Pretreatment SUV of the metastatic neck lymph nodes predicts neck control and survival in patients with stage IV oro/hypopharyngeal cancers

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ABSTRACT

Purpose To investigate the prognostic significance of standardized uptake value (SUV) of metastatic neck lymph nodes measured on FDG PET/CT in patients with stage IV oro/hypopharyngeal cancers treated by definitive chemoradiotherapy (CCRT).

Methods Retrospective analysis of 65 patients with clinically N+ stage IV SCC of the oro/hypopharyngeal squamous cell carcinoma (SCC) who underwent FDG PET/CT scans for primary staging. Follow-up continued till death or at least 24 months from the start of treatment. The primary study endpoint was neck control (NC). The log-rank test and Cox proportional hazard analysis were used to identify significant prognostic factors.

Results The 3-year NC rate was 53%. In univariate analysis, N3 status and nodal SUV $\geq$ 9.8 were significantly associated with reduced NC. In multivariable analyses, nodal SUV retained its independent prognostic significance as a predictor of NC. Lymph node stage was an independent predictor of disease specific survival (DSS). A prognostic scoring system was constructed as follows: score 0 = N0-N2 and nodal SUV < 9.8; score 1 = N3 or nodal SUV $\geq$ 9.8; and score 2 = N3 and nodal SUV $\geq$ 9.8. Patients with a score of 2 showed the worst NC (hazard ratio [HR], 95% confidence interval [CI] = 10.5, 3.3-33.1; *P* < 0.001) and the lowest DSS (HR, 95% CI = 6.4, 2.2-18.7; *P* = 0.001).

Conclusion The combination of high nodal SUV and N3 neck disease identifies a subgroup of high-risk stage IV oro/hypopharyngeal SCC patients. Further prospective studies are warranted to validate this finding.

Keywords
Neck lymph nodes · FDG PET SUV · Hypopharynx · Oropharynx · Prognosis · Concomitant chemoradiotherapy

Introduction

Metastasis to the neck lymph nodes predicts adverse outcomes in patients with head and neck cancers; even worse outcomes would be expected with regional treatment failure [1, 2]. Definitive concurrent chemoradiotherapy is emerging as an alternative therapeutic approach for patients with advanced oro/hypopharyngeal cancers [3]; however, the necessity of planned neck dissection remains a controversial issue for patients with advanced neck stage ($\geqq$N2) [4, 5]. Many established clinical and pathological features are important contributors to the development of neck recurrence [6]; yet, the investigation of pre-treatment clinicobiological predictors of neck control, as well as survival, remains an important issue.

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Research suggests that the standardized uptake value (SUV) – a semiquantitative measure of 18-F-fluorodeoxyglucose (FDG) uptake on positron emission tomography (PET) – can predict tumor control and/or survival rates in patients with head and neck cancers [7-12]. However, most previous studies have focused on the prognostic value of primary tumor SUV, rather than of the neck lymph nodes [10, 13-16]. The tumor behaviors of metastatic nodes would be different from its original parent tumor cells, since it has gained genetic mutations of invasiveness and metastatic potential [17]. The aims of this study was to identify whether SUV at the neck lymph nodes is a significant prognostic factor in patients with stage IV oro/hypopharyngeal squamous cell carcinoma (SCC) treated by CCRT with curative intent.

Materials and methods

Study population
This retrospective study included a total of 65 patients, who presented to Chang Gung Memorial hospital between June 2006 and January 2009. All participants: (a) had a histologically-proven diagnosis of squamous cell carcinoma (SCC) of the oro/hypopharynx, (b) stage IV disease according to the 2002 American Joint Committee on Cancer (AJCC) staging criteria [18] with clinically positive neck nodes (cN+), (c) underwent PET/CT studies for primary staging, (d) completed the scheduled CCRT protocol, and (e) were followed-up for at least 24 months after the beginning of their primary definitive treatment or until death. We excluded patients with distant metastases at the time of diagnosis, synchronous primary tumors, or a previous history of head and neck cancer.

All patients had an extensive staging work-up, which included head and neck contrast-enhanced computed tomography (CE-CT) or magnetic resonance imaging (MRI), abdominal ultrasound (US). Questionable lesions were discussed jointly by our multidisciplinary head and neck team and solved by consensus. Echo-guided neck needle biopsy is indicated for inconsistent image findings. The study protocol was approved by the Institutional Review Board of the Chang Gung Memorial Hospital. All participants gave their written informed consent.

^{18}F-FDG PET/CT
All patients were required to fast for at least 6 hours before PET imaging. Serum glucose levels were measured before the intravenous injection of 370 MBq (10 mCi) of ^{18}F-FDG. PET/CT imaging was performed with a modern hybrid PET/CT scanner (Discovery ST 16, GE Healthcare). Before PET acquisition, helical CT was performed from the head to the proximal thigh using a standardized protocol. The following settings were utilized: transverse 10-mm collimation × 16 modes, 120 kVp, auto mAs (range: 10–300), 0.5 s tube rotation, 17.5 mm/s table speed, pitch 1.75. No oral or intravenous contrast agents were used. CT data were resized from a 512 × 512 matrix to a 128 × 128 matrix to match the PET data. Emission scans from the head to the proximal thigh were acquired at 50 min after injection of the tracer. Images were acquired in two-dimensional mode, 3 min per table position. PET images were reconstructed using CT for attenuation correction with the ordered-subset expectation maximization iterative reconstruction algorithm (4 iterations and 15 subsets). The maximum standardized uptake value of the neck lymph nodes (nodal SUVmax) was determined in all cases with PET-defined positive nodes. In the presence of multiple positive nodes, the highest SUV value was considered for the purpose of analysis. In PET-negative patients, a value of 2 was used to account for the typical head and neck background. Regions of interest (ROIs) were placed and measured over the lesions by PET on simultaneously displayed axial, coronal, and sagittal tomograms. The SUVmax was defined as the highest activity concentration per injected dose per body weight (kg) after correction for radioactive decay.

Treatment and follow-up protocol
All patients were treated by primary CCRT with or without neoadjuvant chemotherapy. The drug scheme used in the majority of patients treated by neoadjuvant or concurrent chemotherapy consisted of cisplatin 50 mg/m^2 biweekly plus daily oral 5-florouracil prodrug and leucovorin every 14 days [19]. All participants received intensity-modulated radiotherapy (IMRT) delivered through a 6-megavolt (MV) photon beam at 2 Gray (Gy) per fraction, with five fractions per week. The RT dose was 46–50 Gy for prophylaxis, and 70–76 Gy for the gross tumor and involved lymph nodes.

Follow-up visits were scheduled every 1–2 months for the first 2 years, then every 3–4 months between the third and the fifth year. The tumor control status was assessed 3 months after ending treatment using different imaging modalities (PET/CT and MRI/CT) as well as by fiberoptic nasopharyngoscopy. Suspicious lesions were either biopsied or closely monitored. The diagnosis of recurrence was based either on positive histopathological findings or evidence of progression at follow-up imaging studies. If the patient has a resectable locoregional disease and with a good performance status, salvage surgery by curative intent will be evaluated. If salvage surgery is not amenable, palliative chemotherapy or best supportive care will be given.

Statistical analysis
The primary study endpoint was the 3-year neck control (NC) rate. Local control (LC), distant metastasis-free survival (DMFS), disease-specific (DSS) and overall survival (OS) served as secondary analyses. Survival times were calculated by Kaplan-Meier analysis and compared using the log-rank test. Cox proportional hazards models were used to identify independent prognostic factors. All time intervals were calculated from the beginning of treatment. We examined nodal SUVmax values (as a continuous variable) in relation to N status and other clinicopathological characteristics of the study participants using the Student's t-test for independent samples. The associations of nodal SUVmax (dichotomized according to the optimal cutoff value) with the study variables were examined using the χ^2 test or Fisher's exact test. The optimal cutoff value for SUV was identified using the log-rank test based on the 3-year disease-specific survival rate. All statistical analyses were performed with the SPSS package (version 15, SPSS Inc. Chicago, IL, USA). Values of $P < 0.05$ (two-tailed) were considered statistically significant.

Results
Patient characteristics This study included 65 patients with oropharyngeal (OPC, n = 28) or hypopharyngeal (HPC, n = 37) SCC. The clinicopathological characteristics of the study participants are summarized in Table 1. At the end of the study, 33 patients died (3-year overall survival = 49%) and 26 had neck failure (3-year NC = 53%). Isolated neck failure was noted in 12 patients (46%). Neck failure was associated with local failure in 5 (19%), with distant failure in 2 (8%), and with both local and distant failures in

the remaining 7 patients (27%). LC, DMFS, DSS and OS were 62, 70, 59 and 49%, respectively. Nodal SUV cut-off value 9.8 g/mL was identified as the best cut-off for 3-year DSS.

Table 1 Clinicopathological characteristics of the study participants ($n = 65$)

Parameter	n	%
TNM Stage		
IV-A	40	(61.5)
IV-B	25	(38.5)
T status		
T1	5	(7.7)
T2	11	(16.9)
T3	7	(10.8)
T4a	22	(33.8)
T4b	20	(30.8)
N status		
N1	3	(4.6)
N2b	29	(44.6)
N2c	22	(33.8)
N3	11	(16.9)
Differentiation		
Well-differentiated	1	(1.5)
Moderately-differentiated	42	(64.6)
Poorly-differentiated	11	(16.9)
Unknown	11	(16.9)
Age, years		
Median (range) [a]	54	(36-74)
Radiotherapy dose		
Median Gy (Range) [a]	72	(66-90)
SUV_{max} of the neck lymph nodes		
Median (Range) [a]	10.1	(2.0-25.7)

[a] *Data in parenthesis indicate the range*

Nodal SUV associations with other study variables

Nodal SUV (analyzed as a continuous variable) was signifycantly higher in N3 patients (mean = 15.3 ± 5.7) than N1 (mean ± SD = 5.3 ± 1.4; $P = 0.02$) and N2 (mean ± SD = 10 ± 5.4; $P = 0.01$). Similarly, high nodal SUV values ($\geq$ 9.8 mg/mL) were significantly associated with nodal status. Ten out of 11 patients with N3 had nodal SUV $\geq$ 9.8($P = 0.02$). No other associations between the nodal SUV and other parameters were observed.

Univariate analysis

Univariate analysis for neck events demonstrated a significantly lower NC rate for patients with high nodal SUV (26 vs. 81%; P < 0.001) or N3 neck disease (25 vs. 76%; P = 0.003), and tended to be lower with stage IV-b disease (41 vs. 60%; P = 0.056). Further, betel quid chewing was associated with lower NC rate, albeit not significantly so.

Patients with high nodal SUV values or N3 disease had worse disease-specific and overall survival rates compared with those who do not have these risk factors (Table 2). In addition, the overall survival rate was lower in patients with HPC than in those with OPC (38 vs. 63%; P = 0.027).

Table 2 *Univariate analysis of 3-year local control (LC), neck control (NC), distant metastasis-free survival (DMFS), disease-specific survival (DSS), and overall survival (OS) rates in 65 patients with stage IV oro/hypopharyngeal cancer*

Risk factor	n	LC		NC		DMFS		DSS		OS	
		(Events,%)	P	(Events,%)	P	(Events,%)	P	(Events,%)	P	(Events,%)	P
Cancer site											
Oropharynx	28	(4, 83)	0.014*	(9, 64)	0.141	(3, 87)	0.041*	(9, 68)	0.238	(10, 63)	0.027*
Hypopharynx	37	(15, 42)		(17, 43)		(10, 54)		(15, 52)		(23, 38)	
Differentiation											
WD-MD	43	(12, 63)	0.816	(16, 57)	0.533	(6, 77)	0.566	(13, 66)	0.638	(20, 53)	0.623
PD SCC	11	(3, 64)		(5, 40)		(2, 74)		(4, 61)		(6, 45)	
Stage											
IVa	40	(11, 66)	0.371	(13, 60)	0.056	(6, 78)	0.087	(10, 72)	0.011*	(17, 57)	0.069
IVb	25	(8, 55)		(13, 41)		(7, 57)		(14, 40)		(16, 36)	
T status											
T1-T3	23	(3, 79)	0.040*	(11, 46)	0.751	(4, 73)	0.529	(6, 70)	0.175	(10, 55)	0.338
T4	42	(16, 52)		(15, 58)		(9, 69)		(18, 54)		(23, 45)	
N status											
N1-N2	54	(14, 67)	0.044*	(18, 59)	0.003*	(9, 76)	0.018*	(16, 67)	0.005*	(24, 55)	0.017*
N3	11	(5, 24)		(8, 22)		(4, 25)		(8, 21)		(9, 18)	
Treatment											
CCRT	36	(9, 70)	0.596	(12, 59)	0.474	(5, 81)	0.263	(14, 57)	0.518	(19, 46)	0.509
C/T+CCRT	29	(10, 50)		(14, 46)		(8, 58)		(10, 62)		(14, 52)	
Nodal SUV											
< 9.8	29	(7, 73)	0.065	(5, 81)	< 0.001*	(4, 83)	0.033*	(6, 78)	0.006*	(9, 69)	0.003*
≥ 9.8	36	(12, 48)		(21, 26)		(9, 53)		(18, 43)		(24, 32)	

WD/MD/PD well/moderately/poor differentiated, SCC squamous cell carcinoma, CCRT concomitant chemoradiotherapy, C/T neoadjuvant chemotherapy, SUV standardized uptake value
• Indicates significant results (P < 0.05)

Multivariate analysis and prognostic scoring system

All variables with P < 0.10 in univariate analysis were tested in a Cox proportional hazard model. (Table 3) shows the results of multivariable Cox regression analysis. High nodal SUV ≥ 9.8 and N3 neck status were the only two variables to retain their independent prognostic significance

for NC and DSS after allowance for potential confounders. Based on the presence or absence of the two independent variables, we constructed a prognostic scoring system that identified three distinct prognostic subgroups **(Table 4)**, as follows: score 0 = N0-N2 and nodal SUV < 9.8; score 1 = N3 or nodal SUV ≥ 9.8; and score 2 =

N3 and nodal SUV ≥ 9.8. Cox regression analysis, corrected for both T status and cancer site, showed that patients with a score of 2 experienced the worst outcomes in terms of NC (HR, 95% CI = 13.9, 3.1-62.8; $P = 0.001$) and DSS (HR, 95% CI = 6.7, 1.9-23.6; $P = 0.003$) as well as other endpoints **(Figure 1), (Table 5).**

Table 3 *Multivariable analyses of 3-year local control (LC), neck control (NC), distant metastasis-free survival (DMFS), disease-specific survival (DSS), and overall survival (OS) rates in 65 patients with stage IV oro/hypopharyngeal cancer*

Outcome	N status (N1-N2/N3) (n = 54/11)		Nodal SUV (<9.8/≥9.8) (n = 30/35)	
	HR (95% CI)	*P*	HR (95% CI)	*P*
LC	1.7 (0.6-5)	0.356	2.8 (1-7.8)	0.056
NC	2.2 (0.9-5.5)	0.100	4.9 (1.7-14)	0.003 *
DMFS	3.1 (0.9-11.1)	0.080	2.8 (0.8-10.4)	0.116
DSS	2.6 (1-6.5)	0.048 *	3.1 (1.1-8.4)	0.026 *
OS	1.9 (0.8-4.4)	0.129	2.7 (1.2-6)	0.020 *

HR hazard ratio (stepwise forward method), *CI* confidence interval, *SUV* standardized uptake value
* Indicates significant results, results corrected for T status and tumor site

Table 4 *Cox regression analysis of 3-year local conrol (LC), neck control (NC), distant metastasis-free survival (DMFS), disease-specific survival (DSS), and overall survival (OS) rates in 65 patients with stage IV oro/hypopharyngeal cancer according to the prognostic risk score*

Outcome	Score 0 (n = 28) [a]			Score 1 (n = 27)			Score 2 (n = 10)		
	(Events, %)	HR (95% CI)	P_0	(Events, %)	HR (95% CI)	P_1	(Events, %)	HR (95% CI)	P_2
LC	(6, 76)	1	0.104	(9, 47)	2.2 (0.7-6.4)	0.166	(4, 39)	3.9 (1.1-14.3)	0.038 *
NC	(5, 80)	1	<0.001	(13, 36)	3.3 (1.1-9.7)	0.029*	(8, 13)	10.5 (3.3-33.1)	< 0.001 *
DMFS	(3, 87)	1	0.044	(7, 51)	3 (0.7-12.2)	0.122	(3, 37)	8.4 (1.6-45.2)	0.013 *
DSS	(6, 77)	1	0.003	(10, 58)	2.4 (0.8-6.8)	0.101	(8, 11)	6.4 (2.2-18.7)	0.001 *
OS	(9, 68)	1	0.004	(15, 42)	2.1 (0.9-5)	0.086	(9, 10)	4.9 (1.9-12.5)	0.001 *

HR hazard ration, *CI* confidence interval, *SUV* standardized uptake value
[a] *Score 0* (N0-N2 & nodal SUV < 9.8, reference group), *score 1* (N3 or nodal SUV ≥ 9.8), *score 2* (N3 & nodal SUV ≥ 9.8)
P_0 represents the within-groups difference, P_1 & P_2 represents the difference between score 1 & score 2 to the reference group respectively
• Indicates significant results, results were corrected for tumor site and T stage

Table 5 Stratification of N1-N2 patients by nodal SUV according to 3-year local control (LC), neck control (NC), distant metastasis-free survival (DMFS), disease-specific survival (DSS), and overall survival (OS) rates

Outcome	Nodal SUV < 9.8 (n = 28)	Nodal SUV ≥ 9.8 (n = 26)	P
	(Events, %)	(Events, %)	
LC	(6, 76)	(8, 53)	0.141
NC	(5, 80)	(13, 32)	0.002 *
DMFS	(3, 87)	(6, 57)	0.062
DSS	(6, 77)	(10, 56)	0.092
OS	(9, 68)	(15, 40)	0.034 *

SUV standardized uptake value

• Indicates significant results ($P < 0.05$)
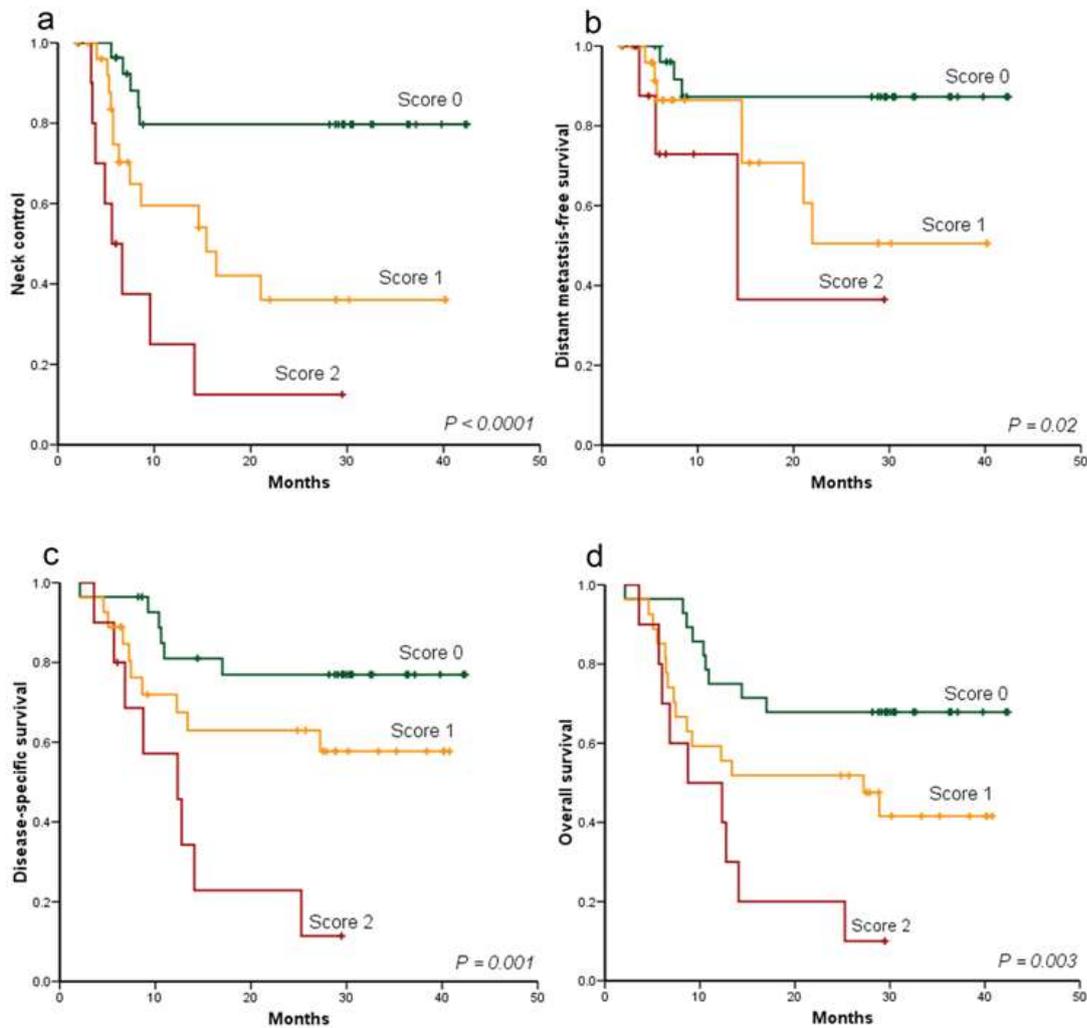
Fig. 1 Neck control (a), distant metastasis free survival (b), disease-specific survival (c) and overall survival (d) according to the proposed risk score [a] in 65 patients with stage IV oro/hypopharyngeal cancer

[a] *Score 0* (N0-N2 & nodal SUV < 9.8), *score 1* (N3 or nodal SUV ≥ 9.8), *score 2* (N3 & nodal SUV ≥ 9.8)
P value obtained from log-rank test

The oro/hypopharynx harbors a rich lymphatic network, and more than 60% of cancers arising in this area present in advanced stage [20]. The regional response to therapy is an established prognostic factor for oro/hypopharyngeal squamous cell carcinomas and the identification of novel predictors of neck control may be useful for individualizing treatment approaches.

The FDG uptake in the primary tumor (as measured by the SUV) has been shown to correlate with both tumor proliferation rates [21] and clinical outcomes [7-12] in head and neck cancers. Although the potential prognostic significance of nodal SUV values at oral cavity cancer and some other cancers has been reported [14-16, 22, 23], a paucity of data exists on the potential prognostic significance of nodal SUV values in oro/hypopharyngeal cancer.

Herein we have shown that a nodal SUV of 9.8 or higher may independently predict the 3-year NC and survival rates in stage IV oro/hypopharyngeal cancer patients treated by CCRT with curative intent. Importantly, we have developed a prognostic scoring system that incorporates nodal SUV values and identifies three distinct prognostic subgroups.

Patients with a score of 2 showed the highest rates of neck and distant failures, cancer deaths, and poor overall survival. Seventy percent of patients with a score of 2 died of disease within 15 months after the beginning of CCRT. Although our results cannot be presented as practice-changing, the poor prognosis within this group may prompt further studies to evaluate the potential usefulness of novel approaches such as early salvage surgery for resectable disease, more effective chemotherapy regimens, radiotherapy dose escalation or biological therapies.

Patients with score 0 showed the lowest rate of distant failures (3/28) when compared to score 1 (7/27) and score 2 (3/10). DMFS was 87% for score 0, 51% for score 1 ($P = 0.03$) and 37% for score 2 ($P = 0.02$). Closely systemic workup may be advised for early detection of distant metastases in patients with score 1 or 2.

In our data, 10 of 11 patients with N3 disease had nodal SUV ≥ 9.8 ($P = 0.02$). Although we found that strong association between N3 and high nodal SUV, but that does not reduce -in our opinion- the prognostic importance of nodal SUV. When we stratify N1-N2 patients by the nodal SUV (Table 5) we found strong relation to unfavorable

outcomes in patients with high nodal SUV; neck control and overall survival were significantly lower, while the distant failure and disease specific survival remained marginally significant. Eight patients in this category were successfully salvaged by neck dissection. There might be a potential role of early planned neck dissection for such patient group, who has N1-2 stage but with higher nodal SUV. Further prospective investigation trial is warranted.

We recognize that our study has several limitations. The single-center nature and the retrospective design of our research limit the generalizability of our findings. Second, we did not specifically investigate the accuracy of FDG-PET in the diagnosis of nodal disease. Not with standing these caveats, the potential strengths of our study include the homogenous study population and the use of standardized treatment and follow-up protocols.

Conclusions

Our study suggests that the combination of high nodal SUV and N3 neck disease identifies a subgroup of high-risk stage IV oro/hypopharyngeal SCC patients for both regional recurrence and survival. Further prospective studies are warranted.

Conflicts of interest

The authors do not have anything to disclose

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