Nucl Med Mol Imaging (2015) 49:26–32
DOI 10.1007/s13139-014-0298-9

ORIGINAL ARTICLE

The Clinical Value of Hybrid Sentinel Lymphoscintigraphy to Predict Metastatic Sentinel Lymph Nodes in Breast Cancer

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Received: 24 April 2014 / Revised: 15 September 2014 / Accepted: 19 September 2014 / Published online: 17 October 2014

Abstract
Purpose Hybrid imaging techniques can provide functional and anatomical information about sentinel lymph nodes in breast cancer. Our aim in this study was to evaluate which imaging parameters on hybrid sentinel lymphoscintigraphy predicted metastatic involvement of sentinel lymph nodes (SLNs) in patients with breast cancer.
Methods Among 56 patients who underwent conventional sentinel lymphoscintigraphy, 45 patients (age, 53.1±9.5 years) underwent hybrid sentinel lymphoscintigraphy using a single-photon emission computed tomography (SPECT)/computed tomography (CT) gamma camera. On hybrid SPECT/CT images, we compared the shape and size (long-to-short axis [L/S] ratio) of the SLN, and SLN/periareolar injection site (S/P) count ratio between metastatic and non-metastatic SLNs. Metastatic involvement of sentinel lymph nodes was confirmed by pathological biopsy.
Results Pathological biopsy revealed that 21 patients (46.7 %) had metastatic SLNs, while 24 (53.3 %) had non-metastatic SLNs. In the 21 patients with metastatic SLNs, the SLN was mostly round (57.1 %) or had an eccentric cortical rim (38.1 %). Of 24 patients with non-metastatic SLNs, 13 patients (54.1 %) had an SLN with a C-shape rim or eccentric cortex. L/S ratio was 2.04 for metastatic SLNs and 2.38 for non-metastatic SLNs. Seven (33 %) patients had T1 primary tumors and 14 (66 %) had T2 primary tumors in the metastatic SLN group. In contrast, 18 (75 %) patients had T1 primary tumors and six (25 %) had T2 tumors in the non-metastatic SLN group. S/P count ratio was significantly lower in the metastatic SLN group than the non-metastatic SLN group for those patients with a T1 primary tumor (p=0.007).
Conclusions Hybrid SPECT/CT offers the physiologic data of SPECT together with the anatomic data of CT in a single image. This hybrid imaging improved the anatomic localization of SLNs in breast cancer patients and predicted the metastatic involvement of SLNs in the subgroup of breast cancer patients with T1 primary tumors.

Keywords Hybrid sentinel lymphoscintigraphy · Sentinel lymph nodes · Breast cancer · Metastatic prediction

Introduction

Axillary lymph node status is significant for staging and treatment planning in women with breast cancer, because it is the most important prognostic factor [1]. A sentinel lymph node (SLN) is defined as the first lymph node in the lymphatic drainage of the primary tumor [2]. Tumor cells spread initially through the lymphatic pathway to one or more SLNs. Therefore, the detection and biopsy of SLNs has been implemented in the surgical treatment of breast cancer and malignant melanoma [3]. Based on the concept that the absence of SLN metastasis indicates the absence of metastases in other axillary lymph nodes, axillary lymph node dissection is not performed when no SLN metastasis is present. Sentinel lymph node biopsy has therefore replaced axillary lymph node dissection for nodal staging in recent years [4, 5].

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Planar lymphoscintigraphy with technetium-99m-labeled colloid is currently used to detect sentinel lymph nodes in most patients with breast cancer. The first hot spot in the lymphatic drainage represents the SLN [6]. However, in the planar image, the precise location of a sentinel lymph node may be difficult to determine because of inaccurate anatomical localization.

Recently, hybrid imaging involving use of a single-photon emission computed tomography (SPECT) camera and a computed tomography (CT) scanner in a single device was introduced [7]. The patient's position does not change between the two studies, and fusion of the two images into one image is straightforward [8]. Furthermore, corrections for attenuation and scatter have improved sentinel node visualization on SPECT compared with planar lymphoscintigraphy [9, 10]. Hybrid imaging results in clear depiction of the sentinel node within an anatomical landscape, providing a valuable surgical roadmap [11].

Previous studies have shown that SLN visualization in patients with breast cancer is influenced by several factors, including procedural variation and patient factors such as age, body mass index (BMI), tumor size, and metastasis to the SLN [12–14]. Lee et al. [15] studied predicting nonsentinel lymph node metastasis in patients with breast cancer using sentinel lymphoscintigraphy. Other studies have reported a correlation between SLN count and SLN metastasis. These studies reported a lower SLN detection rate in patients with metastases to the axillary lymph nodes than in patients with no metastases [16, 17].

Most prior studies have predicted lymph node status by assessing the size and shape of lymph nodes [18–21]. Attempts at axillary staging by means of anatomical imaging of the axilla with CT or magnetic resonance imaging (MRI) have proved more useful than clinical examination [22].

The purpose of this study was to determine hybrid lymphoscintigraphy factors predictive of metastatic SLN. We assumed that SLN counts in patients with breast cancer would correlate with the presence or absence of metastasis through hybrid SPECT/CT.

Materials and Methods

Patients

In this prospective study, 56 breast cancer patients (age, 53.1± 9.5 years, range, 39–74 years) with unifocal primary invasive breast cancer who were scheduled for mastectomy/ lumpectomy and axillary LN dissection at Chonbuk National University Hospital between April and December 2012 were examined preoperatively with SPECT/CT. Patients who had received neoadjuvant chemotherapy were excluded from this study. Furthermore, patients with distant metastases and two or more SLNs confirmed by biopsy were excluded. These criteria were instituted to maintain a one-to-one correspondence between the detected node and the SLN removed for biopsy. This study was approved by the institutional review board of our institution. Informed consent was waived because of the retrospective design of this study.

Hybrid Lymphoscintigraphy

A 74-MBq dose of Tc-99m phytate was injected immediately before lymphoscintigraphy. The tracer was injected into the periareolar area, and planar images were obtained 30 min after radiotracer injection (Fig. 1). A dual-head gamma camera equipped with low-energy high-resolution collimators was used. Both anterior images were acquired routinely, with additional images obtained if needed. SPECT/CT images were acquired immediately after acquisition of delayed planar images. SPECT/CT system (Symbia T-16; Siemens, Erlangen, Germany) consisted of a dual-head variable-angle gamma camera equipped with low-energy high-resolution collimators and a multislice spiral CT component optimized for rapid rotation. SPECT acquisition (128×128 matrix, 60 frames, 25 s/frame) was performed using six angular steps in a 20-s time frame. For CT (130 keV, 17 mAs, B60s kernel), 5-mm slices were obtained. After reconstruction, SPECT images

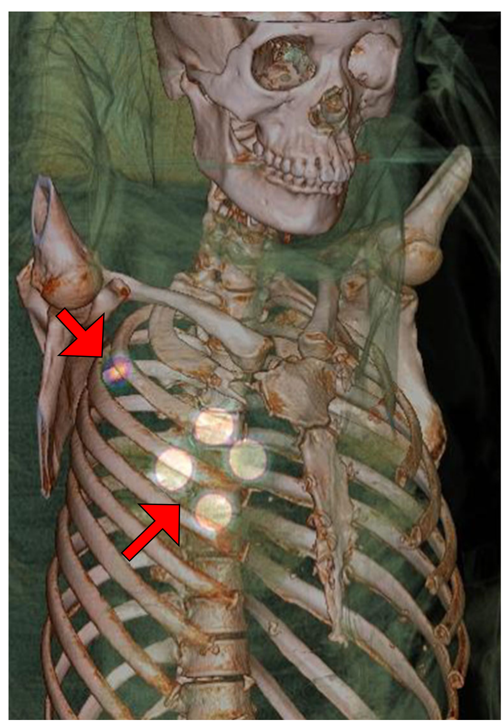

Fig. 1 A representative hybrid lymphoscintigraphy image with breast cancer. This 3D image shows sites of SLNs and the periareolar injection area

were corrected for attenuation and scatter. Both SPECT and CT axial 5-mm slices were generated using a Symbia application package (Siemens). These were transferred to a PACS after generation of DICOM files. SPECT/CT images were also analyzed using two-dimensional orthogonal reslicing in axial, sagittal, and coronal orientations. The size and shape of the SLN as determined by the CT component of hybrid lymphoscintigraphy were used as predictive factors to detect metastatic SLNs.

Predictive Parameters

Patient clinical records were reviewed to collect data such as age, primary tumor size (T stage), L/S axis ratio (long-to-short axis ratio) of the SLN, and S/P count ratio (SLN/periareolar injection site maximum count ratio). All patients had biopsy-proven invasive cancer. We measured the length (cm) of the longitudinal and transverse diameters of the SLN, respectively, and calculated the L/S axis ratio (longitudinal/transverse diameter). S/P count ratio was defined as the ratio of the maximum count in the SLN to that of the periareolar injection site (Fig. 2).

Sentinel Lymph Node Biopsy

Immediately before the operation, 1 ml patent blue dye was injected into or around each tumor (intratumoral or peritumoral injection). Intraoperatively, dye and gamma ray detection were used to localize the sentinel node. If SLN was detected by dye or gamma ray, the result was considered positive and, if no SLN was observed, it was considered negative. Finally, prediction of metastasis was verified by SLN biopsy.

Statistical Analysis

Statistical analyses were performed using SPSS software (Version 20.0; SPSS IBM, Chicago, IL, USA). Differences between metastatic and non-metastatic SLNs were calculated using the Mann–Whitney *U* test and Chi-square test, with *P* values <0.05 defined as statistically significant.

Results

All descriptive patient characteristics of the study population are listed in Table 1. Fifty-six patients were enrolled in this study. Mean age was 53±9.5 years (range, 39–74 years). Mean invasive main tumor size was 1.54 cm (range, 0.1–2.8 cm). Only 45 patients out of 56 underwent SLN mapping with hybrid lymphoscintigraphy.

Pathological biopsy was performed in all 45 of these patients. Twenty-one of 45 patients (46.7 %) had a metastatic SLN, and 24 (53.3 %) had a non-metastatic SLN. In the 21 patients with a metastatic SLN, the SLNs were mostly round (57.1 %) or characterized by an eccentric cortical rim (38.1 %). Of 24 patients with a non-metastatic SLN, 13 patients (54.1 %) had an SLN with a C-shape rim or eccentric cortex, while the SLN was round in the other 11 patients (Fig. 3). The L/S ratio was 2.04 for metastatic SLNs and 2.38 for non-metastatic SLNs. Metastatic SLNs were associated with T1 (n=7, 33 %) or T2 (n=14, 66 %). Non-metastatic SLNs were associated with T1 (n=18, 75 %) and T2 (n=6, 25 %).

Among these parameters, tumor size appeared to be a significant risk factor in univariate analysis (P=0.01). Additionally, S/P count ratio was significantly lower in the metastatic SLN group than the non-metastatic SLN group for

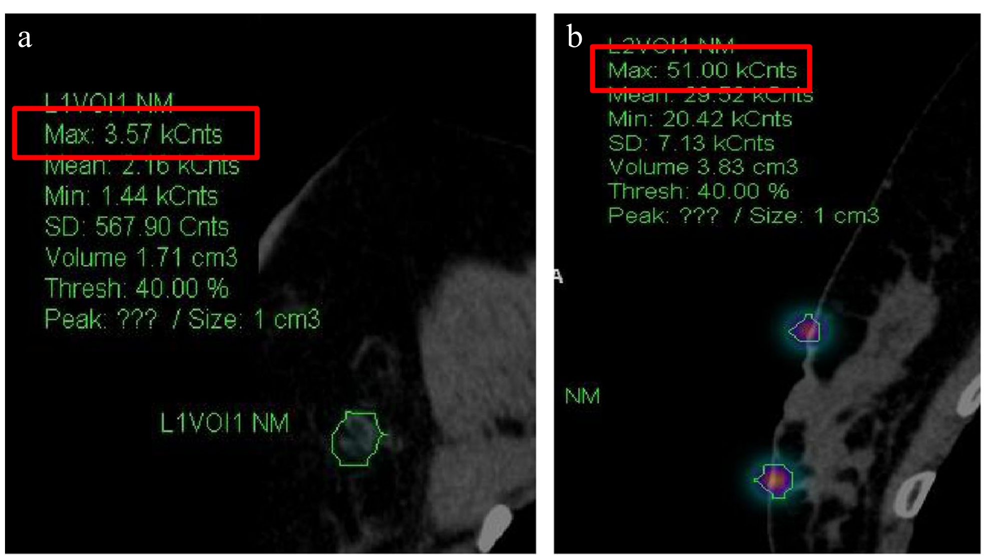

Fig. 2 Examples of S/P count ratio. This representative hybrid lymphoscintigraphy images show the maximum counts of SLN (**a**) and periareolar injection site (**b**). And S/P count ratio was defined as the ratio of the maximum count in the SLN to that of the periareolar injection site

Table 1 Characteristics of patients

Characteristic	Value (number of patients)
Age (years, mean ± SD)	53.1±9.5
T1	33
T1mic	6
T1a	3
T1b	7
T1c	17
T2	23
Tumor location	
Inner quadrant	25
Outer quadrant	31
Patients in SPECT/CT	45
Shape of SLNs	
Round shape	16
Eccentric cortical hypertrophy	15
C-shape cortex	14
L/S ratio)	2.27±0.63
SLN/periareloar injection site maximum count ratio	0.36±0.12

SLN sentinel lymph node, *L/S ratio* long-to-short axis ratio

patients with T1 (P=0.007) (Fig. 4) (Table 2). However, there were no statistically significant differences in the S/P count ratio of metastatic versus non-metastatic SLNs among patients with T2 tumors (P=0.08).

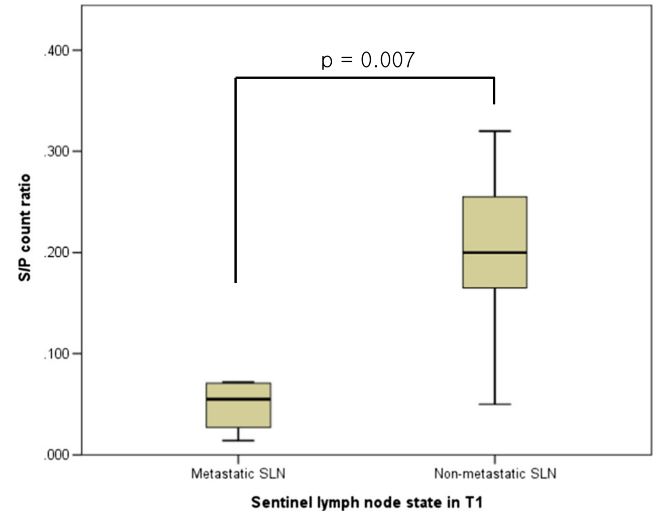

Fig. 4 The distribution of S/P count ratio in T1. S/P count ratio was significantly lower in the metastatic SLN group than the non-metastatic SLN group (P=0.007)

Discussion

In breast cancer patients, regional lymph node removal is considered necessary because these nodes take up malignant cells that detach from the primary tumor, and may be a source of distant metastases. Axillary nodal status is one of the most important prognostic factors in breast cancer [1].

Preoperative lymphatic SLN mapping by lymphoscintigraphy is essential to determine lymphatic drainage pathways. Several

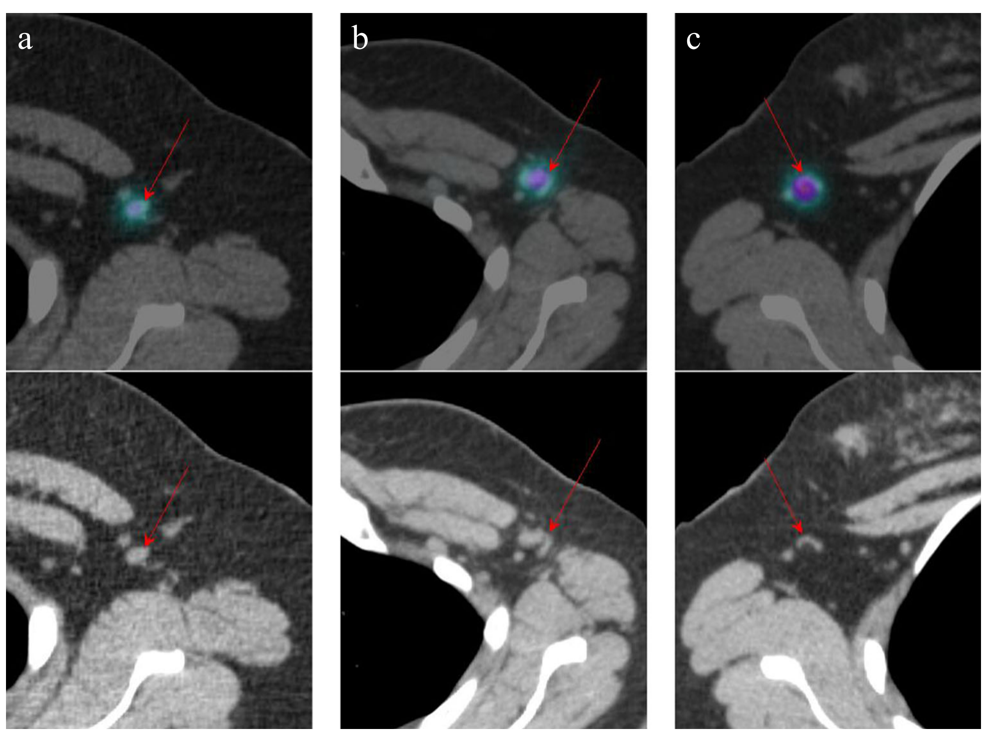

Fig. 3 These representative images show shapes of lymph nodes (**a** round shape, **b** eccentric cortical hypertrophy, **c** C-shape cortex) in hybrid SPECT/CT

Table 2 Parameters for predicting metastatic SLN

Parameter	Metastatic SLN (n=21)	Non-metastatic SLN (n=24)	P value
Age (years)	53.41±10.95	52.74±12.69	0.134
Tumor location			0.133
Inner quadrant	14	13	
Outer quadrant	7	11	
SLN shape			0.0821
Round shape	12	4	
Eccentric cortex	8	7	
C-shape cortex	1	13	
L/S axis ratio			
T1 (n=25)	2.01±0.50 (n=7)	2.51±1.13 (n=18)	0.702
T2 (n=20)	2.14±0.71 (n=14)	2.03±0.81 (n=6)	0.834
Tumor size (cm) in T1	1.7±0.1 (n=7)	0.60±0.47 (n=18)	0.01
S/P count ratio in T1	0.04±0.03 (n=7)	0.20±0.15 (n=18)	0.007

SLN sentinel lymph node, *L/S axis ratio* long-to-short axis ratio of SLN,*S/P count ratio* SLN/periareloar injection site (S/P) maximum count ratio

reports have discussed the protocols and technical details of accurate scintigraphic SLN mapping [2, 23]. One difficulty associated with conventional planar imaging is to preoperatively identify the exact anatomic localization of the detected nodes. SPETCT/CT imaging performed for SLN mapping of breast cancer has been shown to improve anatomic localization and identification of the SLN. Anatomical information provided by CT makes precise localization of the SLN possible [7]. In the current study, all 45 SLNs confirmed by pathological biopsy were detected by hybrid lymphoscintigraphy. The additional information provided by SPECT/CT allowed more accurate characterization of the size, shape, and depth of the SLN [24].

There are many anatomical factors that can be used to predict metastatic SLNs. A study by Gajdos et al. [25] found that main tumor size and age were independently associated with lymph node metastases. Yoshimura et al. [18] studied axillary lymph node status in breast cancer patients. Of 97 axilla lymph nodes, 27 showed eccentric cortical hypertrophy, and all were pathologically malignant. Thirty-eight axilla had lymph nodes with a C-shaped cortex, and 26 of the 38 axilla (68 %) were pathologically benign. Furthermore, the mean long-to-short (L/S) ratio of metastatic nodes was significantly less than that of non-metastatic nodes (1.484±0.368 versus 1.694±0.621, P<0.0001). In our study, primary tumor size was significantly associated with SLN metastasis (P=0.01). However, other factors—such as age, shape of SLN, and L/S axis ratio—were not related to metastases.

The S/P count ratio was significantly lower in the metastasis-positive group than in the metastasis-negative group in patients with T1 primary tumors (P=0.007) (Fig. 5). This finding suggests that the radioactivity of the SLN on SPECT/CT may be used preoperatively to predict SLN metastasis. SLN detection strongly reflected the presence or absence of metastases, with lymph node counts lower in the metastases-positive group than the metastases-negative group. Radioactive tracer does not accumulate in metastatic lesions within an SLN. Accordingly, metastatic prediction is potentially possible through lymph node assessment. In patients with T2, the S/P count ratio was not significantly different between metastatic and non-metastatic SLNs (P=0.08). However, the risk of axillary lymph node metastases increases as tumor size increases. One study showed that for patients

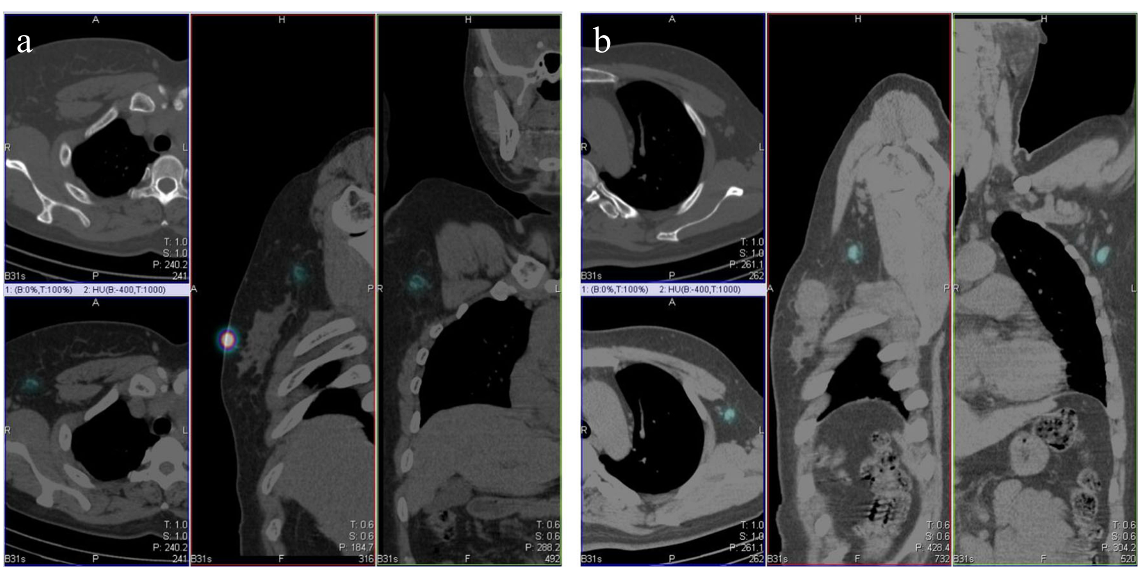

Fig. 5 Fifty-five-year-old and 54-year-old patients with breast cancer were referred for the evaluation of SLNs. **a** The SLN had C-shape cortex and a S/P count ratio of 0.00484. SLN metastasis was confirmed histopathologically. **b** The SLN was oval in shape and the S/P count ratio was 0.1829. A metastasis-free SLN was confirmed

with T2 tumors, of which 48.2 % had nodal metastases, full axillary clearance should be carried out [26]. SLN biopsy is therefore needed in patients with T2 breast cancer.

A limitation of this study was the relatively small size of the patient group. Furthermore, this study was limited to patients with only a single SLN. Cases with two or more SLNs should be investigated in the future. Martin et al. [27] reported that when metastases-positive and metastases-negative lymph nodes were mixed in patients with multiple SLNs, metastasis was found in the lymph nodes with lower counts. This suggests that metastatic prediction may also be possible in cases with multiple SLNs.

Conclusions

Hybrid SPECT/CT combines the physiologic data of SPECT with the anatomic data of CT in a single image. This hybrid imaging improved the anatomic localization of the SLN in the breast cancer patients we examined. Additionally, the S/P count ratio detected with hybrid lymphoscintigraphy was significantly lower in metastasis-positive lymph nodes than in metastasis-negative lymph nodes in patients with T1 primary tumors. These findings suggest that hybrid sentinel lymphoscintigraphy can potentially be used to detect SLNs and predict metastatic involvement of SLNs in patients with T1 breast cancer.

Acknowledgments This study was supported by a grant from the National R&D Program for Cancer Control, Ministry of Health, Welfare and Family Affairs, Republic of Korea (No. 0620220). This work was also supported by a grant from the Nuclear Research & Development Program of the National Research Foundation of Korea (NRF) funded by the Korean government (No. 2009–0078422).

Conflict of Interest Chang Ju Na, Jeonghun Kim, Sehun Choi, Yeon-Hee Han, Hwan-Jeong Jeong, Myung-Hee Sohn, H yun Jo Youn, and Seok Tae Lim declare that they have no conflict of interest.

Ethics Statement This study was approved by the ethics committee in our institution and was performed in accordance with the Helsinki Declaration of 1975, as revised in 2000. All patients enrolled gave their informed consent prior to their inclusion in the study.

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