Prognostic factors for bone metastases from head and neck squamous cell carcinoma: A case series of 97 patients

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Abstract. Although bone is the second-most frequent site of distant metastases of head and neck squamous cell carcinoma (HNSCC), variable prognostic factors in patients with bone metastases from HNSCC have not been fully investigated. The aim of the present study was to assess the prognostic factors affecting overall survival (OS) in these patients. The medical records of 97 patients at two institutions who developed bone metastases from HNSCC between January 2010 and December 2020 were retrospectively reviewed. A multivariate analysis using a Cox proportional hazards model was performed to identify potential clinical predictive factors for longer OS. The median OS was 7 months, and the 1- and 2-year OS rates for all patients were 35.4 and 19.2%, respectively. The independent predictive factors for longer OS were single bone metastasis, good performance status and administration of systemic chemotherapy. The median OS with each predictor was 10, 10 and 10.5 months, respectively. In a selected group of patients with these three factors, the OS was 14.5 months. In conclusion, single bone metastasis, a good performance status and systemic chemotherapy were independent predictors of longer OS in patients with HNSCC, but their contributions were limited.

Introduction

Although squamous cell carcinoma (SCC) of the head and neck (HNSCC) is predominantly a locoregional disease, the incidence of distant metastasis in high-risk patients (≥3 lymph node metastases, bilateral lymph node metastases, lymph nodes metastases >6 cm, low jugular lymph node metastases, locoregional tumor recurrence, or second primary tumor) is relatively high, ranging from 8.9 to 23.8% (1-4). Previously, distant metastases from HNSCC were mainly considered to be lung metastases, as the lung is the most frequent site, accounting for 59% of all distant metastases (5,6). Bone metastases (BM) from HNSCC have attracted little attention, as their incidence was reported to be low (1.3%) in the literature (7), and BM from HNSCC were considered to occur as part of widespread metastatic disease (6). However, the recent increase in the availability of fluorodeoxyglucose-positron emission tomography for HNSCC staging has increased the incidence of detection of clinically relevant BM from HNSCC to 3.4-4.8% (8-10). Conversely, data regarding the prognosis after BM development are limited. Only a few studies are available, which have reported dismal prognosis, with a median overall survival (OS) of 6.0-6.6 months (8,11), whereas a full investigation of variable prognostic factors has not been performed to date, to the best of our knowledge. Therefore, the purpose of the present study was to identify clinical factors predicting longer survival in the largest cohort of patients with BM from HNSCC to date.

Materials and methods

Patients. The present study was approved by our Institutional Review Board (Osaka University Hospital Interventional and Observational Studies Review Committee; reference no. 19341). The need for informed consent was waived due to the retrospective nature of this study. The data of 518 otolaryngology patients with suspected or confirmed diagnosis of BM were collected from the hospital and radiology information system databases of two university hospitals (Kindai University Hospital and Osaka University Hospital), by using the search terms 'bone metastasis' as the disease name, 'from

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January 2010 to December 2020' as the date of diagnosis, and 'otolaryngology' as the department. After reviewing the individual electronic charts, a total of 108 Japanese patients with BM from HNSCC were identified according to the following criteria: i) Histological diagnosis of the primary tumor as SCC, ii) histological diagnosis of the bone lesion as SCC, or iii) diagnosis of BM on imaging. The exclusion criteria were as follows: i) Presence of other synchronous malignancies that could develop distant metastases and ii) age <20 years. After excluding patients lost to follow-up, a total of 97 patients were finally included.

Definition of variables affecting OS. The following possible predictive factors for longer OS were selected by reviewing the literature describing the prognostic factors for recurrent and/or metastatic HNSCC as follows: Good performance status (PS) (0-1) (12-15), administration of systemic chemotherapy (6,11,12), less prominent weight loss (<10%) (13,14), bone-exclusive metastasis (absence of metastases to other organs) (10,16), distant metastasis only (locoregional control in patients with metachronous BM) (17,18), positive human papillomavirus (HPV) status in oropharyngeal SCC (19-21), nasopharyngeal primary site (22), poor tumor cell differentiation (13), and a longer time interval from the primary diagnosis (>19 months) (18).

Additional possible predictive factors for longer OS were selected by reviewing the literature reporting prognostic factors for BM from other common type of cancer, including lung, breast, prostate, esophageal, gastrointestinal, colorectal and pancreatic cancer. These included single BM (23-28), good PS (23,25,26,29), systemic chemotherapy (29-31), absence of skeletal-related events (SREs) (23,32), younger age (<61 years) (33), distribution of metastatic sites confined to the vicinity of the primary tumor (24), lower serum alkaline phosphatase (ALP) level (26), a longer time interval from the primary diagnosis (31), and osteoblastic morphology on CT images (34).

Data acquisition. Data on the baseline characteristics of the patients and clinical characteristics of BM were collected. Baseline characteristics included the patient's sex, age, primary site, histological differentiation of the primary tumor and the HPV status of oropharyngeal SCC. Clinical characteristics of BM included the time interval from primary diagnosis to BM, the disease extent in patients with metachronous BM (distant metastasis only or distant metastasis and locoregional disease), the presence of distant metastasis to other organs, number of BM, the BM sites, morphological patterns on CT, the PS at the time of BM development, SREs at the time of developing BMs, and administration of systemic chemotherapy for BM. A positive HPV status was determined by positive expression of p16 on immunohistochemistry, defined as strong and diffuse nuclear and cytoplasmic staining in ≥70% of tumor cells (35). Metachronous metastasis was defined as BM found at >60 days from the time of primary diagnosis. The BM sites were divided into five areas: Above the clavicle (craniofacial bones and cervical spine), shoulder and thorax (clavicle, scapula, sternum and ribs), thoracolumbar spine, pelvis (ilium, ischium, pubis, hip and sacrum-coccyx), and the extremities. Morphological patterns on CT images were evaluated independently by two radiologists and classified into osteolytic, intertrabecular, mixed and osteoblastic types. Discrepancies between the assessments of the two radiologists were resolved through consensus. PS was classified according to the Eastern Cooperative Oncology Group criteria, and a good PS was defined as 0 and 1. SREs were defined as pathological fractures, spinal cord compression, hypercalcemia, or the requirement for radiation therapy or surgery for symptomatic BM (36). OS was defined from the date of BM diagnosis to the date of death from any cause or the end of data collection (December 31, 2020). As regards body weight loss and serum ALP level, sufficient data for statistical analyses were not available.

Statistical analysis. The Kaplan-Meier method was used to estimate cumulative survival, depict survival curves, and calculate the median 1- and 2-year OS rates. Univariate and multivariate analyses of the associations between the variables and OS were conducted using a log-rank test and a Cox proportional hazards model, respectively. Factors with $P<0.1$ on univariate testing were evaluated using multivariate analysis. The reason for adopting the high threshold of $P<0.1$ in the univariate screening was to eliminate the influence of potential confounders. $P<0.05$ on the multivariate analysis was considered to indicate a statistically significant difference. All statistical analyses were performed using the IBM SPSS Statistics software, version 24 (IBM Corp.).

Results

Baseline characteristics of patients and clinical characteristics of BM. The baseline characteristics of the patients are presented in Table I. The patients included 80 men (80.5%) and 17 women (19.5%), with a mean age of 63.8 years (range: 21-87 years). The primary sites were the nasopharynx in 19 patients (19.6%), oropharynx in 16 (16.5%), oral cavity in 20 (20.6%), hypopharynx in 26 (26.8%), larynx in 9 (9.3%) and other sites in 7 patients (7.2%). The histological differentiation was high in 22 patients (22.7%), moderate in 23 (23.7%), poor in 30 (30.9%) and undifferentiated in 1 patient (1.0%), whereas data on differentiation were not available (N/A) in 21 patients (21.7%). Of the 16 patients with oropharyngeal SCC, the HPV status was positive in 7 and negative in 9 patients. The clinical characteristics of BM are summarized in Table II. Regarding the time interval from the primary diagnosis to BM development, synchronous BM were observed in 36 patients (37.1%) and metachronous BM in 61 patients (62.9%). Of the 61 patients with metachronous BM, 31 (32.0%) developed BM 1 year after the initial diagnosis. As regards the disease extent of patients with metachronous BM, 28 patients (45.9%) had only distant metastases (locoregional disease was controlled) and 33 patients (54.1%) had both distant metastases and locoregional disease. A total of 43 patients (44.3%) presented with bone-exclusive metastasis, whereas 54 patients (55.7%) had distant metastasis to other organs, including the lung in 38, liver in 20, and other sites in 41 patients. BM were single in 40 patients (41.2%) and multiple in 57 patients (58.8%). BM were located above the clavicle (cervical spine and craniomaxillofacial bones) in 28 patients (28.9%), the shoulder and thorax in 39 (40.2%), the thoracolumbar spine in 62 (63.9%), the pelvis in 39 (40.2%), and the extremities in

Table I. Baseline characteristics of patients with BM from HNSCC (n=97).

Characteristics	No. (%)
Sex	
Male	80 (80.5)
Female	17 (19.5)
Age, years [mean (range)]	63.8 (21-87)
<60	29 (29.9)
≥60	68 (70.1)
Primary site	
Nasopharynx	19 (19.6)
Oropharynx	16 (16.5)
Oral cavity	20 (20.6)
Hypopharynx	26 (26.8)
Larynx	9 (9.3)
Sinonasal cavity	6 (6.2)
Unknown	1 (1.0)
Histological differentiation	
High	22 (22.7)
Moderate	23 (23.7)
Poor	30 (30.9)
Undifferentiated	1 (1.0)
Not available	21 (21.7)
Human papilloma virus status (oropharyngeal SCC, n=16)	
Positive	7
Negative	9

BM, bone metastasis; HNSCC, head and neck squamous cell carcinoma.

Table II. Clinical characteristics of BM (n=97).

Characteristics	No. (%)
Time interval from primary diagnosis	
Synchronous metastases	36 (37.1)
2 months to 1 year	30 (30.9)
≥1 year	31 (32.0)
Disease extent (metachronous metastases, n=61)	
Only distant metastases	28 (45.9)
Distant metastases and locoregional disease	33 (54.1)
Metastases to other organs	
None (bone-exclusive metastasis)	43 (44.3)
Present	54 (55.7)
Number of BM	
Single	40 (41.2)
Multiple	57 (58.8)
BM sites	
Above the clavicle/only above the clavicle	28 (28.9)/13 (13.4)
Shoulder and thorax	39 (40.2)
Thoracolumbar spine	62 (63.9)
Pelvis	39 (40.2)
Extremities	17 (17.5)
CT morphology	
Osteolytic type	45 (46.4)
Intertrabecular type	31 (32.0)
Mixed type	7 (7.2)
Osteoblastic type	14 (14.4)
Performance status	
0	25 (25.8)
1	37 (38.1)
2	8 (8.2)
3	13 (13.4)
4	3 (3.1)
Not available	11 (11.4)
Skeletal-related events	
None	67 (69.1)
Pathological fracture	2 (2.1)
Neurological symptoms	5 (5.2)
Hypercalcemia	7 (7.2)
Requirement for radiotherapy or surgery	21 (21.6)
Systemic chemotherapy for BM	
Received	62 (63.9)
Not received	35 (36.1)

BM, bone metastases.

17 patients (17.5%). In 13 of the 28 patients with BM above the clavicle, the BM were confined to the area above the clavicle. The morphological types on CT imaging were osteolytic in 45 patients (46.4%), intertrabecular in 31 (32.0%), mixed in 7 (7.2%) and osteoblastic in 14 patients (14.4%). The PS was 0 in 25 patients (25.8%), 1 in 37 (38.1%), 2 in 8 (8.2%), 3 in 13 (13.4%), 4 in 3 (3.1%), and N/A in 11 patients (11.4%). SREs were not observed in 67 patients (69.1%) and occurred in 30 patients (30.9%). SREs included pathological fracture in 2, neurological symptoms in 5, hypercalcemia in 7, required radiotherapy in 16 and required surgery in 5 patients. Systemic chemotherapy was administered to 62 patients (63.9%).

Overall survival and prognostic factors. The mean and median follow-up periods were 21.8 and 17 months, respectively (range, 1-119 months); 85 patients (85.6%) succumbed to the disease. The median OS time was 7 months, and the 1- and 2-year OS rates for all patients were 35.4 and 19.2%, respectively (Fig. 1). Tables III and IV present the univariate and multivariate analysis results for the possible predictive factors of longer OS. In the univariate analyses, the following factors had P<0.05 or P<0.1: Nasopharynx as the primary site, bone-exclusive metastasis, single BM, osteoblastic morphology, a good PS (0-1) and systemic chemotherapy. After multivariate analyses, single BM [hazard ratio (HR)=0.543; 95% confidence interval (CI): 0.330-0.894; P=0.016], a good PS (HR=0.458; 95% CI: 0.267-0.787; P=0.005), and administration of systemic

Table III. Univariate analysis of possible predictive factors for longer OS.

Factors	Number (%)	Median OS (months)	1-year OS rate (%)	2-year OS rate (%)	P-value
Age, years					0.106
<60	29 (29.9)	11	44.8	29.9	
≥60	68 (70.1)	6	31.3	14.3	
Primary site					0.037
Nasopharynx	19 (19.6)	10	42.1	42.1	
Others	78 (80.4)	6.5	33.8	12.7	
Histological differentiation					0.710
High to moderate	45 (59.2)	8	39.2	13.8	
Poor to undifferentiated	31 (40.8)	6	26.7	16.7	
HPV status					0.851
Positive HPV in oropharyngeal cancer	7 (7.2)	10	17.1	0.0	
Others	90 (92.8)	7	36.5	20.4	
Time interval from primary diagnosis					0.258
≥1 year	31 (32.0)	7	42.2	19.8	
<1 year	66 (68.0)	7.5	32.4	18.8	
Disease extent					0.176
Only distant metastases	28 (28.9)	11	44.6	24.3	
Distant metastases and locoregional disease	69 (71.1)	6	31.7	17.1	
Metastases to other organs					0.001
None (bone-exclusive metastasis)	43 (44.3)	10	45.3	35.2	
Present	54 (55.7)	6	27.4	5.1	
Number of BM					0.073
Single	40 (41.2)	10	41.1	24.1	
Multiple	57 (58.8)	6	31.4	15.8	
BM sites					0.532
Only above the clavicle	13 (13.4)	10	46.2	27.7	
Others	84 (86.6)	7	33.7	17.9	
CT morphology of BM					0.064
Osteoblastic type	14 (14.4)	16.5	54.5	46.8	
Others	83 (85.6)	6	32.2	14.4	
Performance status					<0.001
0-1	62 (72.1)	10	47.8	27.3	
2-4	24 (27.9)	4.5	8.3	4.2	
Skeletal-related events					0.273
Present	30 (30.9)	5.5	29.6	14.8	
None	67 (69.1)	10	37.9	21.1	
Systemic chemotherapy for BM					<0.001
Received	62 (63.9)	10.5	42.8	27.1	
Not received	35 (36.1)	3	21.6	3.6	

OS, overall survival; HPV, human papillomavirus; BM, bone metastasis.

chemotherapy (HR=0.547; 95% CI: 0.321-0.93; P=0.026) were independent predictors of longer OS. The overall median OS time for patients with single BM was 10 months, and the 1- and 2-year OS rates were 41.1 and 24.1%, respectively. For patients with a good PS, the overall median OS was 10 months, and the 1- and 2-year OS rates were 47.8 and 27.3%, respectively. For patients receiving systemic chemotherapy, the overall median OS was 10.5 months, and the 1- and 2-year OS rates were 42.8 and 27.1%, respectively. Due to the limited influence of each independent predictor, the patients were stratified according to the number of the predictors and Kaplan-Meier curves were drawn (Fig. 2). The median OS in patients with all

Table IV. Multivariate analysis using a Cox proportional hazards model.

Factors	P-value	Hazard ratio	95% CI	
			Upper limit	Lower limit
Primary site	0.118	0.617	1.131	0.267
Metastases to other organs	0.365	0.781	1.333	0.458
Number of BM	0.016	0.543	0.894	0.330
CT morphology of BM	0.120	0.579	1.154	0.290
Performance status	0.005	0.458	0.787	0.267
Systemic chemotherapy for BM	0.026	0.547	0.931	0.321

BM, bone metastases.

Table V. Stratification according to the number of predictive factors of longer OS.

Number of factors	Number of patients (%)	Median OS (months)	1-year OS rate (%)	2-year OS rate (%)
3	18 (19)	14.5	55.6	42.3
2	43 (44)	10	41.9	22.2
1	24 (25)	7	26.3	5.3
None	12 (12)	2	0	0

OS, overall survival.

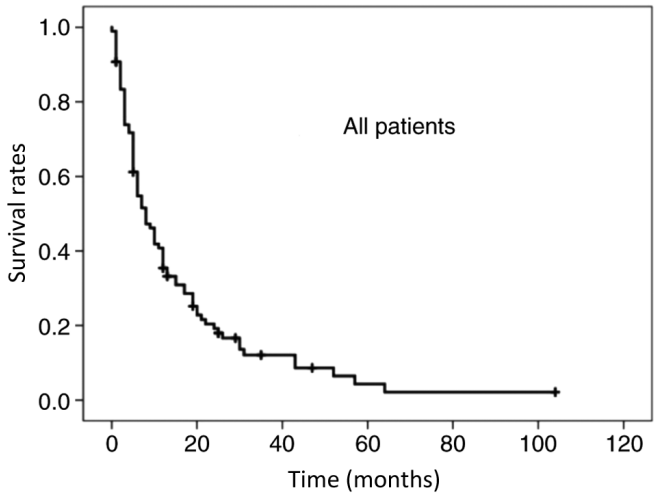

Figure 1. Kaplan-Meier overall survival curve of all patients with bone metastases from head and neck squamous cell carcinoma.

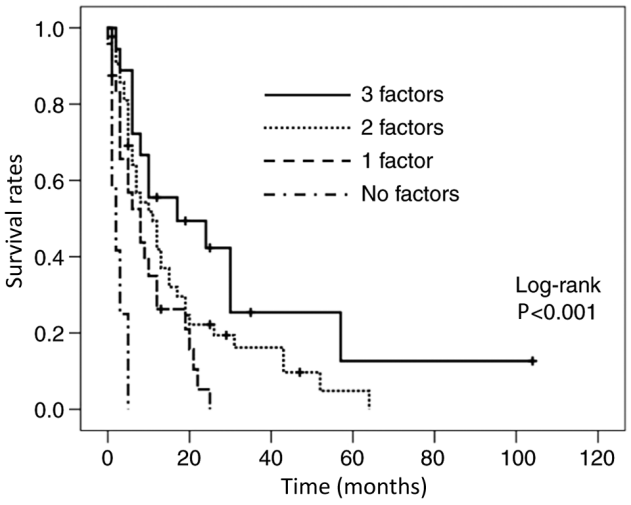

Figure 2. Kaplan-Meier curves of OS stratified according to the number of independent predictors of longer OS, including single bone metastasis, a good performance status, and administration of systemic chemotherapy. OS, overall survival.

three predictive factors (n=18) was 14.5 months, in those with two factors (n=43) it was 10 months, in those with one factor (n=24) it was 7 months, and in those with no factor (n=12) the OS was 2 months (Table V).

Discussion

In addition to the dismal prognosis in patients with BM from HNSCC, BM are clinically important because they represent a major cause of morbidities, such as severe pain, pathological fractures, spinal cord compression and hypercalcemia. Therefore, elucidating the prognostic characteristics of BM from HNSCC is helpful for appropriate management. Data of 10 years from two reference centers were reviewed to comprise the largest patient cohort of BM from HNSCC to date, which allowed for multivariate analyses. Consequently, three independent factors for longer OS, including single BM, a good PS and systemic chemotherapy, were identified.

Comparable to the results of the present study, single or few BM have been reported as predictors of longer OS in patients with BM from several common types of cancer, including lung, breast, prostate and gastrointestinal cancers (23-28). A possible explanation is that the bone is not a vital organ, which indicates that a relatively lower tumor volume (single or only a few BM) may not affect the general condition of the patients. Another possible explanation is that cases with a single BM without metastases to other organs can be classed as an oligometastatic state, which is an intermediate state between the purely localized and widely metastatic state. The oligometastatic state, termed as a limited number of metastases restricted to a single organ, is increasingly considered to be associated with a better prognosis in common types of cancer, such as colorectal or prostate cancer (37,38). Although the concept of oligometastases in HNSCC is not well established, our data may support the concept that oligometastatic HNSCC has a better prognosis and is potentially amenable to local therapy (8,39,40). Therefore, although further prospective analysis is needed, local resection followed by systemic chemotherapy may be a viable treatment option for patients with oligo BM from HNSCC.

Consistent with several previous studies indicating that PS was a favorable prognostic factor for recurrent and metastatic HNSCC (12-15), the current study confirmed that PS was a predictive factor for longer OS, even in patients with BM. PS has also been reported as a prognostic factor in patients with BM from other common types of cancer, including breast, lung and gastric cancers (23,25,26,29). This is explained by the fact that a good PS is associated with a lower risk of pulmonary infection (41), a higher tolerance to chemotherapy, and the selection of more aggressive chemotherapy (42). A good PS may also indicate that the BM may not be that widely disseminated so as to affect daily activities.

Palliative therapy is the usual management strategy for patients with HNSCC who develop distant metastases (5,6), and systemic chemotherapy has been reported to improve OS to a certain degree (6,11,12,17). Compared with lung metastases and locoregional recurrence, systemic chemotherapy was expected to contribute more to BM from HNSCC, as the red marrow, in which BM develop, has a richer blood supply compared with the lung and locoregional area. Although the prognostic influence of systemic chemotherapy reached statistical significance in the present study, it had only a limited influence, with a median OS of 10.5 months. This result is largely consistent with previous analyses of chemotherapy for overall recurrent and/or metastatic HNSCC (6,11,12). Therefore, the indication of systemic chemotherapy for BM from HNSCC should be carefully considered by taking into account its adverse effects. Moreover, novel therapies for BM from HNSCC are warranted.

In accordance with the short life expectancy of patients with distant metastatic HNSCC (6,10,11), the median OS in all our patients was 7 months. Even in patients with predictors for longer OS, the prognosis was still dismal, with a median overall survival of <11 months. Therefore, the data that were further extracted on the patient group with all the three predictors were added, and it was found that they had a relatively longer median OS of 14.5 months. These data appear to suggest that prognosis is determined by multiple factors, and they may serve as a reference for patient counseling on survival expectations.

One major change in HNSCC over the last two decades is the increase in the number of patients with HPV-positive oropharyngeal SCC and the confirmation of their longer survival, resulting in the distinction of staging and treatment guidelines for oropharyngeal SCC depending on HPV status (43,44). Additionally, recent studies reported that HPV-positive recurrent and/or metastatic HNSCCs, including non-oropharyngeal SCC, were also characterized by longer survival compared with their HPV-negative counterparts (19-21). However, a positive HPV status was not a predictor for longer OS in the present study, which may be explained by the small number of patients with HPV-positive oropharyngeal SCC. Therefore, further evaluation in a larger patient cohort, including non-oropharyngeal SCC cases with known HPV status is needed.

The major limitation of the present study was the inherent bias of its retrospective design. For example, the demographic data showed varied primary locations with inhomogeneous proportions, and the patients received various managements for BM, including palliative radiotherapy, systemic chemotherapy and supportive care. Additionally, several factors that may affect survival could not be evaluated owing to the lack of data. Therefore, based on our results, further prospective studies in selected cohorts are warranted. Another limitation is that histological confirmation of BM was performed in only 6 cases. The diagnosis of BM from HNSCC by imaging studies alone cannot fully exclude other bone diseases, such as multiple myeloma or metastases from other occult malignancies. However, histopathological confirmation of all cases is impractical, and even unethical in patients who are in a poor condition and eligible for palliative treatment.

In conclusion, to the best of our knowledge, the present study was the first to evaluate the variable potential factors predicting longer OS in patients with BM from HNSCC. Single BM, a good PS and administration of systemic chemotherapy were independent factors for longer OS, but the median survival did not exceed 11 months, whereas the selected group of patients with all three factors had a relatively longer median OS of 14.5 months.

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Availability of data and materials

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

Authors' contributions

TS wrote the manuscript, and performed data collection and analysis; NK designed the study and wrote the manuscript; HD performed data analysis; HT, AA, CM, YM, KS, HO and KI performed data collection; HI edited and critically reviewed

the manuscript for important intellectual content; NT edited and critically reviewed the manuscript for important intellectual content, and supervised the study. TS and NK confirm the authenticity of the raw data. All the authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Institutional Review Board (Osaka University Hospital Interventional and Observational Studies Review Committee; reference no. 19341), which waived the requirement for informed consent given the retrospective nature of the study.

Patient consent for publication

Not applicable.

Competing interests

All the authors declare that they have no competing interests.

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