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^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography for the prediction of survival in patients with advanced esophageal cancer who have undergone neoadjuvant chemotherapy

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Abstract. Neoadjuvant chemotherapy (NAC) is a promising treatment strategy for advanced esophageal cancer. However, measures of NAC response assessment and prognostic prediction have not yet been established. The aim of this study was to evaluate the usefulness of combined ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT). A total of 77 patients with stage IB-IV esophageal cancer who were treated with NAC followed by curative resection were retrospectively analyzed. PET/CT was performed before and after NAC and 56 patients were clinical responders. The pretreatment maximal standardized uptake value (pre-SUV_{max}), post-SUV_{max} and %SUV_{max} were 11.3±5.8, 5.1±4.8 and 49.0±35.1%, respectively, for the main tumors (T) and 4.3±2.8, 2.5±1.9 and 67.0±39.6%, respectively, for the metastatic nodes (N). Among the preoperatively available factors, clinical response (P=0.018), post-SUV_{max}-N (P=0.0001) and %SUV_{max}-T (P=0.0031) were significant prognostic factors by univariate analysis. The multivariate analysis identified post-SUV_{max}-N as the only significant prognostic predictor (P=0.0254). Patients with a post-SUV_{max}-N of <3.0 exhibited significantly fewer pathological metastatic nodes and better disease-free survival compared with patients with a post-SUV_{max}-N >3.0. Therefore, post-SUV_{max}-N may be a useful prognostic predictor in patients with advanced esophageal cancer who are treated with NAC followed by surgery.

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Introduction

The standard and most effective treatment for thoracic esophageal cancer is currently esophagectomy with extended three-field lymph node dissection, which eradicates a wide range of clinically apparent and subclinical lymph node metastases in the cervical, mediastinal and abdominal fields. Although this state-of-the art surgical therapy has improved the prognosis of patients to a certain extent, recurrence occurs in over half of the patients who undergo curative resection (1,2). This suggests that systemic micrometastases that cannot be eradicated by surgery may exist in more than half of patients at the time of surgery, and that multidisciplinary treatment is necessary for such patients. The use of neoadjuvant chemotherapy (NAC) has increased the hope of improvement in prognosis (3-7).

Several investigators have reported that responders to NAC exhibit a better prognosis compared with non-responders (8,9). This suggests that NAC may lead to disease downstaging and increase the curability of subsequent surgery in responders, whereas it may provide no clinical benefit, or may even be harmful, to non-responders (5,8). Although the precise assessment of the efficacy by NAC is crucial for decision-making regarding subsequent treatment, conventional imaging modalities, such as computed tomography (CT) and magnetic resonance imaging (MRI), appear to be unsatisfactory, due to their limited sensitivity and specificity.

Positron emission tomography with ^{18}F-fluorodeoxyglucose (FDG-PET) is a metabolic imaging modality that has recently been used for preoperative staging (10-13) or for assessment of the efficacy of NAC for esophageal cancer (14-17). Specifically, combined PET/CT has been reported to be more effective compared with PET alone in the preoperative diagnosis of lymph node metastasis from thoracic esophageal cancer (18).

The present study was designed to evaluate the potential benefits of PET/CT in the preoperative assessment of the efficacy of NAC and prognostic prediction in patients with esophageal cancer.

Patients and methods

Patients. Between January, 2007 and December, 2013, a total of 405 patients with thoracic esophageal cancer underwent surgery at the Osaka Medical Center for Cancer and Cardiovascular Diseases (Osaka, Japan). Among these, 157 patients were treated with NAC followed by surgery. Of these 157 patients, 77 fulfilled the following inclusion criteria: i) New diagnosis and no other previous anticancer treatment; ii) ≤80 years of age; iii) Eastern Cooperative Oncology Group performance status scores ≤3; iv) T1-T3; v) any N (N0-N3); vi) no distant node metastasis or distant organ metastasis except for supraclavicular nodes (M1LYM); vii) evaluation by PET/CT both before and after NAC; viii) adequate bone marrow function (leukocyte count >3,500 cells/mm^3, platelet count >100,000 cells/mm^3); xi) normal renal function (serum creatinine level <1.2 mg/dl or creatinine clearance >50 ml/dl); and x) normal liver function (serum transaminases <twice the upper limit of normal). The disease stage was assigned according to the 7th edition of the Union for International Cancer Control TNM classification (19). The T and N status of the disease was diagnosed by chest and abdominal CT scans, esophagography and/or bronchoscopy. The diagnostic criteria by CT scan for clinically positive nodes included a round-shaped node measuring ≥10 mm in diameter. MRI was used in certain cases to improve the accuracy of the T4 diagnosis. Bronchoscopy was performed when tracheal invasion was suspected on the basis of the CT scan. The study protocol was approved by the Human Ethics Review Committee of Osaka Medical Center for Cancer and Cardiovascular Diseases, and written informed consent was obtained from each patient prior to inclusion.

Treatment regimen. In 47 patients, NAC consisted of a cisplatin, adriamycin and 5-fluorouracil (5-FU) combination (FAP); 27 patients were treated with 5-FU, cisplatin and docetaxel (DCF); the remaining 3 patients received 5-FU plus cisplatin (FP). For the administration of FAP, 5-FU was administered intravenously (i.v.) at 750 mg/m^2/day on days 1-7 in a continuous manner; adriamycin was administered on day 1 at a dose of 30 mg/m^2/day by i.v. injection; and cisplatin was administered on day 1 at 70 mg/m^2/day by drip infusion for 2 h with sufficient pre- and post-treatment hydration to prevent renal toxicity. For the administration of DCF, 5-FU was administered i.v. at 700 mg/m^2/day on days 1-5 in a continuous manner, whereas docetaxel (70 mg/m^2/day) and cisplatin (70 mg/m^2/day) were administered on day 1. For the administration of FP, 5-FU (750 mg/m^2/day) and cisplatin (70 mg/m^2/day) were administered on days 1-7 and on day 1, respectively. After a 2-3-week interval, the same regimens were repeated.

Two weeks after completing NAC, the patients were re-evaluated for their response to the abovementioned treatment regimens. These examinations included observation of the main tumor and metastatic lymph nodes by barium study, tissue biopsy obtained by endoscopy, and chest and abdominal CT scans. The treatment response was classified using general criteria that have been previously described (20). Complete response (CR) was defined as 100% regression of the disease. Partial response (PR) was defined as regression of >50% of the tumor and metastatic lymph nodes, as confirmed by esophagography and CT scans. Progressive disease (PD) was defined as an increase in the tumor mass and/or metastatic nodes, or the appearance of new lesion(s). Patients who were not classified as CR, PR or PD were defined as non-responders (NC). The patients were scheduled for surgery ~4 weeks after the last day of chemotherapy. Histological effectiveness was defined as follows: Grade 3, complete disappearance of cancer cells; grade 2, >2/3 disappearance; grade 1b, 1/3-2/3 disappearance; and grade 1a, <1/3 disappearance.

PET/CT imaging. All the patients received whole-body ^{18}F-FDG-PET/CT scans prior to NAC. Additional PET scans were performed 14-21 days after the completion of NAC. PET/CT scans were performed as previously described (21). Briefly, patients were asked to fast, except for glucose-free oral hydration, for at least 5 h prior to the injection of ^{18}F-FDG (3.5 MBq/kg body weight). After injection of the tracer, the patients remained in a comfortable position on the bed. Combined PET/CT scanning was performed 1 h after the injection using either a dual-slice CT Biograph Duo LSDPET-CT imaging system (Siemens-Asahi Medical Technologies, Tokyo, Japan) or a 12-slice CT Discovery LS PET-CT imaging system (Philips Medical Systems Inc., Cleveland, OH, USA) and covering the area from the top of the brain to the upper thigh. Images were reconstructed using an iterative procedure with an ordered subset expectation maximization algorithm.

For the quantitative evaluation of regional ^{18}F-FDG uptake, regions of interest (ROIs) were manually placed over the primary tumor or the metastatic lymph nodes in areas devoid of prominent artifacts and overlapping with organs with increased FDG uptake. If no focal ^{18}F-FDG uptake was visible in the follow-up examinations, the ROI was placed in the same location as the previously identified lesion using the landmarks of the transmission images (apex of the lungs, bifurcation of the trachea) as a reference. The standardized uptake value (SUV) was measured for each ROI and was determined using the whole-body attenuation-corrected image according to the following equation: SUV=[regional activity (mCi/ml)]/[injected dose (mCi)/body weight (g)]. SUV_{max} was adopted for analysis. The reduction in tumor SUV_{max} was calculated as follows: $\%SUV_{max}$ = 100 x (SUV_{max} after NAC)/(SUV_{max} before NAC). When there were >2 PET-positive metastatic nodes, the lesion with the highest SUV_{max} was used for response evaluation.

Surgical procedures. All 77 patients underwent subtotal esophagectomy with two- or three-field lymph node dissection, according to the procedures described by Akiyama *et al* (2). Three-field lymph node dissection was performed for patients with upper or middle thoracic esophageal cancer and for patients with supraclavicular and/or recurrent laryngeal nerve node metastases.

Statistical methods. Statistical analyses were performed using StatView 5.0 J software (SAS Institute Japan, Tokyo, Japan). For ordered categorical data, the Mann-Whitney U test was used for comparisons among subgroups of patients for each clinicopathological factor. Student's t-test was used to compare the number of lymph node metastases. Survival time was calculated by the

Table I. Clinicopathological characteristics of the enrolled patients (n=77).

Characteristics	Values
Age (years)	64.7±7.1 (46-77)
Sex (male/female)	71/6
Tumor location (Ut/Mt/Lt/Ae)	5/35/34/3
Histology (SCC/adeno/basaloid)	72/4/1
cT (cT1/cT2/cT3/cT4)	6/22/49/0
cN (cN0/cN1/cN2/cN3)	10/41/25/1
cM (cM0/cM1)	72/5
cStage (IB/IIA/IIB/IIIA/IIIB/IIIC/IV)	5/5/15/32/15/0/5
Pre-SUV_{max}-T	11.3±5.8 (2.3-28.4)
Pre-SUV_{max}-N	4.3±2.8 (1.0-13.5)
Preoperative chemotherapy (FAP/DCF/FP)	47/27/3

Data are presented as mean ± standard deviation (range). Ut, upper thoracic; Mt, middle thoracic; Lt, lower thoracic; Ae, abdominal esophagus; SCC, squamous cell carcinoma; adeno, adenocarcinoma; SUV_{max}, maximum standardized uptake value; pre-SUV_{max}-T, pre-chemotherapeutic $SUV_{max}$of the main tumor; pre-SUV_{max}-N, pre-chemotherapeutic SUV_{max} of the metastatic lymph nodes; FAP, 5-fluorouracil/adriamycin/cisplatin; FP, 5-fluorouracil/cisplatin; DCF, docetaxel/cisplatin/5-fluorouracil.

Table II. Efficacy of preoperative therapy and pathological stage.

Factors	
Clinical effects (CR/PR/NC/PD)	0/56/18/3
Pathological effects (grade 3/2/1b/1a)	5/15/16/41
pT (pCR/pT1/pT2/pT3/pT4)	5/22/13/37/0
pN (pN0/pN1/pN2/pN3)	24/26/17/10
pM (pM0/pM1)	71/6
pStage (pCR/IA/IB/IIA/IIB/IIIA/IIIB/IIIC/IV)	3/9/3/9/18//14/8/7/6
%SUV_{max}-T	49.0±35.1 (3.5-177.3)
%SUV_{max}-N	67.0±39.6 (15.0-190.3)
Post-SUV_{max}-T	5.1±4.8 (1.0-27.0)
Post-SUV_{max}-N	2.5±1.9 (1.0-10.6)

Data are presented as mean ± standard deviation (range). CR, complete response; PR, partial response; NC, no change; PD, progressive disease; SUV_{max}, maximum standardized uptake value; %SUV_{max}, post-treatment SUV_{max}/pretreatment SUV_{max}x 100; %SUVmax-T, %SUV_{max} of the main tumor; %SUV_{max}-N, %SUVmax of the metastatic lymph nodes; post-SUV_{max}, post-chemotherapeutic SUVmax.

Kaplan-Meier method and was statistically compared among patient subgroups by the log-rank test. A two-sided P<0.05 was considered to indicate statistically significant differences. All the statistically significant variables identified in the univariate analysis were included in the multivariate survival analysis using the Cox's proportional hazards model.

Results

Patient and tumor characteristics. The clinicopathological characteristics of the 77 patients are summarized in Table I. A total of 72 patients had squamous cell carcinoma and 67 patients had clinically apparent lymph node metastases. All 5 cM1 cases were supraclavicular node metastases. The mean SUV_{max} values of the main tumor and the metastatic lymph nodes were 11.3±5.8 and 4.3±2.8, respectively.

Clinical and pathological responses to NAC. Table II shows the clinical and pathological responses to NAC in the 77 patients. The clinical response was fairly good, with a major response rate of 72.7% (no CRs and 56 PRs). A pathological response of grade ≥2 was observed in 20 patients (26.0%). A total of 24 patients (31.7%) were pathologically node-negative. The %SUV_{max} of the main tumors (T) and metastatic lymph nodes (N) was 49.0±35.1 and 67.0±39.6% of the pretreatment values, respectively. The post-SUV_{max}-T and post-SUV_{max}-N were 5.1±4.8 and 2.5±1.9, respectively.

Prognostic predictors among preoperatively available factors. As previously reported by several investigators, we also observed that clinical responders exhibited a significantly better DFS compared with non-responders (P=0.015, Fig. 1). We next examined which preoperatively available clinical

Table III. Univariate analysis of preoperative prognostic factors.

Variables	HR	95% CI	P-value
Age	0.957	0.914-1.001	0.056
Sex (male/female)	0.634	0.152-2.645	0.532
Tumor location (Ut/Mt vs. Lt/Ae)	0.776	0.397-1.516	0.458
cT (T1-2 vs. T3)	0.791	0.394-1.592	0.512
cN (N0-1 vs. N2-3)	1.008	0.502-2.027	0.982
cM (M0 vs. M1)	0.646	0.198-2.110	0.469
cStage (IB-IIB vs. IIIA-IV)	0.722	0.347-1.505	0.385
Clinical response (responder vs. non-responder)	2.299	1.155-4.576	0.0178
Pre-SUV_{max}-T	0.977	0.924-1.034	0.427
Pre-SUV_{max}-N	1.102	0.994-1.221	0.064
Post-SUV_{max}-T	1.053	0.996-1.114	0.071
Post-SUV_{max}-N	1.317	1.143-1.516	0.0001
%SUV_{max}-T	3.834	1.572-9.351	0.0031
%SUV_{max}-N	1.623	0.709-3.717	0.252

HR, hazard ratio; CI, confidence interval; Ut, upper thoracic; Mt, middle thoracic; Lt, lower thoracic; Ae, abdominal esophagus; SUV_{max}, maximum standardized uptake value; pre-SUV_{max}-T, pre-chemotherapeutic SUV_{max} of the main tumor; pre-SUV_{max}-N, pre-chemotherapeutic SUV_{max} of the metastatic lymph nodes; post-SUV_{max}, post-chemotherapeutic SUV_{max}; %SUV_{max}, post-treatment SUV_{max}/pretreatment SUV_{max} x 100; %SUV_{max}-T, %SUV_{max} of the main tumor; %SUV_{max}-N, %SUV_{max} of the metastatic lymph nodes.

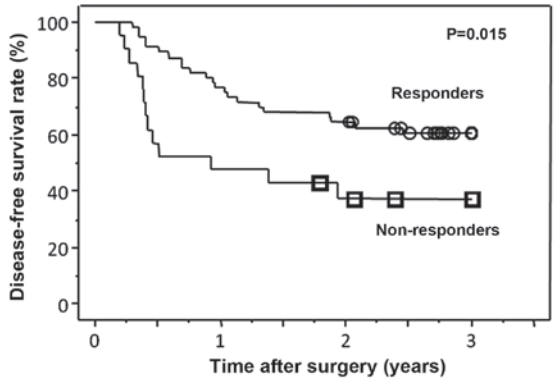

Figure 1. Comparison of disease-free survival curves according to clinical response. The 77 patients were divided into two groups by clinical response: Responders (open circle, n=56) and non-responders (open square, n=21).

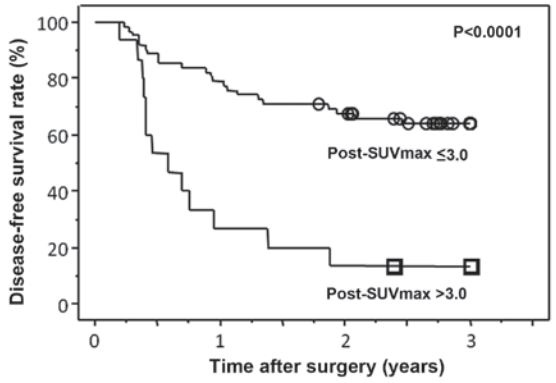

Figure 2. Comparison of disease-free survival curves according to the post-SUV_{max}-N value. The 77 patients were divided into two groups according to the post-SUV_{max}-N value: patients with post-SUV_{max}-N equal to or lower than 3.0 (open triangle, n=62) and patients with post-SUV_{max}-N higher than 3.0 (open square, n=15). SUV_{max}, maximal standardized uptake value; N, metastatic lymph node status.

factors were significantly associated with DFS by univariate analysis (Table III). Clinical non-responder (P=0.0178), post-SUV_{max}-N (P=0.0001) and %SUV_{max}-T (P=0.0031) were found to be significant predictors of poor prognosis. We then incorporated 6 factors with P-values in the univariate analysis of <0.1 into a multivariate analysis. As shown in Table IV, the post-SUV_{max}-N was identified as the only independently significant prognostic factor (P=0.0254).

Finally, for a better prediction of prognosis, a cut-off value was set for post-SUV_{max}-N. When the patients were divided into two groups according to the cut-off value of 3.0, the DFS curves were most clearly separated (P<0.0001) (Fig. 2).

Association between pathological findings and post-SUV_{max}-N. A comparison of the pathological findings between the two groups classified by post-SUV_{max}-N (cut-off at 3.0) is shown in Table V. The group of patients whose post-SUV_{max}-N was <3.0 exhibited significantly fewer pathologically metastatic nodes 2.0±3.3 vs. 6.1±5.9 compared with the other group (P=0.0006).

Discussion

This study investigated whether preoperative evaluation by PET/CT performed before and after NAC may serve as a useful predictor of prognosis in patients with locally advanced esophageal cancer who had undergone NAC followed by surgery. The results demonstrated that the post-SUV_{max}-N was the only significant prognostic predictor among several

Table IV. Multivariate analysis of preoperative prognostic factors.

Variables	HR	95% CI	P-value
Age	0.970	0.928-1.014	0.181
Clinical response (responder vs. non-responder)	1.331	0.592-2.995	0.490
Pre-SUV_{max}-N	1.085	0.955-1.233	0.210
Post-SUV_{max}-T	0.978	0.884-1.082	0.670
Post-SUV_{max}-N	1.220	1.025-1.451	0.025
%SUV_{max}-T	3.827	0.780-18.777	0.098

HR, hazard ratio; CI, confidence interval; SUV_{max}, maximum standardized uptake value; pre-SUV_{max}-N, pre-chemotherapeutic SUV_{max} of the metastatic lymph nodes; post-SUV_{max}-T, post-chemotherapeutic SUV_{max} of the main tumor; post-SUV_{max}-N, post-chemotherapeutic SUV_{max}; %SUV_{max}, post-treatment SUV_{max}/pretreatment SUV_{max} x 100.

Table V. Comparison of pathological findings between the high and low post-SUV_{max}-N groups.

Findings	Post-SUV_{max}-N ≥3.0 (n=62)	Post-SUV_{max}-N <3.0 (n=15)	P-value
Pathological effects (grade 3/2/1b/1a)	4/14/12/32	1/1/4/9	0.414
pT (CR/1/2/3)	4/19/11/28	1/3/2/9	0.357
pN (N0/N1/N2/N3)	23/21/14/4	1/5/3/6	0.002
pStage (CR/I/II/III/IV)	3/12/21/22/4	0/0/6/7//2	0.063
Number of metastatic nodes (mean ± standard deviation)	2.0±3.3	6.1± 5.9	0.0006

Post-SUV_{max}-N, post-chemotherapeutic SUV_{max} of the metastatic lymph nodes; CR, complete response.

preoperatively available factors. The use of a cut-off value of 3.0 for the post-SUV_{max}-N allowed the prediction of long-term DFS. Patients with a post-SUV_{max}-N <3.0 had significantly fewer pathologically metastatic nodes compared with patients with a post-SUV_{max}-N >3.0. By contrast, post-SUV_{max}-T, %SUV_{max}-T and %SUV_{max}-N were not found to be associated with patient prognosis.

Patients with lower post-SUV_{max}-N had a better prognosis, partly due to those patients having fewer metastatic nodes. The number of pathological lymph node metastases is known to be the strongest prognostic predictor in patients with esophageal cancer who have undergone surgical resection without preoperative therapy (22-24). Recent studies have also demonstrated that the number of pathological nodes is a strong prognostic factor for patients who have undergone neoadjuvant therapy followed by surgery (25,26). Although a precise preoperative diagnosis of pathological lymph node status has thus far been considered impossible by conventional imaging modalities, PET/CT would be a useful tool to accurately assess pathological N status following neoadjuvant therapy. Another possible explanation is that the higher SUV_{max} of the lymph nodes reflects the larger size of metastatic foci or higher malignant potential of cancer cells. Several investigators have recently reported that the size of the metastatic lymph node is one of the strongest prognostic factors in esophageal cancer (27-29). Moreover, higher SUV_{max} values indicate a higher malignant potential of cancer cells through a variety of mechanisms, such as cell proliferation, tissue hypoxia and angiogenesis (30-33).

A number of investigators use the reduction rate in SUV_{max} as a criterion for the assessment of the tumor response to NAC (34,35), and several groups reported that a 50% reduction in SUV_{max} following NAC is a more significant predictor of DFS compared with pathological findings (36,37). Roedl *et al* (38) demonstrated that a reduction in tumor length between the pre- and post-NAC PET scans is a better predictor of pathological effectiveness and time-to-recurrence than a reduction in SUV. In our study, neither a 50% reduction in SUV_{max}-T nor a 50% reduction in SUV_{max}-N were found to be correlated with DFS. The reason for this discordance between our results and previously reported results is unknown. However, one possible explanation is that, in this study, we only enrolled patients with potentially resectable tumors and excluded patients with unresectable, non-responding tumors from the analysis. Therefore, downstaging of the T factor may not have a stronger impact on prognosis than downstaging of the N factor and, as a result, the effects of %SUV_{max}-T may have been underestimated (34-37). Compared with post-SUV_{max}, %SUV_{max} did not correlate well with prognosis. In a clinical setting, in which patients with potentially resectable cancers are treated with NAC followed by surgery, the finding that the residual tumor volume within the metastatic node, as

assessed by PET/CT, becomes minimal just prior to surgery, is the most important predictor for postoperative survival.

Neither pre-SUV_{max}-T nor pre-SUV_{max}-N were found to be correlated with DFS, which suggests that prognosis is not affected by the initial stage, but by the post-treatment stage. In other words, even if the initial stage is advanced, downstaged patients who respond more effectively to the treatment have a more favorable prognosis compared with non-responding patients. Recently, Suzuki *et al* (39) reported the significance of baseline SUV in the prediction of prognosis in patients with esophageal and gastroesophageal cancers who were treated with definitive chemoradiotherapy. These authors demonstrated that a higher initial SUV is significantly associated with higher T-stage, positive N-stage, higher overall stage and poorer overall survival. As all the patients in their study were treated with definitive chemoradiotherapy and were not routinely treated by surgery, the CR rate by chemoradiotherapy appears to be the most important prognostic factor. Therefore, the initial tumor volume as assessed by PET/CT may have directly affected the outcome. In general, the larger the initial tumor mass, the lower the CR rate. By contrast, in our study, all the patients received NAC followed by surgery. In this situation, regardless of whether there are more or fewer residual tumors, they may be easily eradicated by surgery. Therefore, the preoperative tumor status may have less of an impact on prognosis.

In conclusion, in patients with locally advanced potentially resectable esophageal cancer who were treated with NAC followed by surgery, post-SUV_{max}-N was significantly correlated with the number of pathological lymph node metastases and DFS. Furthermore, a SUV_{max} cut-off value of 3.0 for the metastatic nodes clearly differentiated the patients with good prognosis from those with poor prognosis. As this was a retrospective study with a small number of patients, our results require validation by a future prospective, large-scale study.

Competing interests

The authors declare that they have no competing interests.

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