 patients (85.0%). Table I shows the patient characteristics.

Table I. Patient characteristics.

Characteristics	Values[a]
Age, year	47 (36-66)
T stage	
Tis	2 (10.0)
T1	18 (90.0)
Pathology	
DCIS	2 (10.0)
IDC	17 (85.0)
ILC	1 (5.0)
Volumes of structures	
Body	19,180.5 (13,984.4-27,079.2)
PTV	446.3 (102.9-1,174.6)
Heart	605.9 (516.0-968.7)
Spinal cord	50.4 (36.9-66.9)
Ipsilateral lung	927.8 (627.3-1,324.5)
Total lung	2,162.3 (1,573.9-2,996.6)
Axilla	
Level I	63.6 (35.7-106.0)
Level II	20.7 (13.3-41.8)
Level III	13.5 (9.3-24.3)

[a]Values are presented as median (range) or number (%). DCIS, ductal carcinoma *in situ*; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; PTV, planning target volume.

Doses of PTV and OARs. VMAT afforded ≥90% PTV coverage more reliably than did 3D-CRT. The $V45_{Gy}$ of VMAT was 99.7±0.2%, vs. 99.2±0.9% for 3D-CRT (P=0.002). However, the mean PTV dose did not differ between the two plans. Fig. 1 shows a representative image of both plans with the PTV and isodose lines.

Table II lists the OAR and ID data of the two plans and Fig. 2 shows the cumulative dose-volume histograms. In brief, moderate-to-high doses ($V25_{Gy}$ and $V40_{Gy}$) of VMAT were lower than the 3D-CRT doses in all OARs. For the heart, VMAT was significantly lower than 3D-CRT ($V25_{Gy}$, 6.3% vs. 14.8%; $V40_{Gy}$, 1.8% vs. 12.1%, respectively, P<0.001). For the ipsilateral lung, the moderate-to-high VMAT doses were lower than those for 3D-CRT ($V25_{Gy}$, 10.9% vs. 21.3%; $V40_{Gy}$ 3.4% vs. 16.2%, respectively, P<0.001). However, $V5_{Gy}$ was higher for VMAT than 3D-CRT. For the heart, the $V5_{Gy}$ for VMAT was higher than that for 3D-CRT (69.9% vs. 27.1%, respectively, P<0.001). For the ipsilateral lung, the $V5_{Gy}$ for VMAT was higher than that for 3D-CRT (74.5% vs. 39.1%, respectively, P<0.001). The mean dose to the ipsilateral lung and spinal cord was higher for VMAT than 3D-CRT (P<0.001), while for the heart there was no difference between the two plans (9.5 Gy vs. 9.3 Gy, respectively). Lastly, the ID to the body was higher for VMAT than 3D-CRT (82.7 Gy·L vs. 64.6 Gy·L, respectively, P<0.001).

Comparison of axillary doses. The doses to axillary levels I-III were analyzed separately. The mean, maximum, $V25_{Gy}$ and

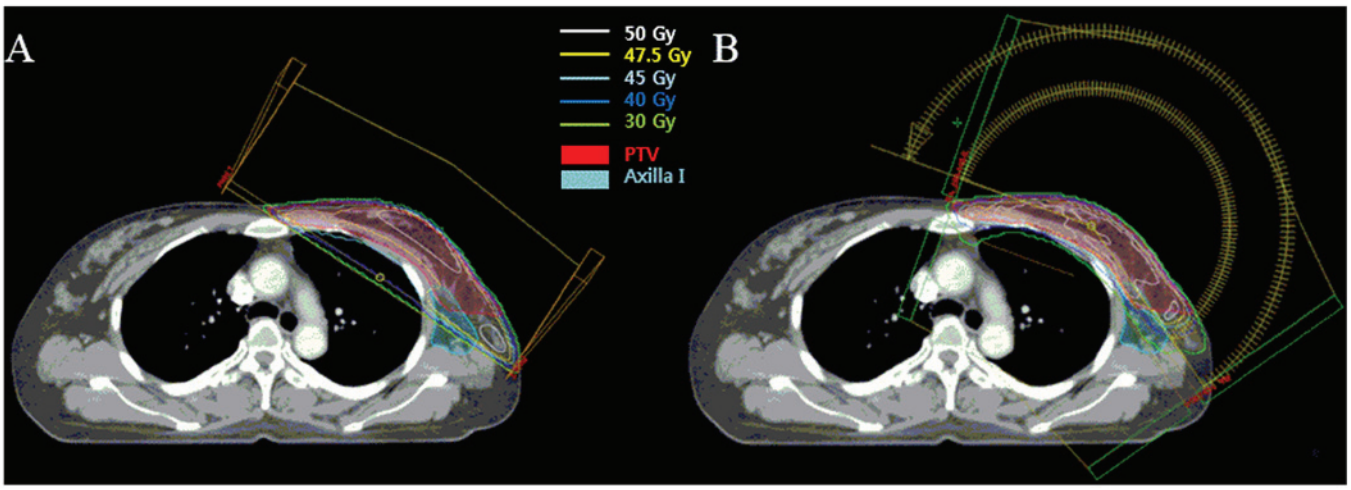

Figure 1. Typical radiotherapy plans of three-dimensional conformal radiotherapy and volumetric modulated arc therapy. (A) Each of two tangent angles used two portals with physical wedges in the x- and y-axis. (B) Two arcs, clockwise and counterclockwise, were from 290 to 145°. PTV is indicated by the red translucent area; axilla level I is indicated by the dark green translucent area; the white line indicates 50 Gy; the yellow line indicates 47.5 Gy; the cyan line indicates 45 Gy; the blue line indicates 40 Gy; the green line indicates 30 Gy. PTV, planning target volume.

Table II. Dosimetric comparison of radiation dose delivered to PTV, organs at risk and integral dose between 3D-CRT and VMAT plans.

Structure	Parameters	3D-CRT	VMAT	P-value
PTV	D_{Mean} (Gy)	49.8±0.2	49.8±0.0	0.709
	$V45_{Gy}$ (%)	99.2±0.9	99.7±0.2	0.002
	$V47.5_{Gy}$ (%)	90.4±2.5	93.1±1.7	0.001
Heart	D_{Mean} (Gy)	9.5±0.8	9.3±1.8	0.575
	$V5_{Gy}$ (%)	27.1±8.9	69.9±14.4	<0.001
	$V25_{Gy}$ (%)	14.8±5.4	6.3±2.8	<0.001
	$V40_{Gy}$ (%)	12.1±5.0	1.8±1.4	<0.001
Ipsilateral lung	D_{Mean} (Gy)	12.4±2.1	10.9±1.5	0.001
	$V5_{Gy}$ (%)	39.1±5.3	74.5±10.7	<0.001
	$V25_{Gy}$ (%)	21.3±4.3	10.9±3.0	<0.001
	$V40_{Gy}$ (%)	16.2±4.5	3.4±1.8	<0.001
Total lung	D_{Mean} (Gy)	5.9±1.1	7.1±1.0	<0.001
	$V5_{Gy}$ (%)	16.9±2.9	48.8±9.4	<0.001
	$V25_{Gy}$ (%)	9.2±2.2	4.7±1.4	<0.001
	$V40_{Gy}$ (%)	7.0±2.2	1.5±0.8	<0.001
Spinal cord	D_{Mean} (Gy)	0.7±0.2	1.7±0.5	<0.001
	$V5_{Gy}$ (%)	0.0±0.0	0.1±0.1	0.001
	$V25_{Gy}$ (%)	0.0±0.0	0.0±0.0	-
	$V40_{Gy}$ (%)	0.0±0.0	0.0±0.0	-
Body	ID (Gy·L)	64.6±17.7	82.7±20.3	<0.001

Data are presented as the mean ± SD. 3D-CRT, three-dimensional-conformal radiotherapy; D_{mean}, mean dose; PTV, planning target volume; VMAT, volumetric modulated arc therapy; Vn, percentage of volume receiving at least n Gy.

Table III. Dosimetric comparison of radiation dose delivered to axilla level I-III between 3D-CRT and VMAT.

Structure	Parameters	3D-CRT	VMAT	P-value
Level I	D_{Mean} (Gy)	39.5±4.7	36.8±6.4	0.010
	D_{Max} (Gy)	49.3±7.2	52.4±0.8	<0.001
	$V25_{Gy}$ (%)	83.2±12.2	80.0±17.2	0.313
	$V40_{Gy}$ (%)	74.3±15.1	54.3±16.1	<0.001
Level II	D_{Mean} (Gy)	18.0±12.4	14.2±11.3	<0.001
	D_{Max} (Gy)	37.4±11.7	33.5±18.9	0.391
	$V25_{Gy}$ (%)	32.6±32.1	24.0±30.3	0.001
	$V40_{Gy}$ (%)	19.8±26.9	6.5±11.8	0.002
Level III	D_{Mean} (Gy)	8.0±8.7	6.3±6.5	0.025
	D_{Max} (Gy)	24.0±18.2	19.1±17.1	0.003
	$V25_{Gy}$ (%)	11.7±20.6	5.1±11.9	0.005
	$V40_{Gy}$ (%)	5.2±11.2	0.6±2.2	0.018

Data are presented as the mean ± SD. 3D-CRT, three-dimensional-conformal radiotherapy; D_{max}, maximum dose; $D_{mean,}$ mean dose; VMAT, volumetric modulated arc therapy; Vn percentage of volume receiving at least n Gy.

$V40_{Gy}$ are shown in Table III and Fig. 3. The mean doses to each axillary level were significantly lower for VMAT vs. 3D-CRT. The $V25_{Gy}$ and $V40_{Gy}$ for VMAT were significantly lower than those for 3D-CRT, except the $V25_{Gy}$ of axillary level I. The max VMAT doses to axillary levels II and III were lower than those for 3D-CRT, while that to axillary level I was not.

Thus, target conformity was better for VMAT than the 3D-CRT; the incidental axillary dose with VMAT was lower than that with 3D-CRT, despite non-imposition of an axillary dose-volume constraint. The moderate-to-high doses delivered to the OARs were lower with VMAT than 3D-CRT, while the low dose and ID to the body were higher with VMAT than 3D-CRT.

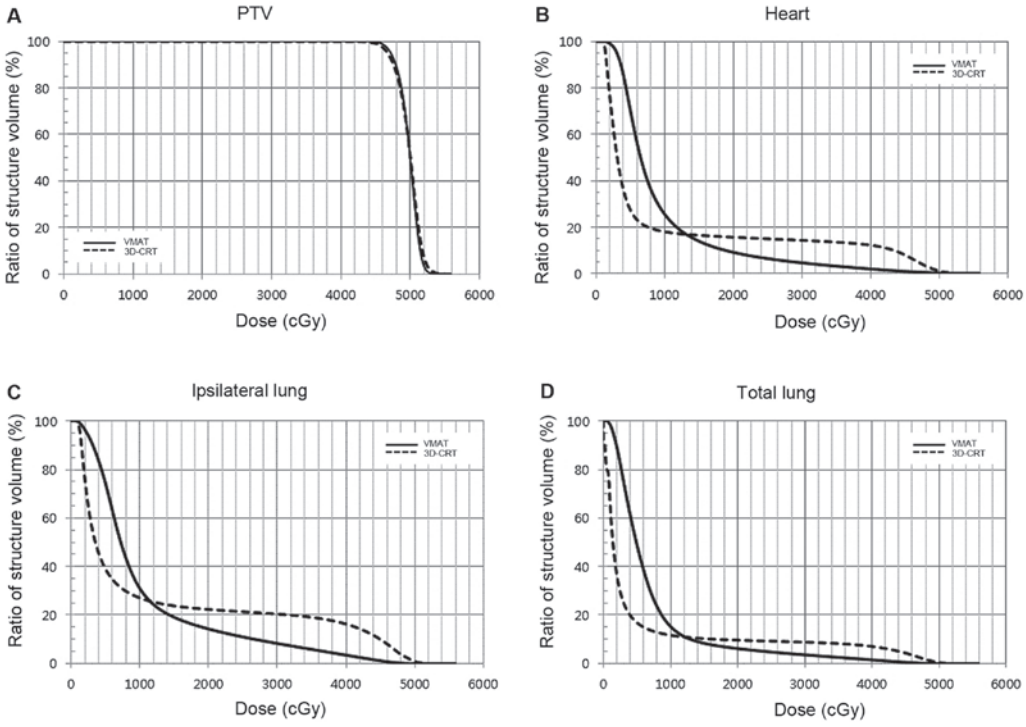

Figure 2. Cumulative dose-volume histogram of (A) PTV and organs at risk, including (B) heart, (C) ipsilateral heart and (D) total lung between 3D-CRT (dashed line) and VMAT (solid line) in all patients. PTV, planning target volume; 3D-CRT, three-dimensional conformal radiotherapy; VMAT, volumetric modulated arc therapy.

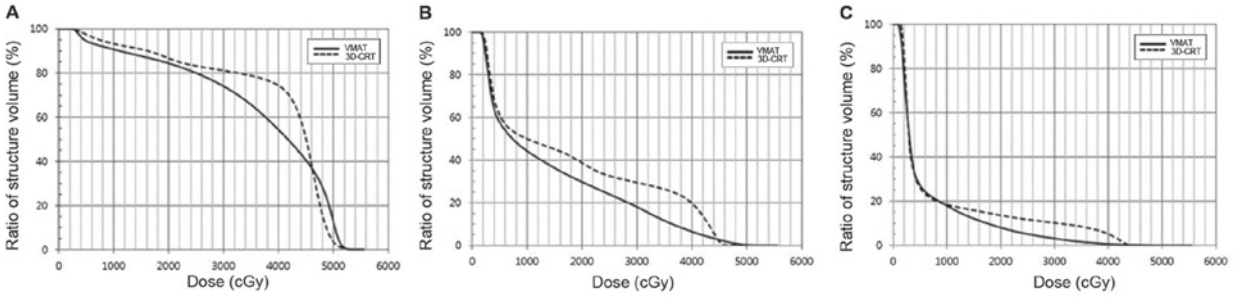

Figure 3. Cumulative dose-volume histogram of axilla (A) level I, (B) level II and (C) level III between 3D-CRT (dashed line) and VMAT (solid line) in all patients. 3D-CRT, three-dimensional conformal radiotherapy; VMAT, volumetric modulated arc therapy.

Discussion

Radiation-related side effects in breast cancer patients vary. One of the most common is ipsilateral arm edema (3-7). In the After Mapping of the Axilla: Radiotherapy Or Surgery (AMAROS) study, 15% of patients showed clinical signs of lymphedema 1 year after axillary RT without ALND, 14% at 3 years, and 11% at 5 years (6). Interruption of the axillary lymphatic system due to breast cancer treatment results in BCRL, which has a negative effect on quality of life in breast cancer patient (26-28).

We did not impose a dose-volume constraint on the axilla to ensure similar conditions between VMAT and 3D-CRT. Nevertheless, we found that VMAT significantly lowered the incidental axillary radiation dose and, at the same time, increased the target conformity compared with 3D-CRT. During the VMAT optimization process, an option of normal tissue objective and the ring structure would also have been helpful to reduce axillary irradiation and improve target conformity (29,30). The better conformity reduces unnecessary radiation doses to tissues other than targets, thereby effectively reducing RT-related side effects, including lymphedema (31,32).

A few studies have reported on reducing incidental axillary irradiation in breast cancer patients using several RT techniques. According to Kataria *et al*, who did not impose a dose-volume constraint on the axilla, as in the present study, when comparing IMRT (two tangential semi-opposed beams with gantry angles of 130-145 and 305-320 for the medial and lateral fields, respectively) with 3D-CRT (tangential beams with the same angles and orientations as IMRT), the incidental axillary irradiation with IMRT was lower than with 3D-CRT at levels I and II (19). Zhang *et al* also imposed no constraint on the axilla and compared between conformal techniques such as simplified-IMRT (s-IMRT; five to seven beams) with forward IMRT (for-IMRT; two tangential

opposite beams with the field-in-field technique) (33). The unintended dose to the axilla, especially level I, was lower with s-IMRT than for-IMRT. The mean $V40_{Gy}$, $V45_{Gy}$, and $V47.5_{Gy}$ of axillary levels II and III were very low in both conformal techniques, and the results were similar to the VMAT plans in the present study. Lee *et al* showed that IMRT (seven fields with a skin-sparing technique) delivered significantly less incidental axilla radiation than 3D-CRT (parallel-opposite tangential fields with the field-in-field technique), although they did not report whether axilla constraint was considered during IMRT (34). To our knowledge, some studies have compared incidental axillary irradiation with IMRT, but none discussed incidental axillary irradiation with VMAT. According to the aforementioned studies and the present study, even if there is no constraint on the axillary region, it is possible to reduce the incidentally irradiated dose to the axilla by using advanced RT techniques, especially with VMAT.

However, this incidental or unintended axillary irradiation may not always be harmful. Although it comes short of a therapeutic dose, incidental irradiation of the axilla from tangential fields may exert some effects on controlling axillary occult disease (35). Krasin *et al* stated that treatment with tangential fields using three-dimensional techniques still had a role in controlling subclinical disease of axilla, despite a significant incidental dose to the axilla (36). Fisher *et al* reported that in early breast cancer patients, the axillary recurrence rate following postoperative breast RT was 4.5% compared with 7.2% in the surgery alone group (37). Further studies are necessary to determine whether reducing incidental axillary irradiation with advanced RT techniques, including VMAT, will have a negative impact on regional axillary recurrence.

There is a concern that patients treated with the VMAT technique are exposed to a higher ID to the body, unwanted spinal cord irradiation and higher low-level doses to other OARs such as lung and heart, compared with 3D-CRT. Because patients with early-stage breast cancer have a relatively long life expectancy, the higher ID to the body and low-dose bath of normal organs has been criticized due to the potential risk of secondary cancer (38,39). However, there is no evidence that this has a role in carcinogenesis (40), and even if secondary cancers develop from RT, the attributable mortality rate was estimated to be only 1~2% after 10 years (41). Although malignant potential risks are suspected low, it should be noted that other clinical side effects such as symptomatic lung injury or cardiac events can be caused by low radiation doses (42,43). Therefore, the risk should be balanced against the apparent benefits of decreasing the side effects.

In conclusion, this study showed that VMAT, even without dose-volume constraint on the axilla, significantly reduces incidental axillary irradiation compared with 3D-CRT. Clinical studies should be followed to prove that this dosimetric change with advanced RT techniques can reduce BCRL while maintaining efficacy in disease control.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

IYJ analyzed and interpreted patient data, and wrote the manuscript. ESK analyzed and interpreted data. WCK and CKM acquired and analyzed data. SGY designed the study and critically revised the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by The Institutional Review Board of Soonchunhyang University Cheonan Hospital (approval no. SCHCA 2019-11-015-001) (Cheonan, Republic of Korea). Due to the retrospective nature, the requirement to obtain informed consent of the patients was waived by the board. All the procedures in this study were in accordance with the Declaration of Helsinki. Patients who participated in this research had complete clinical data. The signed informed consents were obtained from the patients or the guardians.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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