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Editorial Board Member of *World Journal of Clinical Oncology*, Niccolò Giaj-Levra, MD, PhD, Advanced Radiation Oncology Department, IRCCS Ospedale Sacro Cuore Don Calabria, Via Don A Sempreboni, 37024, Negrar di Valpolicella, Italy. niccolo.giajlevra@sacrocuore.it

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ORIGINAL ARTICLE

Observational Study

Factors predicting upstaging from clinical N0 to pN2a/N3a in breast cancer patients

Goshi Oda, Tsuyoshi Nakagawa, Hiroki Mori, Iichiro Onishi, Tomoyuki Fujioka, Mio Mori, Kazunori Kubota, Ryoichi Hanazawa, Akihiro Hirakawa, Toshiaki Ishikawa, Kentaro Okamoto, Hiroyuki Uetakesszsz

Goshi Oda, Tsuyoshi Nakagawa, Department of Breast Surgery, Tokyo Medical and Dental University, Tokyo 1138519, Japan

Hiroki Mori, Department of Plastic and Reconstructive Surgery, Tokyo Medical and Dental University, Tokyo 1138519, Japan

Iichiro Onishi, Department of Pathology, Tokyo Medical and Dental University, Tokyo 1138519, Japan

Tomoyuki Fujioka, Mio Mori, Kazunori Kubota, Department of Radiology, Tokyo Medical and Dental University, Tokyo 1138519, Japan

Ryoichi Hanazawa, Akihiro Hirakawa, Department of Clinical Biostatistics, Tokyo Medical and Dental University, Tokyo 1138519, Japan

Toshiaki Ishikawa, Kentaro Okamoto, Hiroyuki Uetakesszsz, Department of Specialized Surgeries, Tokyo Medical and Dental University, Tokyo 1138519, Japan

Corresponding author: Goshi Oda, MD, PhD, Assistant Lecturer, Doctor, Department of Breast Surgery, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo 1138519, Japan. odasrg2@tmd.ac.jp

Abstract

BACKGROUND
With sentinel node metastasis in breast cancer (BC) patients, axillary lymph node (ALN) dissection is often omitted from cases with breast-conserving surgery. Omission of lymph node dissection reduces the invasiveness of surgery to the patient, but it also obscures the number of metastases to non-sentinel nodes. The possibility of finding ≥ 4 lymph nodes (pN2a/pN3a) preoperatively is important given the ramifications for postoperative treatment.

AIM
To search for clinicopathological factors that predicts upstaging from N0 to pN2a/pN3a.

METHODS
Patients who were sentinel lymph node (SLN)-positive and underwent ALN

dissection between September 2007 and August 2018 were selected by retrospective chart review. All patients had BC diagnosed preoperatively as N0 with axillary evaluation by fluorodeoxyglucose (FDG) positron emission tomography/computed tomography and ultrasound (US) examination. When suspicious FDG accumulation was found in ALN, the presence of metastasis was reevaluated by second US. We examined predictors of upstaging from N0 to pN2a/pN3a.

RESULTS
Among 135 patients, we identified 1-3 ALNs (pN1) in 113 patients and ³4 ALNs (pN2a/pN3a) in 22 patients. Multivariate analysis identified the total number of SLN metastasis, the maximal diameter of metastasis in the SLN (SLNDmax), and FDG accumulation of ALN as predictors of upstaging to pN2a/pN3a.

CONCLUSION
We identified factors involved in upstaging from N0 to pN2a/pN3a. The SLNDmax and number of SLN metastasis are predictors of ≥ 4 ALNs (pN2a/pN3a) and predictors of metastasis to non-sentinel nodes, which have been reported in the past. Attention should be given to axillary accumulations of FDG, even when faint.

Core Tip: This is the first report to include the results of preoperative positron emission tomography/computed tomography (PET/CT) and to examine results related to the upstaging of pN2a/pN3a (more than 4 axillary lymph node metastases) in breast cancer (BC) patients. Specifically, 135 patients who were sentinel lymph node (SLN)-positive and underwent ALN dissection were selected by retrospective chart review, all of whom had BC diagnosed preoperatively as N0 with axillary evaluation by fluorodeoxyglucose (FDG) PET/CT and ultrasound. Our results suggest that the size and number of SLN metastases were still important factors. And, attention should be given to axillary accumulations of FDG, even when faint.

INTRODUCTION

Sentinel lymph node (SLN) biopsy is usually performed in N0 cases. If SLN biopsy yields a positive result, an axillary lymph node (ALN) dissection is performed. However, since the publication of findings from the American College of Surgeons Oncology Group (ACOSOG) Z-0011 trial, many cancer centers have been omitting ALN dissection from breast-conserving surgeries[1]. The problem with omitting axillary dissection is that the number of non-SLN metastases cannot be ascertained, which may lead to over or under-treatment with adjuvant chemotherapy and radiation therapy. For example, patients with pN2a [4-9 ALN metastases (ALNMs)] or pN3a (³10ALNMs) need to be irradiated to not only the residual breast, but also the supraclavicular region after breast-conserving surgery. However, without knowing the number of metastases, no accurate decision on the need for irradiation can be made. Post-mastectomy radiation (PMRT) is also required for pN2a/N3a patients. Some reports have noted that PMRT after reconstruction impairs conformity[2-4]. Further analyses have shown that direct implants and autologous tissue reconstruction have fewer complications from PMRT[5,6]. The ability to predict the necessity of postoperative irradiation before surgery would affect surgical planning, including reconstructive surgery. A variety of factors and nomograms have been reported to allow preoperative prediction of the presence or absence of ALNMs[7-9], but few reports have examined factors predicting the presence of ³4 ALNMs. Preoperative fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) is reportedly excellent for predicting metastasis preoperatively and may have influenced the prediction of ALNMs in the present study. Although many

papers have described predictors of non-SLN metastasis, few have rigorously assessed ALNM preoperatively using PET/CT. In this study, all patients were evaluated preoperatively by PET/CT, and cases with false-negative results on other imaging modalities were excluded. This is the first report to include the results of preoperative PET/CT and to examine results related to the upstaging of pN2a/pN3a.

MATERIALS AND METHODS

Patients

A retrospective chart review was conducted for patients who were SLN-positive and underwent ALND between September 2007 and August 2018. All patients had breast cancer (BC) diagnosed preoperatively as N0 with axillary evaluation by PET/CT and ultrasound (US) examination. This study was conducted with approval from the institutional review board and with the informed consent of each patient. Axillary dissection was performed in all patients with SLN metastasis > 2 mm in diameter. In the case of total mastectomy, axillary dissection was performed for metastases > 0.2 mm in diameter. A flow chart of the eligible/included patients is shown in Figure 1.

About ultrasound examination

A EUB-7500 scanner with a EUP-L54MA 9.75-MHz linear probe (Hitachi Medical Systems, Tokyo, Japan) or Aplio XG scanner with a PLT-805AT 8.0-MHz linear probe (Toshiba Medical Systems, Tochigi, Japan) was used for US examinations. If ultrasound or PET/CT findings were suspicious for metastatic lymph nodes, cytology was performed.

Protocol for FDG-PET/CT

All patients were intravenously administered ^{18}F-FDG (3.7 MBq/kg; 0.1 mCi/kg) after a minimum 4-h fasting period. Next, whole-body images were routinely obtained using a PET/CT system (Aquiduo; Toshiba Medical Systems, Tokyo, Japan). In addition, CT was performed using the following parameters: pitch factor, 0.938; gantry rotation time, 0.5 s; table time, 30 mm/s; auto-exposure control (SD20), 120 kVp; and slice thickness, 2.0 mm. Notably, contrast media were not used for CT examinations. Approximately 60 min after ^{18}F-FDG administration, whole-body PET was performed using the following parameters: emission time per bed, 2 min; bed positions, 7-8; slice thickness, 3.375 mm; and matrix, 128 × 128.

Data analysis of FDG-PET/CT

In the present study, ^{18}F-FDG-PET/CT findings at each examination were assessed using a consensus reading by two breast radiologists (T.F. with 14 years of experience in breast imaging; M.M. with 10 years of experience in breast imaging). We performed visual analysis of primary lesions and ALNs without defining a cut-off value. Of note, lesions with an ^{18}F-FDG uptake value higher than that of the background tissue were defined as FDG-positive.
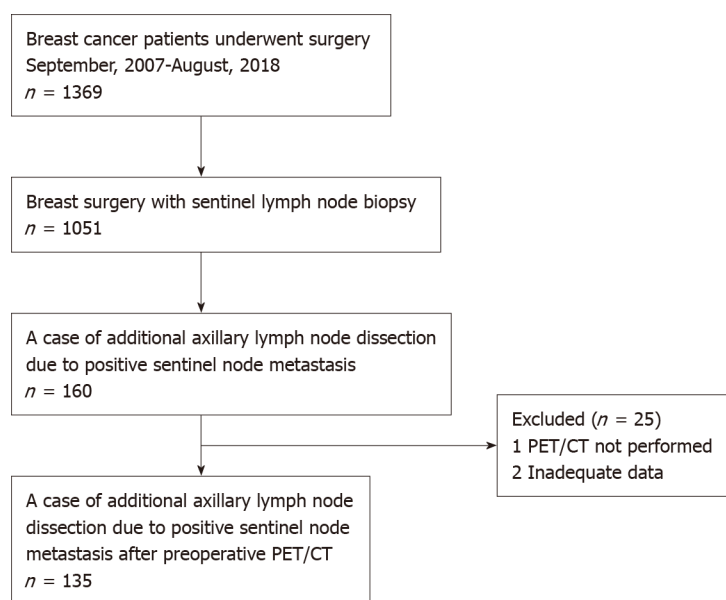
Immunohistochemical examination

All specimens were analyzed by pathologists from our institution, and specimens were considered estrogen receptor (ER) positive on immunohistochemistry (IHC) for staining rates higher than 10%. For human epidermal growth factor receptor 2 (HER2) values, and IHC result of 3+ was defined as BC with strong, complete membrane staining observed in at least 10% of tumor cells. For HER2 overexpression of 2+, gene amplification with fluorescence in situ hybridization was performed in this study.

Statistical analysis

Differences in proportions of categorical data were tested using Fisher's exact probability test. Unless otherwise indicated, significant differences among mean values of numerical data were analyzed using Mann-Whitney test. Relationships between the size of SLN metastases and the number of ALNMs were measured using Spearman rank correlation analysis, which can have a magnitude ranging from 0 to 1, with 0 denoting no correlation at all and 1 denoting complete correlation. Predictors of upstaging to pN2a/pN3a were determined by univariate and multivariate logistic regression analyses. Values of $P < 0.05$ were regarded as statistically significant. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interfaces for R (The R Foundation for Statistical Computing, Vienna, Austria)[10]. More precisely, EZR is a modified version of R Commander designed to add statistical functions frequently used in biostatistics.

Figure 1 A flowchart of eligible patients. PET/CT: Positron emission tomography/computed tomography.

RESULTS

Demographic and clinical characteristics of study subjects

We retrospectively analyzed 135 BC patients who were SLN-positive and had undergone ALN dissection. FDG-PET/CT was performed in all cases preoperatively. The detailed clinicopathological characteristics of subjects are summarized in Table 1. Among these, 113 patients showed 1-3 ALNMs (pN1) and 22 patients had ³4 ALNMs (pN2a/pN3a). FDG accumulation in ALNs was found on PET/CT in 19 cases (14.1%). The mean standardized uptake value (SUV) max was 1.48 (range, 0.8-2.0). Preoperative PET/CT showed accumulation in the ALNs, and second-look US was performed in cases where metastasis could not be ruled out. The mean number of excised SLNs was 1.6 (range, 1-5) and the mean number of SLN metastasis was 1.2 (range, 1-3). The median maximal diameter of metastasis in the SLN (SLNDmax) was 3 mm. The correlation between the SLNDmax and the number of ALNMs is shown in Figure 2. A strong correlation was identified between SLNDmax and the number of ALNMs ($P < 0.001$). We measured the cut-off value for the SLNDmax from the receiver operating characteristic (ROC) curve and the cut-off value for upstaging from N0 to pN2a/pN3a was set at 5 mm (area under the curve: 0.873; 95%CI: 0.808–0931) (Figure 3). Table 2 shows a comparison between pN1 and pN2a/pN3a.

Univariate logistic regression analysis of risk factors associated with upstaging

To search for risk factors for upstaging to pN2a/N3a, univariate and multivariate analyses were performed for associations with clinicopathological factors in two groups of pN1 and pN2a/N3a cases. Invasive diameter at the primary site, number of SLN metastasis, FDG accumulation in ALNs, and SLNDmax were associated with upstaging to pN2a/pN3a, but age, ER status, HER 2 status, tumor grade, and SUVmax at the primary site were not (Table 3).

Multivariate logistic regression analysis of risk factors associated with upstaging

Multivariate logistic regression analysis of clinicopathologic factors was used to examine risk factors for upstaging to pN2a/pN3a. The number of SLN metastasis, SLNDmax, and FDG accumulation in ALNs were associated with upstaging (Table 3).

DISCUSSION

The ACOSOG Z-0011 trial concluded that ALN dissection is not always necessary for women undergoing breast-conserving surgery with 1-2 positive SLNs[1]. However, the overall number of ALNMs represents crucial clinical information. Although avoidance of ALN dissection reduces the degree of surgical invasiveness of a procedure, the number of ALNMs cannot be ascertained. If more than 4 metastatic lymph nodes are present, radiation to the breast or chest wall as well as to the supraclavicular area is necessary[11]. Thus, not knowing the number of ALNMs may lead to over-or under-

Table 1 Background characteristics of all patients

Background characteristics (*n* = 135)

Age (yr)	56 (35-84)
SUVmax of primary tumor	3.05 (0.8-11.9)
pN1	113
pN2a or pN3a	22
The invasion diameter of the primary lesion	
≤ 20 mm	67
< 50 mm	55
≥ 50 mm	11
NA	2
Maximal diameter of metastasis in the sentinel lymph nodes (mm)	3 (0.1-25)
The number of SLN metastasis	
1	112
2	19
3	4
ER	
Positive	118
Negative	14
Unknown	3
HER2	
Positive	8
Negative	125
Unknown	2
Nuclear grade of biopsy specimen	
1, 2	103
3	26
Unknown	6
FDG accumulation of axillary lymph nodes	
Yes	19
No	116

SUV: Standardized uptake value; NA: Not applicable; SLN: Sentinel lymph node; ER: Estrogen receptor; HER2: Human epidermal growth factor receptor 2; FDG: Fluorodeoxyglucose.

treatment with radiation therapy postoperatively. The presence or absence of postoperative radiation may also affect the choice of reconstructive technique. Radiation during the insertion of an expander is associated with a greater risk of complications, while radiation after implant placement or to autologous tissue is reported to have fewer complications[2,3]. Pre- and postoperative prediction of the number of ALNMs affects not only the optimal extent of axillary dissection, but also the choice of radiotherapy and, indirectly, reconstruction methods. In the present study, we searched for predictors of upstaging from clinical N0 to pN2a/pN3a using factors identified pre- or intraoperatively, including FDG-PET/CT. This imaging modality is generally considered useful in searching for ALNMs[12]. However, few reports have specified whether preoperative PET/CT was performed when examining factors predicting non-SLN metastasis. As a result of examining various factors for upstaging, we extracted SLNDmax, mild accumulation of FDG in the axilla, and the number of SLN metastasis. The SLNDmax and the number of SLN metastasis have been reported in the past as predictors of metastasis to non-SLNs[13-16]. This is the first study to show that these factors are also important in upstaging from N0 to pN2a/pN3a. Various cut-offs for the SLNDmax have been reported as a predictor of non-SLN

Table 2 Comparison between pN1 and pN2a/pN3a

Total (*n* = 135)	pN1	pN2a/pN3a	*P* value
	n = 113	*n* = 22	
Age	57.96 ± 12.14	59.64 ± 12.73	0.56
The invasion diameter of the primary lesion (mm)	22.77 ± 14.76	39.86 ± 21.73	< 0.001
Maximal diameter of metastasis in the SLNs	3.46 ± 2.80	9.19 ± 5.66	< 0.001
The number of SLN metastasis			0.014
1	98	14	
2 and more	15	8	
ER			0.47
Positive	100	18	
Negative	11	3	
Unknown	2	1	
HER2			1
Positive	7	1	
Negative	104	21	
Unknown	2	0	
Nuclear grade of biopsy specimen			0.77
1, 2	87	16	
3	21	5	
Unknown	4	1	
SUVmax of the primary tumor	3.80 ± 2.50	4.13 ± 2.77	0.61
FDG accumulation of axillary lymph nodes			< 0.001
No	104	11	
Yes	8	11	
Unknown	1	0	

ER: Estrogen receptor; HER2: Human epidermal growth factor receptor 2; SLN: Sentinel lymph node; SUV: Standardized uptake value; FDG: Fluorodeoxyglucose.
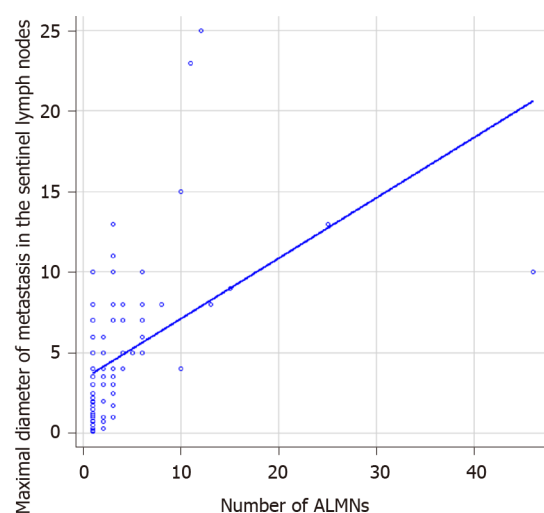
metastasis, and we used ROC curves in our search. As a result, the predictor for upstaging from N0 to pN2a/pN3a was set at 5 mm. If the number of SLN metastasis is large (that is, two or more) or the diameter of metastasis is large (more than 5 mm), or if FDG accumulation in the axilla is mild even if no metastases have been confirmed, irradiation to the chest wall and supraclavicular region may need to be considered even in cases where axillary dissection has been omitted. PET/CT is often performed preoperatively for different cancers. On the other hand, findings from this modality are reportedly less significant for low-stage BC, given the low likelihood of distant metastasis. Some reports have suggested that SUV at the primary site may offer a useful predictor of metastasis to non-SLNs[17]. Ueda *et al*[18] evaluated ALNMs using PET/CT and reported low sensitivity but high specificity. In the present study, we found PET/CT to be useful in predicting multiple ALNMs, but the positive predictive value was not particularly high (57.9%). Many questions remain unanswered, such as the optimal cut-off value for integrated SUV, the influence of the histological type of the primary tumor, and the suitable timing of biopsy.

Further accumulation and analysis of cases are needed. Institutions that aggressively omit axillary dissection should be aware of the dangers of remaining ignorant of the number of ALNMs when multiple risk factors are identified pre- or intraoperatively.

Table 3 Uni- and multivariate logistic regression analysis of risk factors associated with upstaging pN2a/pN3a

Factors	Univariate logistic regression analysis to predictive factors of pN2a/pN3a			Multivariate logistic regression analysis to predictive factors of pN2a/pN3a		
	Odds ratio	95%CI	*P* value	Odds ratio	95%CI	*P* value
Age (yr) (< 50 *vs* ≥ 50)	0.863	0.333-2.24	0.76			
ER (positive *vs* negative)	0.66	0.167-2.60	0.55			
HER2 (positive *vs* negative)	0.833	0.954-7.28	0.87			
Invasive diameter of the primary site (≤ 20 mm *vs* > 20 mm)	4.3	1.48-12.50	0.007	3.53	0.963-13.0	0.057
Nuclear grade (1, 2 *vs* 3)	1.29	0.426-3.393	0.65			
Total positive SLNs (1 *vs* 2 and more)	3.73	1.34-10.40	0.012	3.92	1.01-15.3	0.048
Maximal diameter of metastasis in the SLNs (< 5 mm *vs* ≥ 5 mm)	21.2	4.68-96.3	< 0.001	15.6	3.08-79.2	< 0.001
SUVmax of primary tumor (< 3.1 *vs* ≥ 3.1)	0.96	0.351-2.62	0.94			
FDG accumulation of axillary lymph nodes (yes *vs* no)	13	4.32-39.2	< 0.001	4.84	1.29-18.2	0.02

ER: Estrogen receptor; HER2: Human epidermal growth factor receptor 2; SLN: Sentinel lymph node; SUV: Standardized uptake value; FDG: Fluorodeoxyglucose.
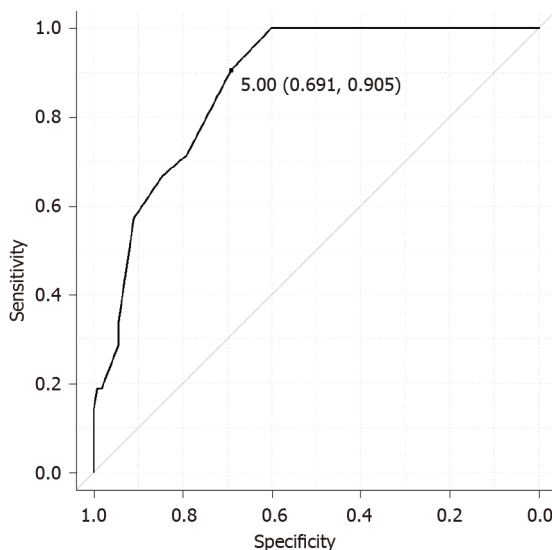

DOI: 10.5306/wjco.v13.i9.748 **Copyright** ©The Author(s) 2022.

Figure 2 Correlation between the maximal diameter of metastasis in the sentinel lymph nodes and number of axillary lymph node metastases. A strong correlation is evident between maximal diameter of metastasis in the sentinel lymph nodes and the number of axillary lymph node metastases (*P* < 0.001). ALMNs: Axillary lymph node metastases.

CONCLUSION

The present study investigated factors predictive of upstaging from clinical N0 to pN2a/pN3a. Factors such as the number of metastases and SLNDmax, which have previously been reported as predictors of metastasis to non-SLNs, were also useful in predicting upstaging to pN2a/pN3a and emphasized the utility of FDG-PET/CT. The only factor that predicts preoperatively, but not intraoperatively, is the result of FDG-PET/CT.

Figure 3 Cut-off value for the maximal diameter of metastasis in the sentinel lymph node from the receiver operating characteristic curve and cut-off for upstaging from N0 to pN2a/pN3a set to 5 mm (area under the curve: 0.873, 95%CI: 0.808-0931).

ARTICLE HIGHLIGHTS

Research background
With sentinel node metastasis in breast cancer (BC) patients, axillary lymph node (ALN) dissection is often omitted from cases with breast-conserving surgery. Omission of lymph node dissection reduces the invasiveness of surgery to the patient, but it also obscures the number of metastases to non-sentinel nodes.

Research motivation
The possibility of finding ≥ 4 lymph nodes (pN2a/pN3a) preoperatively is important given the ramifications for postoperative treatment.

Research objectives
The purpose of this study is to search for clinicopathological factors that predict upstaging from N0 to pN2a/N3a.

Research methods
Patients who were SLN-positive and underwent ALN dissection between September 2007 and August 2018 were selected by retrospective chart review. All patients had BC diagnosed preoperatively as N0 with axillary evaluation by fluorodeoxyglucose (FDG) positron emission tomography/computed tomography and ultrasound (US) examination. When suspicious FDG accumulation was found in ALN, the presence of metastasis was reevaluated by second US. We examined predictors of upstaging from N0 to pN2a/pN3a.

Research results
Among 135 patients, we identified 1-3 ALNs (pN1) in 113 patients and ³4 ALNs (pN2a/pN3a) in 22 patients. Multivariate analysis identified the total number of SLN metastasis, the maximal diameter of metastasis in the SLN (SLNDmax), and FDG accumulation of ALN as predictors of upstaging to pN2a/pN3a.

Research conclusions
We identified factors involved in upstaging from N0 to pN2a/pN3a. The SLNDmax and number of SLN metastasis are predictors of ≥ 4 ALNs (pN2a/pN3a) and predictors of metastasis to non-sentinel nodes, which have been reported in the past. Attention should be given to axillary accumulations of FDG, even when faint.

Research perspectives
It is somewhat possible to predict upstaging to pN2a/pN3a by searching for clinicopathological factors

FOOTNOTES

ORCID number: Goshi Oda 0000-0002-9431-1330; Tsuyoshi Nakagawa 0000-0003-1967-0445; Hiroki Mori 0000-0003-1967-0445; Iichiro Onishi 0000-0001-9744-0114; Tomoyuki Fujioka 0000-0002-7141-8901; Mio Mori 0000-0002-6107-4519; Kazunori Kubota 0000-0002-3240-4910; Ryoichi Hanazawa 0000-0002-4230-7356; Akihiro Hirakawa 0000-0003-2580-7460; Toshiaki Ishikawa 0000-0003-0102-8462; Kentaro Okamoto 0000-0002-1021-6417; Hiroyuki Uetake 0000-0001-7162-6842.

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