^{18}F-FDG PET/CT代谢参数对接受非手术治疗的复发性舌鳞状细胞癌患者生存的预测价值

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[摘 要] 目的：非手术治疗的复发性舌鳞状细胞癌(recurrent tongue squamous cell carcinoma，RTSCC)患者预后差。本研究旨在探讨接受非手术治疗的RTSCC患者生存相关的独立危险因素，以及治疗疗效对其生存情况的影响。**方法：**回顾性收集2017年1月至2024年7月在湖南省肿瘤医院接受非手术治疗的RTSCC患者，测量其治疗前^{18}F-氟代脱氧葡萄糖正电子发射计算机体层显像仪(^{18}F-fluorode-oxyglucose positron emission tomography/computed tomography，^{18}F-FDG PET/CT)的代谢参数，包括经瘦体重校准的病灶最大、平均和峰值标准化摄取值(maximum, mean and peak standardized uptake value corrected for lean body mass，SULmax、SULmean、SULpeak)、病灶与纵隔血池SULmean比值(lesion-to-mediastinal-blood-pool SULmean ratio，SULR)、全身总代谢肿瘤体积(metabolic tumor volume，MTV)、全身总病灶糖酵解(total lesion glycolysis，TLG)，同时收集患者临床基本信息、首次手术病理特征、复发后治疗方式等信息，依据实体肿瘤疗效评价标准1.1版(response evaluation criteria in solid tumors version 1.1，RECIST 1.1)或实体肿瘤免疫治疗疗效评价标准(immune response evaluation criteria in solid tumors，iRECIST)评估治疗疗效(将患者分为治疗缓解组与治疗非缓解组)，并追踪患者的疾病无进展生存期(progression-free survival，PFS)及总生存期(overall survival，OS)。采用单因素及多因素Cox回归分析，筛选出与PFS及OS相关的独立危险因素，通过仅纳入使用同一扫描机型的患者和仅纳入完成全身扫描的患者进行2项敏感性分析，以评估主要结果的稳健性。通过一致性指数(concordance index，C-index)、时间依赖性接受者操作特征曲线及校准曲线等评估模型性能。通过时间依赖性Cox回归和Landmark分析比较治疗疗效对患者生存情况的影响。**结果：**本研究共纳入93例RTSCC患者，随访时间为2~81(中位数38)个月，出现进展者72例，死亡者66例。患者的PFS为1~81(中位数4)个月，OS为2~81(中位数11)个月。在主要分析中，复发后放疗是PFS的独立保护因素(*HR*=0.461，95% *CI* 0.233~0.912，*P*=0.026)，其在仅限同一扫描机型的敏感性分析中仍为独立保护因素(*P*=0.032)，在仅限全身扫描的敏感性分析中无统计学意义(*P*=0.159)。PFS预测模型的校正C-index为0.609，模型预测患者3个月及6个月PFS的价值有限。OS相关分析显示，MTV的自然对数ln(MTV)(*HR*=1.299，95% *CI* 1.092~1.546，*P*=0.003)、复发后放疗(*HR*=0.377，95% *CI* 0.180~0.790，*P*=0.010)是患者OS的独立预测因素；2项敏感性分析验证了结果的稳健性。OS预测模型的校正C-index为0.663，模型对1年及2年OS的区分能力为中等。时间依赖性Cox回归分析结果显示治疗缓解与PFS的关联无统计学意义(*HR*=0.618，95% *CI* 0.327~1.167，*P*=0.138，C-index=0.517)；治疗缓解对OS有显著的保护效应(*HR*=0.340，95% *CI 0.*196~0.590，*P*<0.001，C-index=0.620)。Landmark分析(2个月)结果显示治疗缓解组的PFS及OS均长于治疗非缓解组(均*P*<0.001)。**结论：**全身总MTV、复发后放疗对接受非手术治疗的RTSCC患者的OS具有一定预测价值，复发后放疗对PFS的保护作用需进一步验证。治疗缓解者的OS优于非缓解者。

[关键词] 舌鳞状细胞癌；复发；非手术治疗；生存期；^{18}F-FDG PET/CT

收稿日期(Date of reception)：2026-01-21

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基金项目(Foundation item)：湖南省自然科学基金(2026JJ82576)。This work was supported by the Natural Science Foundation of Hunan Province, China (2026JJ82576).

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Predictive value of [18]F-FDG PET/CT metabolic parameters for survival in patients with recurrent tongue squamous cell carcinoma receiving nonsurgical treatment

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ABSTRACT

Objective: Patients with recurrent tongue squamous cell carcinoma (RTSCC) receiving nonsurgical treatment have a poor prognosis. This study aims to identify independent factors associated with survival in these patients and to evaluate the effects of treatment response on survival outcomes.

Methods: Patients with RTSCC who received nonsurgical treatment at Hunan Cancer Hospital between January 2017 and July 2024 were retrospectively enrolled. Pretreatment metabolic parameters derived from [18]F-fluorodeoxyglucose positron emission tomography/computed tomography ([18]F-FDG PET/CT) were measured, including the maximum, mean, and peak standardized uptake values corrected for lean body mass (SULmax, SULmean, and SULpeak), the lesion-to-mediastinal blood-pool SULmean ratio (SULR), whole-body total metabolic tumor volume (MTV), and whole-body total lesion glycolysis (TLG). Baseline clinical characteristics, pathological features from the initial surgery, and treatment modalities after recurrence were also collected. Treatment response was evaluated according to the Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1), or the immune Response Evaluation Criteria in Solid Tumors (iRECIST), and patients were classified into response and nonresponse groups. Progression-free survival (PFS) and overall survival (OS) were followed. Univariate and multivariate Cox regression analyses were performed to identify independent factors associated with PFS and OS. Two sensitivity analyses, restricted to patients scanned using the same scanner model and to those who underwent whole-body scanning, respectively, were conducted to assess the robustness of the primary findings. Model performance was evaluated using the concordance index (C-index), time-dependent receiver operating characteristic (ROC) curves, and calibration curves. Time-dependent Cox regression and landmark analyses were used to assess the effects of treatment response on survival.

Results: A total of 93 patients with RTSCC were included. The follow-up duration ranged from 2 to 81 months, with a median of 38 months. Disease progression occurred in 72 patients, and 66 patients died. PFS ranged from 1 to 81 months, with a median of 4 months, whereas OS ranged from 2 to 81 months, with a median of 11 months. In the primary analysis, radiotherapy after recurrence was an independent protective factor for PFS (*HR*=

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0.461, 95% *CI* 0.233 to 0.912, *P*=0.026). This association remained significant in the sensitivity analysis restricted to patients scanned using the same scanner model (*P*=0.032), but was not significant in the analysis restricted to patients who underwent whole-body scanning (*P*=0.159). The corrected C-index of the PFS prediction model was 0.609, indicating limited predictive performance for 3- and 6-month PFS. In the analysis of OS, the natural logarithm of MTV [ln(MTV); *HR*=1.299, 95% *CI* 1.092 to 1.546, *P*=0.003] and radiotherapy after recurrence (*HR*=0.377, 95% *CI* 0.180 to 0.790, *P*=0.010) were independent predictors of OS. Both sensitivity analyses supported the robustness of these findings. The corrected C-index of the OS prediction model was 0.663, indicating moderate discrimination for 1- and 2-year OS. Time-dependent Cox regression analysis showed that treatment response was not significantly associated with PFS (*HR*=0.618, 95% *CI* 0.327 to 1.167, *P*=0.138; C-index=0.517), whereas treatment response had a significant protective effect on OS (*HR*=0.340, 95% *CI* 0.196 to 0.590, *P*<0.001; C-index=0.620). The 2-month landmark analysis showed that both PFS and OS were significantly longer in the response group than in the nonresponse group (both *P*<0.001).

Conclusion: Whole-body total MTV and radiotherapy after recurrence have potential prognostic value for OS in patients with RTSCC receiving nonsurgical treatment. The protective association between radiotherapy after recurrence and PFS requires further validation. Patients who achieved a treatment response had better OS than those who did not respond.

KEY WORDS tongue squamous cell carcinoma; recurrence; nonsurgical treatment; survival; ^{18}F-FDG PET/CT

舌癌是最常见的口腔恶性肿瘤，其复发率较高、预后较差。据报道，舌癌患者在接受根治性手术后，复发率为20%~67%[1-3]。舌癌患者的预后在肿瘤复发后急剧下降，病死率约为90%[4-5]。复发性舌癌患者的治疗难度往往比初治患者要高，患者的治疗选择包括挽救性手术、放疗、化疗、免疫治疗或多种治疗手段联合应用，但其病死率无显著降低。现有研究[6]表明接受挽救性手术的复发性舌癌患者的预后优于非手术治疗者，然而，鲜有文献报道接受非手术治疗的复发性舌癌患者的生存影响因素。识别接受非手术治疗的复发性舌癌患者生存相关的危险因素，对于调整其治疗策略、改善患者预后至关重要。

^{18}F-氟代脱氧葡萄糖(^{18}F-fluorode-oxyglucose，^{18}F-FDG)正电子发射计算机体层显像仪(positron emission tomography/computed tomography，PET/CT)能够同时提供病灶精确的解剖学范围及肿瘤的代谢信息，通常用于头颈部鳞状细胞癌患者治疗后的随访复查。目前已有研究[7-9]探讨将^{18}F-FDG PET/CT代谢参数作为预测恶性肿瘤预后的生物标志物，其优势在于不额外增加患者的经济成本、时间成本及辐射剂量。研究[7]发现复发性头颈部鳞状细胞癌患者的术前^{18}F-FDG PET/CT代谢参数，比如总代谢肿瘤体积(metabolic tumor volume，MTV)和总病灶糖酵解(total lesion glycolysis，TLG)，与其术后复发后的生存率密切相关。然而，此研究是根据初治患者的基线PET/CT代谢参数进行的，但舌癌复发灶侵袭性更强，肿瘤代谢特征可能发生变化。

因此，本研究假设治疗前的^{18}F-FDG PET/CT代谢参数能够反映复发性舌癌患者的肿瘤负荷，并与患者生存情况相关。本研究旨在基于治疗前的^{18}F-FDG PET/CT代谢参数探讨复发性舌鳞状细胞癌(recurrent tongue squamous cell carcinoma，RTSCC)患者无进展生存期(progression-free survival，PFS)及总生存期(overall survival，OS)的独立危险因素，并探究治疗疗效对其生存情况的影响。

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1 对象与方法

1.1 伦理声明

本研究已获得湖南省肿瘤医院伦理审查委员会的批准(审批号：KY2025706)，因研究性质为回顾性，伦理委员会豁免了对患者知情同意的要求。

1.2 对象

本研究连续性地收集了2017年1月至2024年7月在湖南省肿瘤医院应用^{18}F-FDG PET/CT进行舌癌根治术后复查且明确复发的患者资料。本研究的纳入及排除流程见图1。

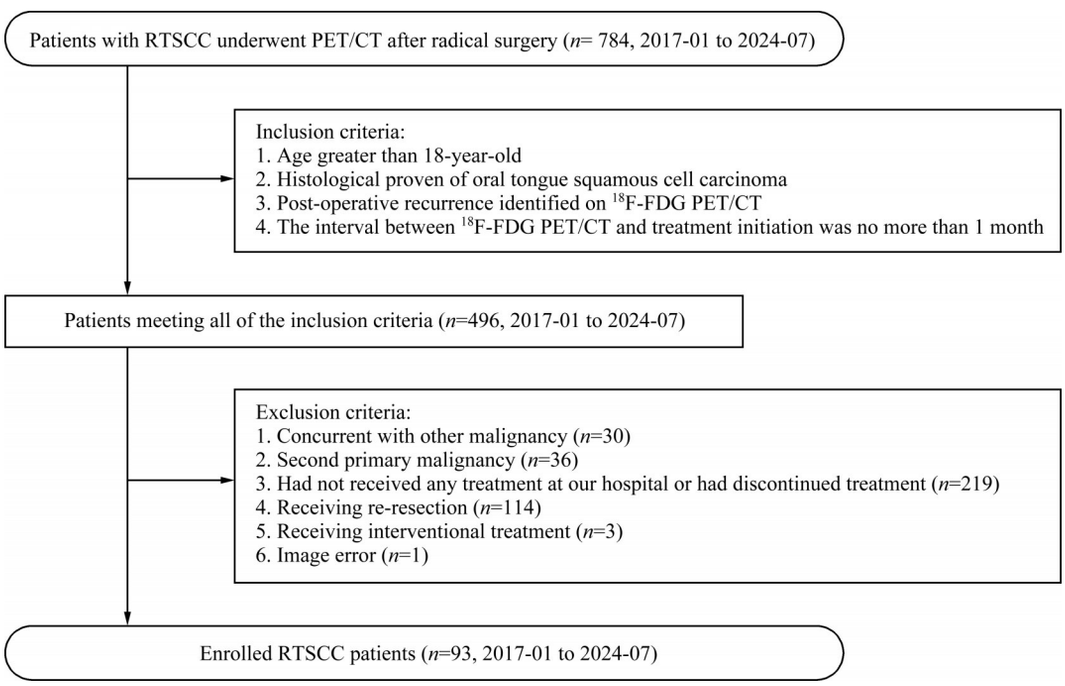


图1　患者纳入及排除流程图

Figure 1　Flowchart for patient inclusion and exclusion

RTSCC: Recurrent tongue squamous cell carcinoma; ^{18}F-FDG PET/CT: ^{18}F-fluorode-oxyglucose positron emission tomography/computed tomography.

1.3 影像检查设备及方法

所有^{18}F-FDG PET/CT扫描在2台PET/CT扫描仪(型号：Discovery ST 8、Discovery MI，美国GE医疗公司)上进行。在^{18}F-FDG PET/CT扫描前，患者需禁食至少6 h，并且在给予^{18}F-FDG前确认血糖水平<110 mg/dL。静脉注射^{18}F-FDG 4.00 MBq/kg后约60 min行PET/CT检查。患者首先行低剂量CT平扫(管电压为110 kV，管电流为120 mA，512×512矩阵，螺距1.75，重建层厚和间隔均为3.75 mm)进行精确的解剖定位和衰减校正，扫描范围为颅顶至纵隔主肺动脉窗水平(局部扫描)或者大腿近端(全身扫描)。随后，在3D采集模式下进行PET扫描，包括5~6个床位置，每个位置持续2 min。将采集的数据转移到Advantage Workstation(AW 4.7，美国GE医疗公司)中，并使用有序子集期望最大化(ordered subset expectation maximization，OSEM)算法进行重建，迭代2次，共21个子集。CT数据用于衰减校正，并将所得图像配准后用于分析。

1.4 PET代谢参数测量

通过基于瘦体重(lean body mass，LBM)校准的病灶的最大、标准及峰值标准化摄取值(maximum, mean and peak standardized uptake value corrected for lean body mass，SULmax、SULmean、SULpeak)、病灶与血池SULmean比值(lesion-to-mediastinal-blood-pool

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SULmean ratio，SULR)，对PET图像进行视觉和半定量分析。LBM依据James公式估算：LBM(男性)=1.10×体重−128×(体重/身高)^2，LBM(女性)=1.07×体重−148×(体重/身高)^2。其中体重的单位为kg，身高的单位为cm。本研究中男性、女性患者的LBM分别为(50.90±6.47)、(44.65±4.64) kg。任何偏离生理分布和背景的局灶性示踪剂摄取均被视为疾病，其定义为目视分析时^{18}F-FDG活性高于周围组织。通过在最大活性区域上绘制感兴趣区(region of interest，ROI)来计算高代谢病灶的SULmax。采用高度为20 mm、直径为10 mm且不包含血管壁在内的ROI，在轴位PET/CT融合图像的主动脉弓处测量纵隔血池的SULmean。当一个患者有多个病灶时，以^{18}F-FDG摄取最高的病灶的SULmax、SULmean、SULpeak和SULR代表该患者的单病灶代谢水平。根据衰减校正的^{18}F-FDG PET/CT图像，使用基于SUL的半自动轮廓绘制程序uWS-MI测量总MTV，并根据欧洲核医学协会推荐将40%的SULmax作为相对阈值[10]。TLG计算公式为：TLG=MTV×SULmean_MTV(SULmean_MTV为MTV区域内的SULmean)。全身总MTV和全身TLG为患者所有肿瘤相关性病变的总和。各代谢参数经自然对数转换后以连续变量形式纳入生存分析。

1.5 局部复发、区域复发及远处转移定义

局部复发的定义是舌癌手术后口腔相同或附近部位复发。颈部淋巴结转移定义为区域复发。颈部以外的部位复发定义为远处转移。

1.6 肿瘤分期、疗效评估、PFS及OS定义

肿瘤分期依据美国癌症联合委员会(American Joint Committee on Cancer，AJCC)肿瘤分期第8版[11]进行。是否进展依据实体肿瘤疗效评价标准1.1版(response evaluation criteria in solid tumors version 1.1，RECIST 1.1)或实体肿瘤免疫治疗疗效评价标准(immune response evaluation criteria in solid tumors，iRECIST)[12-13]进行评估，将完全缓解(complete remission，CR)、部分缓解(partial remission，PR)定义为缓解，疾病稳定(stable disease，SD)、疾病进展(progressive disease，PD)定义为非缓解。疾病PFS是指从复发后治疗开始至影像学检查首次证实疾病进展或任何原因导致死亡的时间，以先发生者为准。OS是指复发后治疗开始至任何原因导致死亡的时间。未发生进展或死亡者，以末次随访日期(2025年12月15日)作为删失数据，失访者以失访日期作为删失数据。

1.7 统计学处理

采用R (v4.5.2)软件及Graphpad Prism 10软件进行统计学分析。正态分布且方差齐的连续变量采用平均数±标准差表示。非正态分布或方差不齐的连续变量以中位数(第1四分位数，第3四分位数)表示。分类变量以频数(构成比)表示。利用单因素及多因素Cox回归分析(向后逐步回归法)筛选与接受非手术治疗的RTSCC患者PFS及OS相关的危险因素，通过Schoenfeld残差检验验证Cox回归模型是否满足等比例风险假设。采用Bonferroni校正的敏感性分析评估单因素分析中采用P<0.100的宽松阈值可能带来的假阳性风险。对单因素分析中P<0.100的变量进行Pearson或Spearman相关性分析，$|r|$>0.800视为强相关。每对强相关变量中仅保留效应较大者进入多因素分析。利用C-指数(C-index)、校准曲线、Brier评分及预测精度指数(index of prediction accuracy，IPA)评估多因素Cox回归模型效能。扫描机型及检查部位差异造成的潜在偏倚利用敏感性分析进行评估。通过时间依赖性Cox回归和Landmark分析比较治疗疗效对患者生存情况的影响。P<0.05为差异有统计学意义。

2 结 果

2.1 研究对象的一般资料

本研究共纳入93例患者，其中男性85例，女性8例，平均年龄为49.8岁，复发前接受手术次数为1、2、3次的患者分别为74、15、4例。前次手术与复发时间间隔为0~113(中位数7)个月。93例患者中，采用GE Discovery ST 8、GE Discovery MI检查者分别为8、85例，进行全身、头颈部^{18}F-FDG PET/CT检查者分别为78、15例，行头颈部PET/CT检查者同时期进行了胸部及腹部的平扫加增强CT检查，排除了远处转移。患者的临床特征、PET/CT代谢参数及基线病理特征见表1。

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表1　RTSCC患者的基本信息(*n*=93)

Table 1　Baseline information of patients with RTSCC (*n*=93)

Variables	Values	Variables	Values
Sex/[No.(%)]		Surgical margin/[No.(%)]	
Female	8(8.60)	Negative	85(91.40)
Male	85(91.40)	Near or positive or unknown	8(8.60)
Age/Years	49.84±9.98	Time from prior surgery to recurrence/Month	7(0, 113)
Smoking/[No.(%)]		Relapse T classification/[No.(%)]	
Yes	64(68.82)	T0	63(67.74)
No	29(31.18)	T1−2	16(17.21)
Drinking/[No.(%)]		T3−4	14(15.05)
Yes	45(48.39)	Relapse N classification/[No.(%)]	
No	48(51.61)	N0	32(34.41)
Betel quid chewing/[No.(%)]		N1−2	38(40.86)
Yes	65(69.89)	N3	23(24.73)
No	28(30.11)	Relapse M classification/[No.(%)]	
ECOG PS/[No.(%)]		M0	64(68.82)
0	42(45.16)	M1	29(31.18)
≥1	51(54.84)	Recurrent site/[No.(%)]	
Adjuvant therapy after initial surgery/[No.(%)]		Local	15(16.13)
Yes	36(38.71)	Regional	38(40.86)
No	57(61.29)	Loco-Regional	11(11.83)
Number of surgeries/[No.(%)]		Metastasis	29(31.18)
1	74(79.57)	Relapse TNM/[No.(%)]	
≥2	19(20.43)	I−III	14(15.05)
Lesion SULmax	11.53±5.24	IV	79(84.95)
Lesion SULpeak	9.04±4.19	Treatment line/[No.(%)]	
Lesion SULmean	6.51±3.05	First-line	86(92.47)
Lesion SULR	5.10±2.50	Second-line or subsequent	7(7.53)
Total MTV/cm^3	16.17(1.12, 1 835.21)	Post-recurrence radiotherapy/[No.(%)]	
TLG/cm^3	109.98(5.45, 6 793.14)	Yes	19(20.43)
Initial pT/[No.(%)]		No	74(79.57)
T1−2	59(63.44)	Treatment modality/[No.(%)]	
T3−4	34(36.56)	Single	15(16.13)
Initial pN/[No.(%)]		Combined	78(83.87)
−	48(51.61)	Treatment response/[No.(%)]	
+	45(48.39)	CR	4(4.30)
Initial pTNM/[No.(%)]		PR	38(40.86)
I−II	36(38.71)	SD	15(16.13)
III−IV	57(61.29)	PD	36(38.71)
Initial tumor differentiation/[No.(%)]		Time to best response/Month	2(0, 9)
Well	26(27.96)		
Moderate or low or unknown	67(72.04)		

Continuous variables that follow a normal distribution are described by mean±standard deviation; continuous variables that do not follow a normal distribution are described by median (25th, 75th percentile); categorical data are described by frequency (percentage). RTSCC: Recurrent oral tongue squamous cell carcinoma; ECOG: Eastern cooperative oncology group; PS: Performance status; MTV: Metabolic tumor volume; TLG: Total lesion glycolysis; SULR: Lesion-to-mediastinal-blood-pool SULmean ratio; p: Pathology; T: Tumor; N: Node; M: Metastasis; CR: Complete remission; PR: Partial remission; SD: Stable disease; PD: Progressive disease.

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2.2 RTSCC患者的治疗及生存情况

患者从确诊复发至开始治疗的等待时间为2~31(中位数5) d。共19例患者复发后接受放疗，其余74例未接受放疗。在治疗模式方面，接受单一治疗者15例，接受联合治疗者78例。单一治疗包括单用免疫治疗(2例)、单用化疗(13例)。联合治疗包括放化疗(10例)、放疗联合免疫/靶向治疗(2例)、放化疗联合免疫治疗(3例)、放化疗联合靶向治疗(4例)、化疗联合免疫治疗(36例)、化疗联合靶向治疗(15例)、化疗+免疫治疗+靶向治疗(2例)、免疫治疗联合靶向治疗(6例)。

93例患者中，死亡者66例，且有1人失访，其生存时间以末次就诊时间记录。截至2025年12月15日，发生疾病进展者为72例，其中因靶病灶进展者30例，非靶病灶进展者11例，新病灶进展者17例，死亡者14例。93例患者的PFS为1~81(中位数4)个月，OS为2~81(中位数11)个月，其1、2年的疾病无进展生存率为25.25%、20.96%；其1、3、5年总体生存率分别为41.79%、27.73%、25.21%。患者PFS及OS的生存曲线如图2所示。

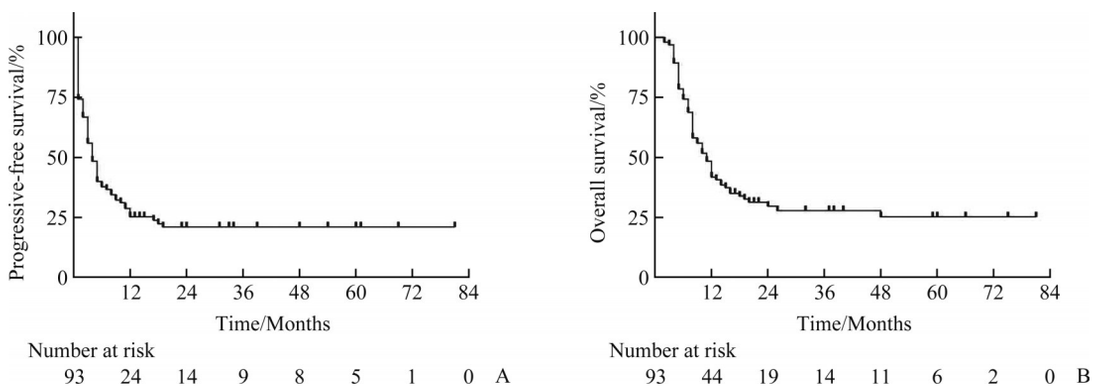


图2 接受非手术治疗的RTSCC患者的PFS(A)和OS(B)的Kaplan-Meier曲线

Figure 2 Kaplan-Meier curves of PFS (A) and OS (B) for RTSCC patients treated with non-surgical treatment

PFS: Progression-free survival; OS: Overall survival.

2.3 生存相关危险因素分析

采用单因素Cox回归筛选与PFS、OS相关的危险因素。单因素Cox分析共纳入28项因素。将单因素筛选中P<0.100的因素纳入多因素Cox回归筛选独立危险因素。由于ln(MTV)与TLG的自然对数ln(TLG)高度相关(r=0.932，P<0.001)，为避免多重共线性，仅将ln(MTV)纳入多因素Cox回归分析。

与PFS相关的多因素Cox回归模型结果(表2)显示，复发后放疗为PFS的独立保护因子(HR=0.461，95% CI 0.233~0.912，P=0.026)，ln(MTV)、吸烟史对PFS的预后在多因素Cox回归中无统计学意义(P=0.067、P=0.064)。PFS相关Cox回归模型满足比例风险假设(P=0.520)，C-index为0.622，经500次Bootstrap内部验证，乐观偏差为0.014，校正C-index为0.609(95% CI 0.554~0.712)。该模型对6个月PFS的区分能力为中等(AUC=0.707，95% CI 0.595~0.818)，优于3个月(AUC=0.658，95% CI 0.540~0.776)；校准曲线预测概率与实际Kaplan-Meier生存概率在3个月与6个月时间点具有可接受的一致性，但误差棒较宽(图3)。该预测模型3个月与6个月PFS的Brier评分分别为0.24与0.23，IPA分别为0.80%与1.90%。

与OS相关的独立危险因素结果见表3，结果显示复发后放疗是患者OS的独立保护因素(HR=0.377，95% CI 0.180~0.790，P=0.010)；ln(MTV)是OS的独立危险因素(HR=1.299，95% CI 1.092~1.546，P=0.003)。OS相关Cox回归模型满足比例风险假设(P=0.340)，C-index为0.670，乐观偏差为0.006，经500次Bootstrap内部验证，校正C-index为0.663(95% CI 0.602~0.751)。该模型对1年、2年OS具有中等区分能力，AUC分别为0.793(95% CI 0.699~0.888)、0.796(95% CI 0.662~0.931)；校准曲线显示，该模型对1年

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OS存在系统性低估，2年OS校准曲线与理想线贴合程度优于1年，整体一致性良好(图4)。该预测模型1年、2年OS的Brier评分分别为0.21、0.13，IPA分别为11.90%、38.50%。全身总MTV对患者生存影响的示例见图5。

表2　PFS的单因素及多因素Cox回归分析结果

Table 2　Results of univariable and multivariable Cox regression analyses for PFS

Factors	Univariable Cox		Multivariable Cox	
	HR(95% *CI*)	*P*	*HR*(95% *CI*)	*P*
Post-recurrence radiotherapy	0.418(0.214 to 0.818)	0.011	0.461(0.233 to 0.912)	0.026
ln(TLG)	1.181(1.012 to 1.378)	0.034		
Treatment modality	0.508(0.281 to 0.918)	0.025		
ln(MTV)	1.225(1.044 to 1.437)	0.013	1.161(0.990 to 1.361)	0.067
Smoking	1.697(0.999 to 2.882)	0.051	1.656(0.972 to 2.822)	0.064
Time from prior surgery to recurrence	2.048(0.937 to 4.479)	0.072		

Only factors with a $P<0.100$ in univariate Cox regression analysis are presented.

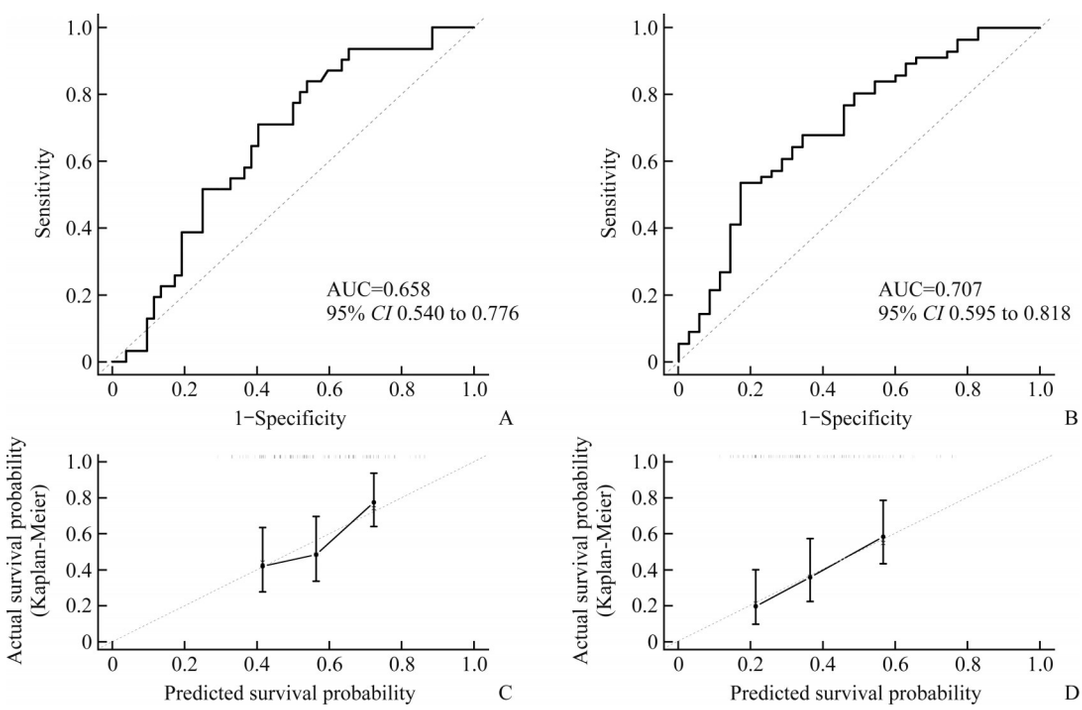


图3　预测PFS的多因素Cox回归模型表现

Figure 3　Performance of multivariable Cox regression model for PFS

A and B: ROC curves for predicting 3-month (A) and 6-month (B) PFS. C and D: Calibration curves for predicted vs observed outcomes at 3 months (C) and 6 months (D). ROC: Receiver operating characteristic; AUC: Area under the curve.

2.4 敏感性分析

为评估单因素分析中采用$P<0.100$的宽松阈值可能带来的假阳性风险，进行了Bonferroni校正。单因素Cox回归共纳入28个变量，校正后的显著性阈值设为α=0.05/28(约0.002)。在PFS分析中，复发后放疗、ln(TLG)、治疗方案、ln(MTV)在校正后仍具有统计学显著意义。在OS分析中，复发后放疗、ln(TLG)、ln(MTV)在校正后仍具有统计学显著意义(均$P<0.001$，表4)。

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表3 OS的单因素及多因素Cox回归分析结果

Table 3 Results of univariable and multivariable Cox regression model analyses for OS

Factors	Univariable Cox		Multivariable Cox	
	HR(95% *CI*)	*P*	*HR*(95% *CI*)	*P*
ln(MTV)	1.334(1.128 to 1.578)	<0.001	1.299(1.092 to 1.546)	0.003
ln(TLG)	1.291(1.093 to 1.524)	0.003		
Post-recurrence radiotherapy	0.401(0.198 to 0.814)	0.011	0.377(0.180 to 0.790)	0.010
Initial tumor differentiation	1.421(0.968 to 2.087)	0.073		

Only factors with a $P<0.100$ in the univariate Cox regression analysis are presented.

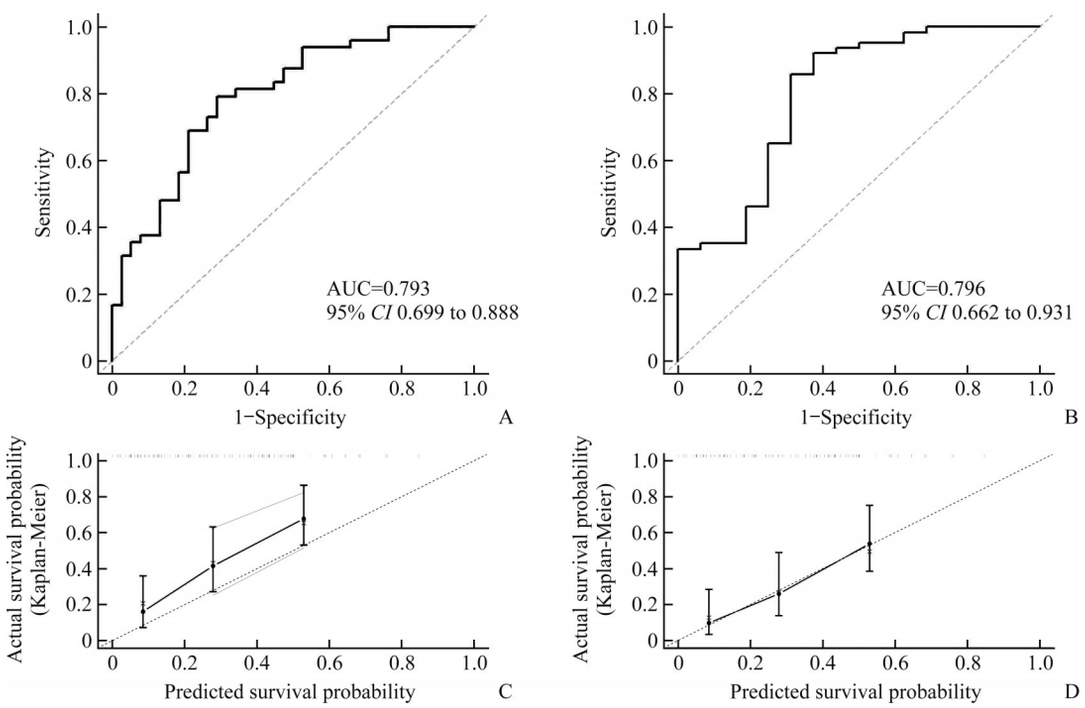


图4 预测OS的多因素Cox回归模型表现

Figure 4 Performance of multivariable Cox regression model for OS

A and B: ROC curves for predicting 1-year (A) and 2-year (B) OS. C and D: Calibration curves for predicted vs observed outcomes at 1 year (C) and 2 years (D).

为评估扫描机型和扫描范围对结果的潜在偏倚，通过仅纳入使用同一扫描机型(敏感性分析1)和仅纳入完成全身扫描(敏感性分析2)的患者进行了2项敏感性分析，纳入分析的变量与主要分析一致。结果显示在PFS方面，2项敏感性分析显示ln(MTV)均为PFS的独立危险因素(均$P<0.05$)，但在主要分析中，ln(MTV)与PFS的关联无统计学意义($P>0.05$)，提示ln(MTV)的预后价值可能受亚组特征修饰(表5)。复发后放疗在限同一扫描机型的敏感性分析中仍为独立保护因素($P=0.032$)，在限全身扫描的敏感性分析中无统计学意义($P=0.159$)。吸烟史在限同一扫描机型的敏感性分析中无统计学意义($P=0.081$)，在限全身扫描的敏感性分析中被剔除。在OS方面，2项敏感性分析均显示ln(MTV)、复发后放疗对OS的效应方向与显著性在2种限定条件下均与主要分析结果一致，提示研究结论稳健(表5)。

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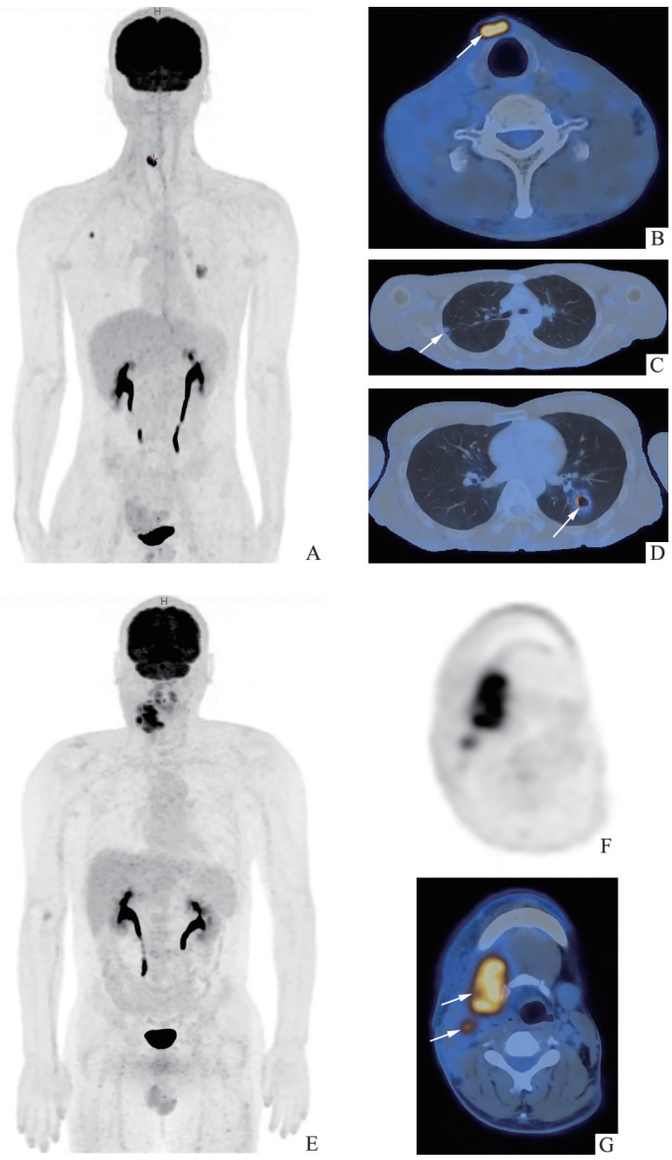


图5　2名采用化疗联合免疫治疗的RTSCC患者的ln(MTV)比较

Figure 5　Comparison of ln(MTV) in 2 cases of RTSCC treated with chemo-immunotherapy

A−D: Case 1 is a 35-year-old male, and ln(MTV) of the patient was 1.92. MIP shows multiple hypermetabolic lesions in the neck and chest (A). ^{18}F-FDG PET/CT fusion images reveal cervical lymph node metastasis (B), and white arrows indicate right (C) and left lung metastases (D). Case 1 is alive with an OS of 66 months. E−G: Case 2 is a 37-year-old male, and ln(MTV) of the patient was 3.50. MIP shows multiple hypermetabolic lesions in the neck (E). PET shows right cervical lymph node metastases (F), with white arrows indicating the same lesions on PET/CT fusion images (G). Case 2 died with an OS of 5 months.

2.5 治疗疗效对生存的影响

本研究进一步探讨了治疗疗效对生存的影响。总体治疗疗效评价为CR、PR、SD、PD的人数分别为4、38、15、36。治疗缓解组(CR/PR)42例，非缓解组(SD/PD)51例。时间依赖性Cox回归分析结果显示，治疗缓解与PFS的关联无统计学意义(*HR*=0.618，95% *CI* 0.327~1.167，*P*=0.138，C-index=0.517)；治疗缓解对OS有显著的保护效应(*HR*=0.340，95% *CI* 0.196~0.590，*P*<0.001，C-index=0.620)，该模型区分能力有限。Schoenfeld残差检验提示PFS、OS模型全局*P*值分别为0.055、0.980，均未拒绝比例风险假设。Landmark分析(以中位缓解时间2个月为界，排除前2个月内发生事件者)显示缓解组PFS及OS均显著优于非缓解组(均*P*<0.001；图6)。

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表4 Bonferroni校正后单因素Cox回归结果

Table 4 Univariable Cox regression results after Bonferroni correction

Factors	PFS			OS		
	HR (95% *CI*)	*P*	Adjusted *P*	*HR* (95% *CI*)	*P*	Adjusted *P*
Post-recurrence radiotherapy	0.418(0.214 to 0.818)	0.011	<0.001	0.401(0.198 to 0.814)	0.011	<0.001
ln(TLG)	1.181(1.012 to 1.378)	0.034	0.001	1.291(1.093 to 1.524)	0.003	<0.001
Treatment modality	0.508(0.281 to 0.918)	0.025	<0.001			
ln(MTV)	1.225(1.044 to 1.437)	0.013	<0.001	1.334(1.128 to 1.578)	<0.001	<0.001
Smoking	1.697(0.999 to 2.882)	0.051	0.002			
Time from prior surgery to recurrence	2.048(0.937 to 4.479)	0.072	0.003			
Initial tumor differentiation				1.421(0.968 to 2.087)	0.073	0.003

Only factors with a $P<0.100$ in the univariate Cox regression analysis are presented.

表5 敏感性分析的多因素Cox回归分析

Table 5 Multivariable Cox regression analysis for sensitivity analysis

End-point	Factors	Sensitivity analysis 1 (*n*=85)		Sensitivity analysis 2 (*n*=78)	
		HR (95% *CI*)	*P*	*HR* (95% *CI*)	*P*
PFS	ln(MTV)	1.176(1.001 to1.382)	0.049	1.206(1.002 to 1.451)	0.047
	Smoking	1.640(0.941 to 2.856)	0.081		
	Post-recurrence radiotherapy	0.456(0.222 to 0.935)	0.032	0.589(0.282 to 1.230)	0.159
	Treatment modality			0.611(0.318 to 1.174)	0.139
OS	ln(MTV)	1.248(1.042 to 1.496)	0.016	1.289(1.058 to 1.570)	0.012
	Post-recurrence radiotherapy	0.431(0.194 to 0.962)	0.040	0.448(0.205 to 0.982)	0.045

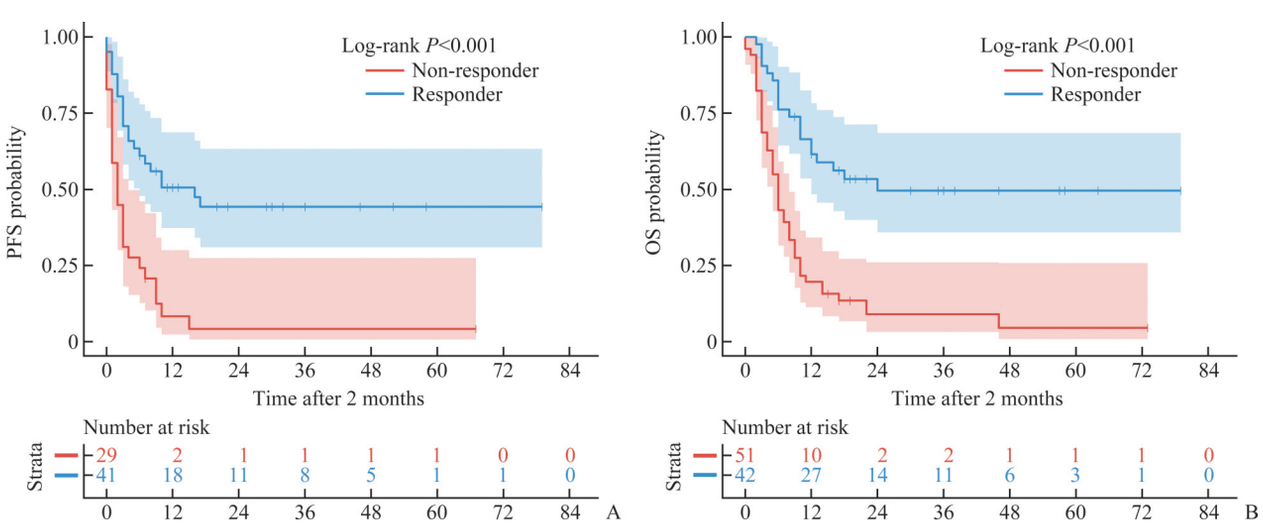


图6 基于治疗后2个月Landmark的治疗缓解状态与预后的相关分析

Figure 6 Landmark analysis at 2 months after treatment for association between treatment response status and prognosis

A: PFS. B: OS.

3 讨 论

本研究对接受非手术治疗的RTSCC患者生存相关的危险因素进行了回顾性分析，发现复发后放疗是OS的独立保护因素，全身总MTV是OS的独立危险因素。本研究的优点在于：1)患者均为接受非手术

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治疗的口腔舌鳞状细胞癌根治术后的复发患者，同质性较高；2)探讨了治疗前PET/CT代谢及体积参数对患者生存的影响。

本研究表明，全身总MTV是OS的独立危险因素，其对PFS的预测作用在多因素分析中无统计学意义(P=0.067)，与单因素结果(P=0.013)存在临界反转，反映研究样本量(n=93，PFS事件数72例)处于统计效能的临界水平，而非真实的生物学无效。鉴于全身总MTV在总体样本及敏感性分析中P值均处于0.05附近的临界范围，ln(MTV)对PFS可能具有真实的预后效应，但现有样本量不足以提供确证性证据。全身总MTV对RTSCC患者OS的预测价值高于代谢参数(SULmax、SULpeak和SULmean)，与既往研究[14]相符。在临床实践中，PET/CT的代谢参数最常用于定量分析[15]。然而肿瘤的异质性、部分容积效应和注射药物与扫描的间隔时间可能限制SUV代表病变确切代谢和准确反映肿瘤特征的能力[16]。除代谢参数外，体积参数也广泛用于分析各种癌症[17-18]。不同于SUV仅反映肿瘤细胞成分的代谢活性，体积参数反映整个肿瘤病变的代谢活性和肿瘤负荷。既往研究[19-23]表明MTV及TLG能够预测接受初次手术治疗的口腔癌患者、接受免疫治疗的口腔癌初治患者、接受挽救性手术的复发性口腔癌患者的生存情况。本研究结果表明，全身总MTV在接受非手术治疗的RTSCC患者中具有一定预后价值，拓宽了体积参数预测患者预后的应用场景。需要指出的是，MTV在临床的实际应用受到测量方法多样、缺乏截断值标准、受肿瘤异质性影响的限制[24]。本研究中MTV仅依据40%的SULmax相对阈值计算。

复发后放疗对OS的保护效应在主要分析及2项敏感性分析中得到一致支持，其对PFS的保护作用在全身扫描亚组分析中无统计学意义(P=0.159)，可能与该亚组样本量进一步减少及事件数不足有关。19例接受放疗的患者中，17例为首次放疗，2例为再放疗。研究[25-26]表明复发后再放疗可提高复发性头颈部癌患者的OS。吸烟在PFS的多因素Cox回归模型中无统计学意义，在敏感性分析中，吸烟仅被纳入限同一扫描机型的PFS回归模型(P=0.081)，在限全身扫描的亚组分析中被剔除。因此，本研究不将吸烟视作RTSCC患者的独立危险因素，这与Contrera等[5]的研究观点一致。

本研究建立的PFS预测模型C-index为0.609，3个月、6个月IPA分别为0.80%、1.90%，临床预测价值有限。因此，PFS预测模型仅作为探索性、假设生成性分析，不宜直接指导个体临床决策。本研究建立的OS预测模型C-index为0.663，1年、2年IPA分别为11.90%、38.50%，提示其具有临床参考价值。OS预测模型对1年OS可能存在系统性低估，原因可能为：1年内死亡事件高度聚集(81.82%，54/66)，在小样本下导致基线风险函数在早期的估计稳定性下降，以及小样本下的Bootstrap内部校正对系统性偏倚的校正效力有限。

时间依赖性Cox回归分析证实治疗缓解可显著降低相对死亡风险，但其对PFS影响的证据尚不充分。Landmark分析显示治疗缓解在PFS和OS上均显著获益，但由于PFS的Landmark分析剔除了23例2个月内发生疾病进展的患者，剔除前与剔除后的缓解比例分别为45.16%(42/93)、58.57%(41/70)，导致剩余样本中缓解组的比例相对升高，可能造成效应估计的夸大。而OS的Landmark分析未排除任何患者，结果稳健。因此，早期(2个月内)疾病缓解状态对RTSCC患者OS的改善可能是可靠的，但对PFS的独立预测价值有待更大样本验证。既往有研究[27-29]表明在局部进展期口腔癌或局部进展期头颈部癌患者中，治疗缓解组的预后优于非缓解组。

本研究存在以下局限性：1)由于研究性质为回顾性，未能对2台设备进行交叉校准，且15例患者仅行头颈部^{18}F-FDG PET/CT检查，尽管同期胸部、腹部增强CT检查未发现远处转移，但仍存在低估全身总MTV和TLG、从而导致全身总MTV与生存之间的关联强度被低估的可能；2)全身总MTV测量仅基于40%的相对阈值，未进行绝对阈值或背景阈值的测量，不同阈值方法可能影响MTV的绝对值，进而影响HR的估计，后续研究应采用多阈值法验证；3)单因素筛选中，以P<0.100为阈值筛选进入多因素模型的变量，未对单因素阶段的多重比较进行校正，可能有个别变量因偶然因素通过P<0.100阈值，但最终独立预测因素的判定基于多因素Cox回归模型，研究结果仍具有可靠性；4)样本量小，限制了同时纳入多因素Cox回归模型的变量数量上限，可能漏检效应量较小但在临床上有意义的预测因子；5)纳入患者的治疗方式多样，根据是否放疗、单一/联合治疗方式分类旨在提高患者之间的可比性，但由于相同治疗方式的患者人数少，限制了进一步探索不同治疗方式对生存的影响；6)多数患者被评估为免疫未确认疾病进展(immune unconfirmed progressive disease，iUPD)后更改治疗方案，使得其PFS终点仅计算首次评估iUPD的时间，未计算至免疫确定疾病进展(immune confirmed progressive disease，iCPD)的时间，导致其PFS缩短；7)绝大多数患者缺乏治疗后的PET/CT复查，未能研究代谢参数的动态变化对生存的影响。

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作者贡献声明：杨晓煌 研究设计，论文撰写与修改，数据分析；郑凯 研究设计，论文修改；曹慧、薛蕾 数据采集、分析与解释；于小平、叶慧 论文指导。所有作者阅读并同意最终的文本。

利益冲突声明：作者声称无任何利益冲突。

参考文献

[1] Kwak JH, Ji YB, Song CM, et al. Long-term oncologic outcomes and prognostic factors related to recurrences in pathologic Stage I/II early oral tongue cancer[J]. Front Surg, 2025, 12: 1534274. https://doi.org/10.3389/fsurg.2025.1534274.

[2] Ghanaati S, Udeabor SE, Winter A, et al. Cancer recurrence in operated primary oral squamous cell carcinoma patients seems to be independent of the currently available postoperative therapeutic approach: a retrospective clinical study[J]. Curr Oncol, 2025, 32(4): 208. https://doi.org/10.3390/curroncol32040208.

[3] Zhang YY, Wang DC, Su JZ, et al. Clinicopathological characteristics and outcomes of squamous cell carcinoma of the tongue in different age groups[J]. Head Neck, 2017, 39(11): 2276-2282. https://doi.org/10.1002/hed.24898.

[4] Safi AF, Kauke M, Grandoch A, et al. Analysis of clinicopathological risk factors for locoregional recurrence of oral squamous cell carcinoma—Retrospective analysis of 517 patients[J]. J Cranio Maxillofac Surg, 2017, 45(10): 1749-1753. https://doi.org/10.1016/j.jcms.2017.07.012.

[5] Contrera KJ, Zafereo ME, Yaniv D, et al. Outcomes for recurrent oral cavity squamous cell carcinoma[J]. Oral Oncol, 2022, 134: 106127. https://doi.org/10.1016/j.oraloncology.2022.106127.

[6] Chen TC, Lo TH, Huang HC, et al. Outcomes of salvage treatment in patients with recurrent oral squamous cell carcinoma[J]. Head Neck, 2021, 43(12): 3764-3774. https://doi.org/10.1002/hed.26862.

[7] Creff G, Jegoux F, Palard X, et al. ^{18}F-FDG PET/CT-based prognostic survival model after surgery for head and neck cancer[J]. J Nucl Med, 2022, 63(9): 1378-1385. https://doi.org/10.2967/jnumed.121.262891.

[8] Wen D, Liu L, Liang Y, et al. Prediction of outcomes in patients with local recurrent nasopharyngeal carcinoma: development and validation of a four-factor prognostic model integrating baseline characteristics and [^{18}F] FDG PET/CT parameters[J]. Eur Radiol, 2023, 33(4): 2840-2849. https://doi.org/10.1007/s00330-022-09232-1.

[9] Zschaeck S, Weingärtner J, Lombardo E, et al. 18F-fluorodeoxyglucose positron emission tomography of head and neck cancer: location and HPV specific parameters for potential treatment individualization[J]. Front Oncol, 2022, 12: 870319. https://doi.org/10.3389/fonc.2022.870319.

[10] Boellaard R, Delgado-Bolton R, Oyen W, et al. FDG PET/CT: EANM procedure guidelines for tumour imaging: version 2.0 [J]. Eur J Nucl Med Mol Imag, 2015, 42(2): 328-354. https://doi.org/10.1007/s00259-014-2961-x.

[11] American Joint Committee on Cancer, Amin MB. AJCC Cancer Staging Manual[M]. 8th ed. Cham: Springer, 2017.

[12] Nishino M, Jagannathan JP, Ramaiya NH, et al. Revised RECIST guideline version 1.1: what oncologists want to know and what radiologists need to know[J]. Am J Roentgenol, 2010, 195(2): 281-289. https://doi.org/10.2214/ajr.09.4110.

[13] Seymour L, Bogaerts J, Perrone A, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics [J/OL]. Lancet Oncol, 2017, 18(3): e143-e152[2026-01-15]. https://doi.org/10.1016/S1470-2045(17)30074-8.

[14] Wang L, Bai J, Duan P. Prognostic value of 18F-FDG PET/CT functional parameters in patients with head and neck cancer: a meta-analysis[J]. Nucl Med Commun, 2019, 40(4): 361-369. https://doi.org/10.1097/MNM.0000000000000974.

[15] Lucignani G. SUV and segmentation: pressing challenges in tumour assessment and treatment[J]. Eur J Nucl Med Mol Imag, 2009, 36(4): 715-720. https://doi.org/10.1007/s00259-009-1085-1.

[16] Thie JA. Understanding the standardized uptake value, its methods, and implications for usage[J]. J Nucl Med, 2004, 45 (9): 1431-1434

[17] Brose A, Miederer I, König J, et al. Prognostic value of metabolic tumor volume on [18F] FDG PET/CT in addition to the TNM classification system of locally advanced non-small cell lung cancer[J]. Cancer Imag, 2024, 24(1): 171. https://doi.org/10.1186/s40644-024-00811-7.

[18] Tatsumi M, Tanaka H, Takenaka Y, et al. Association of circulating tumor HPV16DNA levels and quantitative PET parameters in patients with HPV-positive head and neck squamous cell carcinoma[J]. Sci Rep, 2024, 14: 3278. https://doi.org/10.1038/s41598-024-53894-4.

[19] Büyük BB, Kılıç C, Tunçcan T, et al. Effects of metabolic tumor volume and total glycolytic activity on prognosis in oral cavity cancers[J]. Acta Otolaryngol, 2026, 146(6): 728-733. https://doi.org/10.1080/00016489.2026.2630120.

[20] Chen WL, Zhou B, Huang ZX, et al. Detecting recurrent disease and surgical outcomes in patients with locally advanced tongue cancer after multimodal treatment using ^{18}F-FDG-PET/CT [J]. J Stomatol Oral Maxillofac Surg, 2024, 125(3): 101673. https://doi.org/10.1016/j.jormas.2023.101673.

[21] 蔺楠, 任超, 张桂, 等. 18F-FDG PET/CT体积代谢参数对口腔癌预后价值的研究[J]. 标记免疫分析与临床, 2021, 28(3): 395-401. https://doi.org/10.11748/bjmy.issn.1006-1703.2021.03.008.

LIN Nan, REN Chao, ZHANG Gui, et al. The prognostic value of preoperative metabolic parameters measured by 18F-FDG PET/CT in oral cavity cancer[J]. Labeled Immunoassays and Clinical Medicine, 2021, 28(3): 395-401. https://doi.org/10.11748/bjmy.issn.1006-1703.2021.03.008.

[22] Kwon H, Cho J, Park S, et al. Metabolic parameters on baseline ^{18}F-FDG PET/CT are potential predictive biomarkers

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for immunotherapy in patients with head and neck squamous cell carcinoma[J]. Front Med, 2022, 9: 896494. https://doi.org/10.3389/fmed.2022.896494.

[23] Choi WR, Oh JS, Roh JL, et al. Metabolic tumor volume and total lesion glycolysis predict tumor progression and survival after salvage surgery for recurrent oral cavity squamous cell carcinoma[J]. Head Neck, 2019, 41(6): 1846-1853. https://doi.org/10.1002/hed.25622.

[24] Agarwal A, Wehrle CJ, Satish S, et al. PET-assessed metabolic tumor volume across the spectrum of solid-organ malignancies: a review of the literature[J]. Biomedicines, 2025, 13(1): 123. https://doi.org/10.3390/biomedicines13010123.

[25] Chen AM, Harris JP, Nabar R, et al. Re-irradiation versus systemic therapy for the management of local-regionally recurrent head and neck cancer[J]. Radiother Oncol, 2024, 196: 110278. https://doi.org/10.1016/j.radonc.2024.110278.

[26] Saha S, Mallick I, Mukherjee P, et al. Are oral cancers effectively palliated with radiotherapy? Outcomes of treatment with a modified QUAD SHOT regimen[J]. Head Neck, 2024, 46(6): 1270-1279. https://doi.org/10.1002/hed.27730.

[27] Lee YG, Kang EJ, Keam B, et al. Induction chemotherapy as a prognostication index and guidance for treatment of locally advanced head and neck squamous cell carcinoma: the concept of chemo-selection (KCSG HN13-01) [J]. Cancer Res Treat, 2022, 54(1): 109-117. https://doi.org/10.4143/crt.2020.1329.

[28] Huwyler F, Giger R, Bill R, et al. Response to induction chemotherapy as a prognostic indicator in locally advanced head and neck squamous cell carcinoma[J]. J Cancer Res Clin Oncol, 2024, 151(1): 2. https://doi.org/10.1007/s00432-024-06044-2.

[29] Abdelmeguid AS, Silver NL, Boonsripitayanon M, et al. Role of induction chemotherapy for oral cavity squamous cell carcinoma[J]. Cancer, 2021, 127(17): 3107-3112. https://doi.org/10.1002/cncr.33616.

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