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ORIGINAL RESEARCH

Preoperative Systemic Inflammation Response Index Predicts Survival Outcome for Previously Irradiated Metachronous Secondary Head and Neck Cancer Patients

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Background: This study aimed to evaluate the survival predictability of preoperative systemic inflammation response index (SIRI), calculated as the absolute neutrophil count multiplied by the absolute monocyte count and divided by the absolute lymphocyte count, in patients with metachronous secondary primary head and neck squamous cell carcinoma (mspHNSCC) who had undergone prior radiotherapy for first primary HNSCC (fpHNSCC).

Methods: A total of 101 consecutive patients who underwent upfront surgery for mspHNSCC at a single institute between 2007 and 2016 were retrospectively reviewed between December 2023 and November 2024 and included in the analysis. The baseline leukocyte counts for the fpHNSCC and mspHNSCC were collected. Cox proportional hazards models were constructed using age and variables significant in univariate analysis to assess the impact of SIRI on overall survival (OS) and cancer-specific survival (CSS). Additionally, a SIRI-based nomogram was developed and validated.

Results: Statistically significant declines in baseline leukocyte counts were observed in mspHNSCC compared to fpHNSCC ($p < 0.001$). Among the inflammatory markers, the preoperative SIRI was the most predictive of survival outcomes for mspHNSCC. Higher SIRI values were significantly associated with poorer outcomes in both OS and CSS. The optimal SIRI cutoff for survival prediction was 1.383, as determined by receiver operating characteristic curve analysis with Youden's index; patients with SIRI $\geq$ 1.383 had significantly lower 5-year OS (32.9% vs 60.1%, $p = 0.001$) and CSS (64.7% vs 83.9%, $p = 0.003$). Multivariate analysis revealed lymphovascular invasion, extranodal extension, and high SIRI as independent adverse risk factors for CSS. The SIRI-based nomogram accurately predicted CSS, with a concordance index of 0.773.

Conclusion: Data from preoperative SIRI assessment, coupled with the presence of pathological adverse features, serve as valuable references for risk stratification in patients with previously irradiated mspHNSCC.

Keywords: systemic inflammation response index, metachronous secondary primary, head and neck squamous cell carcinoma, radiotherapy, nomogram

Introduction

Head and neck squamous cell carcinoma (HNSCC) often achieves favorable cure rates with radiotherapy (RT), either alone or combined with chemotherapy. However, among successfully treated patients, a persistent concern is the occurrence of metachronous secondary primary HNSCC (mspHNSCC), defined as a new primary lesion diagnosed more than six months after the first primary HNSCC (fpHNSCC) and distinct from recurrence or metastasis.[1,2] The management of mspHNSCC, particularly within previously irradiated fields, is clinically challenging. Surgical resection is the preferred treatment when feasible, but outcomes following salvage surgery remain unsatisfactory in selected

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cases.[3,4] While established pathological risk factors such as extranodal extension (ENE), perineural invasion (PNI), lymphovascular invasion (LVI), and positive surgical margins are widely used in fpHNSCC to guide adjuvant therapy,[5–8] prognostic markers for mspHNSCC in the previously irradiated setting remain undefined.

Radiotherapy not only exerts cytotoxic effects but also induces radiation-related immune dysregulation and chronic inflammation, often leading to persistent depletion of radiosensitive immune cell populations.[9–11] Increasing evidence underscores that systemic inflammation contributes to tumorigenesis and progression, with inflammatory biomarkers serving as surrogates of host–tumor interactions.[11] Among these, several hematological indices such as the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have been investigated in HNSCC. However, these markers reflect only limited aspects of the immune response.

In contrast, the Systemic Inflammation Response Index (SIRI), proposed by Qi et al in 2016,[12] integrates neutrophil, monocyte, and lymphocyte counts, thereby capturing a broader spectrum of inflammatory and immune status. SIRI has shown superior prognostic value compared to NLR or PLR across multiple malignancies, including HNSCC,[13–18] yet its role in mspHNSCC has not been examined. This knowledge gap is clinically relevant, as mspHNSCC arises in an immune-compromised, previously irradiated host, where standard risk factors may not adequately predict survival outcomes.

The present study addresses this gap by evaluating the prognostic significance of SIRI in patients with previously irradiated mspHNSCC undergoing curative-intent salvage surgery. Specifically, we aim to (1) identify adverse pathological features relevant in this unique cohort, (2) determine the prognostic impact of SIRI relative to traditional risk factors, and (3) develop a predictive nomogram incorporating SIRI to improve individualized prognostication.

Material and Methods

Study Population

This retrospective, single-institution study was conducted between December 2023 and November 2024 and was approved by the Medical Ethics and Human Clinical Trial Committees at Chang Gung Memorial Hospital (Approval No. 202301727B0). The study was performed in accordance with the Declaration of Helsinki. As it involved only anonymized data from existing medical records and no direct patient contact, the requirement for informed consent was waived by the Ethics Committee. This study investigated consecutive patients (n=129) who had previously undergone radiation therapy for fpHNSCC and subsequently received upfront radical surgery as the initial treatment for mspHNSCC at the institute between January 2007 and December 2016. The diagnosis of mspHNSCC in each case was primarily based on the classic criteria proposed by Warren and Gates[2] and confirmed through consensus at the institute's head and neck cancer tumor board, following established definitions.[19] The distinction between mspHNSCC and local recurrence was determined based on differences in anatomical or radiological sites, clinical and pathological evidence, and specifically an interval of more than 6 months between the first and second cancers. Exclusion criteria were as follows: (A) fpHNSCC was not disease-free at the time of mspHNSCC diagnosis (n=6); (B) fpHNSCC was nasopharyngeal carcinoma (n=7); (C) the radiation dose for fpHNSCC was less than 5400 cGy (n=5); (D) mspHNSCC was not treated curatively (n=2); (E) induction chemotherapy and/or RT was administered for mspHNSCC (n=4); and (F) those who had experienced an acute infection, such as cellulitis or pneumonia, within four weeks prior to the preoperative blood tests for mspHNSCC (n=4). The detailed flow chart is illustrated in Figure S1. After applying these criteria, 101 cases were included in the analysis.

Variables and Endpoints

The dataset comprised demographic information such as age, gender, and the clinical variables pertaining to both the fpHNSCC and mspHNSCC. These clinical variables encompassed Eastern Cooperative Oncology Group (ECOG) performance status, lifestyle, treatment for fpHNSCC, tumor sites, treatment modalities, RT dosage, the duration between the fpHNSCC diagnosis and the occurrence of mspHNSCC, as well as the respective baseline inflammatory markers for fpHNSCC or mspHNSCC. These baseline inflammatory markers included Absolute Neutrophil Count (ANC), Absolute Monocyte Count (AMC), Absolute Lymphocyte Count (ALC), as well as derived ratios such as Neutrophil-to-

Lymphocyte Ratio (NLR), Monocyte-to-Lymphocyte Ratio (MLR), and SIRI. Pathological characteristics pertinent to mspHNSCC were examined, encompassing clinical stage, pT classification, pN classification, histological differentiation, PNI, LVI, ENE, and status of surgical margins (≥5 mm or <5 mm). Clinical staging was revised utilizing the 8th edition of the American Joint Committee on Cancer (AJCC) staging system. Baseline inflammatory markers were collected within one week before the initial treatment for fpHNSCC, which consisted of RT alone (n=4), RT plus surgery (n=25), RT plus chemotherapy (n=13), or surgery plus RT and chemotherapy (n=59). For mspHNSCC, markers were obtained within one week prior to surgery. The SIRI was determined as the product of ANC and AMC, divided by ALC. Primary endpoints comprised 5-year overall survival (OS), cancer-specific survival (CSS), and their respective prognostic factors.

Statistical Analysis

Continuous data were presented as medians with ranges, while categorical variables were depicted as counts with frequencies. A paired *t*-test was employed to compare data measured at different time points. Survival time was calculated from the surgery for mspHNSCC until death or the last follow-up. The Kaplan-Meier method, Log rank test, and univariate Cox proportional hazards model were utilized to assess survival probabilities. Multivariate Cox proportional hazards models were constructed by integrating age and significant variables identified in the univariate survival analysis, with the hazard ratio (HR) and 95% confidence interval (CI) for each predictor calculated. Receiver operating characteristic (ROC) curves and Youden's index were used to determine the optimal cutoff value for survival prediction. The predictive efficacy of inflammatory markers was first evaluated using ROC curve analysis, with higher area under the ROC curve (AUC) values indicating superior discrimination. Independent prognostic factors were then identified through multivariate Cox regression analysis and incorporated into the nomogram. In the nomogram, each variable was assigned a weighted number of points proportional to its regression coefficient, reflecting its relative contribution to survival risk. The total score, calculated by summing points across all variables, corresponded to the predicted 5-year CSS probability. Model performance was assessed using Harrell's concordance index (c-index) to evaluate discriminative ability for 5-year CSS. Calibration was examined by plotting predicted versus observed survival probabilities, and internal validation was performed with 1000 bootstrap resamples to reduce overfitting bias. Interpretation of the nomogram allows clinicians to estimate individualized survival probabilities by aligning patient-specific variable values with the assigned point scale. All p values were two-sided, and p values < 0.05 were considered statistically significant. All analyses were performed using R 4.3.1 (R Core Team, 2023).

Results

Patient Characteristics

The clinical characteristics of the study patients are presented in Table 1. The median age at the time of mspHNSCC diagnosis was 55 years (range: 37–79 years). The median interval from the date of the fpHNSCC diagnosis to the date of mspHNSCC diagnosis was 33.1 (range, 5.7–105.2) months. Most patients (n = 97, 96%) underwent a combination of RT with surgery and/or chemotherapy, with a median RT doe of 63.0 Gy (range 54.0–72.0 Gy). The primary site of mspHNSCC was predominantly observed in the oral cavity (n = 75, 74.2%), followed by the oropharynx (n = 21, 20.8%), and the larynx or hypopharynx (n = 5, 5.0%). Histological differentiation predominantly showed moderate differentiation (n = 67, 66.3%), followed by well-differentiated (n = 27, 26.7%) and poorly differentiated (n = 7, 7.0%) cases. Surgical margin status was < 5mm in 51 (50.5%) patients and ≥ 5mm in 50 (49.5%) patients. In terms of AJCC stage, there were 42 (41.6%) in stage I, 20 (19.8%) in stage II, 8 (7.9%) in stage III, and 31 (30.7%) in stage IV. Presence of PNI, LVI, and ENE was observed in 23 (22.8%), 10 (9.9%), and 6 (5.9%) patients, respectively. Adjuvant therapy was administered to 7 (6.9%) patients, including CCRT in 6 patients and RT in 1 patient. The median follow-up months after surgery was 49.1 (range: 2.8–146.9).

Comparison of Leukocyte Counts

The mean values of the baseline leukocytes count (ANC, AMC, and ALC) for mspHNSCC were significantly lower compared to fpHNSCC (all $p < 0.001$, Table 2). When evaluating leukocytopenia criteria, there was a significant increase

Table 1 Patient Characteristics (n=101)

Characteristics	Value	%
Age, median (range), year	55 (37–79)	
Gender, Male/Female	99/2	98.0/2.0
Interval from first primary HNSCC to mspHNSCC, months	33.1 (5.7–105.2)	
Habit of smoking, yes/no	91/10	90.1/9.9
Habit of alcohol consumption, yes/no	94/7	93.1/6.9
ECOG performance status, 0/1/2	79/20/2	78.2/19.8/2.0
fpHNSCC:		
Oral cavity/oropharynx/larynx-hypopharynx	62/20/19	61.4/19.8/18.8
RT/surgery+RT/RT+CT/surgery+RT+CT	4/25/13/59	4.0/24.8/12.9/58.3
RT dose, median (range), Gy	63.0 (54.0–72.0)	
Pretreatment inflammatory markers		
ANC, median (range) $*10^9$/L	5.209 (1.429–15.522)	
AMC, median (range) $*10^9$/L	0.388 (0.118–1.110)	
ALC, median (range) $*10^9$/L	1.722 (0.598–3.833)	
NLR, median (range)	2.912 (0.894–10.756)	
MLR, median (range)	0.214 (0.084–0.820)	
SIRI, median (range)	1.193 (0.207–11.741)	
mspHNSCC:		
Oral cavity/oropharynx/larynx-hypopharynx	75/21/5	74.2/20.8/5.0
Adjuvant therapy, no/yes	94/7	93.1/6.9
AJCC stage, I–II/III–IV	62/39	61.4/38.6
pT classification, T1-2 / T3-4	65/36	64.4/35.6
pN classification, pN0/pN1-3b	92/9	91.1/8.9
Histologic differentiation, WD/MD/PD	27/67/7	26.7/66.3/7.0
Perineural invasion, no/yes	78/23	77.2/22.8
Lymphovascular invasion, no/yes	91/10	90.1/9.9
Extranodal extension, no/yes	95/6	94.1/5.9
Surgical margin, positive/1-4 mm/≧5 mm	4/47/50	4.0/46.5/49.5
Preoperative inflammatory markers		
ANC, median (range) $*10^9$/L	4.065 (1.382–13.746)	
AMC, median (range) $*10^9$/L	0.354 (0.108–1.392)	
ALC, median (range) $*10^9$/L	1.086 (0.356–2.392)	
NLR, median (range)	3.571 (0.737–22.000)	
MLR, median (range)	0.300 (0.110–1.414)	
SIRI, median (range)	1.221 (0.186–12.219)	

Notes: * indicates multiplication.

Abbreviations: HNSCC, head and neck squamous cell carcinoma; ECOG: Eastern Cooperative Oncology Group; RT, radiotherapy; CT, chemotherapy; fpHNSCC: first primary HNSCC; mspHNSCC, metachronous second primary HNSCC; ANC, absolute neutrophil count; AMC, absolute monocyte count; ALC, absolute lymphocyte count; NLR, neutrophil to lymphocyte ratio; MLR, monocyte to lymphocyte; SIRI, systemic inflammation response index (monocyte x neutrophil/lymphocyte); AJCC, American Joint Committee on Cancer staging system, 8th edition; WD, well differentiated; MD, moderately differentiated; PD, poorly differentiated.

in the incidence of monocytopenia (AMC < 0.5 $*10^9$/L), rising from 68.9% to 88.9% ($p < 0.001$), and lymphopenia (ALC < 1.0 $*10^9$/L), escalating from 6.6% to 44.4% ($p < 0.001$). In contrast, the incidence rates of neutropenia (ANC < 2.0 $*10^9$/L) remained low at both time points (3.3% versus 4.4%, $p = 0.657$).

Survival Analyses

During the follow-up period, treatment failure occurred in 32 (31.7%) patients, comprising locoregional failure in 25 cases (24.8%), distant failure in 4 cases (4.0%), and a combination of locoregional and distant failure in 3 cases (3.0%). Additionally, 22 patients died from mspHNSCC, and 39 patients from other causes. Of these 39 patients, 21 died from

Table 2 Comparison of Leukocyte Counts Between fpHNSCC and mspHNSCC (n=101)

Leukocyte Counts	fpHNSCC	mspHNSCC	*p*
ANC, mean (SD) *10^9/L	5.668 (2.735)	4.394 (1.963)	<0.001
>2.0	98 (97.0%)	97 (96.0%)	0.657
1.5–2.0	2 (2.0%)	3 (3.0%)	
1.0–1.5	1 (1.0%)	1 (1.0%)	
AMC, mean (SD) *10^9/L	0.446 (0.190)	0.373 (0.178)	<0.001
>1.0	3 (3.0%)	1 (1.0%)	<0.001
0.8–1.0	2 (2.0%)	2 (2.0%)	
0.5–0.8	27 (26.7%)	8 (7.9%)	
0.2–0.5	68 (67.3%)	82 (81.2%)	
<0.2	1 (1.0%)	8 (7.9%)	
ALC, mean (SD) *10^9/L	1.887 (0.664)	1.178 (0.463)	<0.001
>1.0	95 (94.0%)	56 (55.4%)	<0.001
0.8–1.0	3 (3.0%)	23 (22.8%)	
0.5–0.8	3 (3.0%)	19 (18.8%)	
0.2–0.5	0 (0.0%)	3 (3.0%)	

Notes: * indicates multiplication.
Abbreviations: HNSCC, head and neck squamous cell carcinoma; fpHNSCC: first primary HNSCC; mspHNSCC, metachronous second primary HNSCC; ANC, absolute neutrophil count; AMC, absolute monocyte count; ALC, absolute lymphocyte count, SD: standard deviation.

Table 3 Univariate Survival Analysis Based on Baseline Inflammatory Markers Measured for fpHNSCC or mspHNSCC

	Overall Survival		Cancer Specific Survival	
Inflammatory Marker	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***
fpHNSCC				
ANC	1.000 (1.000–1.000)	0.384	1.000 (1.000–1.000)	0.070
AMC	1.000 (1.001–1.003)	0.137	1.001 (0.999–1.004)	0.264
ALC	1.000 (1.000–1.000)	0.713	1.000 (1.000–1.001)	0.437
NLR	1.082 (0.950–1.232)	0.235	1.148 (0.952–1.384)	0.149
MLR	5.432 (0.789–37.406)	0.086	2.128 (0.068–66.418)	0.667
SIRI	1.094 (0.945–1.266)	0.230	1.107 (0.883–1.389)	0.379
mspHNSCC				
ANC	1.000 (1.000–1.000)	0.001	1.000 (1.000–1.001)	<0.001
AMC	1.003 (1.001–1.005)	0.001	1.005 (1.003–1.007)	<0.001
ALC	1.000 (0.999–1.000)	0.250	1.000 (0.999–1.001)	0.794
NLR	1.070 (1.009–1.134)	0.023	1.096 (1.011–1.189)	0.027
MLR	4.226 (1.481–12.059)	0.007	8.039 (1.761–36.705)	0.007
SIRI	1.220 (1.084–1.374)	0.001	1.338 (1.140–1.572)	<0.001

Abbreviations: HNSCC, head and neck squamous cell carcinoma; fpHNSCC: first primary HNSCC; mspHNSCC, metachronous second primary HNSCC; ANC, absolute neutrophil count; AMC, absolute monocyte count; ALC, absolute lymphocyte count; NLR, neutrophil to lymphocyte ratio; MLR, monocyte to lymphocyte; SIRI, systemic inflammation response index (monocyte x neutrophil/lymphocyte).

other metachronous primary cancers in the head and neck region, 11 from other metachronous primary cancers outside the head and neck region, 4 from cardiovascular disease, and 3 from recurrence of their first primary cancer. The 5-year OS and CSS rates were 47.9% and 75.7%, respectively. Table 3 displays survival analysis results based on univariate inflammatory markers measured for first primary HNSCC and mspHNSCC. There was no statistical significance observed for baseline inflammatory markers measured for fpHNSCC to predict OS or CSS of mspHNSCC.

Conversely, a statistically significant predictability was observed for 5 out of the 6 preoperative inflammatory markers (ANC, AMC, NLR, MLR, and SIRI) measured for mspHNSCC to predict both OS and CSS of mspHNSCC.

The AUC value for preoperative SIRI in predicting OS of mspHNSCC was 0.650, higher than that of ANC (0.603), AMC (0.606), ALC (0.535), NLR (0.617), PLR (0.585), and MLR (0.622). This trend was consistently observed in predicting CSS, with the AUC value for SIRI reaching 0.692, exceeding those for ANC (0.656), AMC (0.662), ALC (0.466), NLR (0.622), PLR (0.498) and MLR (0.622).

As shown in Table 3, a statistically significant trend was observed, suggesting that individuals with a higher preoperative SIRI value in mspHNSCC had an inferior outcome in OS (HR: 1.220, 95% CI: 1.084–1.374, p = 0.001) and CSS (HR: 1.338, 95% CI: 1.140–1.572, p < 0.001). The optimal cutoff value for preoperative SIRI was determined to be "1.383" (sensitivity: 60.4% and specificity: 65.6%). Using this threshold, individuals with preoperative SIRI < 1.383 were classified as the "low SIRI" group, while those with SIRI ≥ 1.383 were categorized as the "high SIRI" group. The association analysis between the SIRI group and other clinicopathological factors is presented in Table 4. Among these factors, only histological grading showed a statistically significant association with SIRI group. Specifically, the low SIRI group was significantly more common in patients with well-differentiated tumors (p = 0.017). In the univariate survival analysis (Table 5), high SIRI, the presence of LVI, and the presence of ENE were identified as statistically significant adverse predictors for 5-year OS and CSS. In the multivariate survival analysis (Table 6), high SIRI, presence of LVI, and presence of ENE remained statistically significant predictors of CSS. Conversely, only high SIRI was found to be significantly predictive of OS. Patients with a high SIRI demonstrated significantly lower 5-year OS (32.9% vs 60.1%, p = 0.001) and CSS (64.7% vs 83.9%, p = 0.003) compared to those with a low SIRI (Figure 1A and 1B).

Table 4 Association Analysis Between Preoperative SIRI and Other Clinicopathological Factors

Variable		Preoperative SIRI		*p*
		Low	High	
Sex	Male	57	42	0.51
	Female	2	0	
Cancer location	Oral cavity	44	31	0.059
	Oropharynx	14	7	
	Hypopharynx	0	4	
	Larynx	1	0	
Pathological stage	I–II	35	27	0.614
	III–IV	24	15	
T classification	T1-2	37	28	0.683
	T3-4	22	14	
N classification	N0	53	39	0.732
	N+	6	3	
Histological Grade	WDSCC	21	6	0.017
	Non-WDSCC	38	36	
Perineural invasion	Absent	47	31	0.489
	Present	12	11	
Lymphovasuclar invasion	Absent	54	37	0.569
	Present	5	5	
Extranodal extension	Absent	57	38	0.23
	Present	2	4	
Surgical margin	< 5mm	28	23	0.469
	≥ 5mm	31	19	
Adjuvant therapy	No	56	38	0.446
	Yes	3	4	

Abbreviations: SIRI, systemic inflammation response index; WDSCC, well differential squamous cell carcinoma.

Table 5 Univariate Survival Analysis Based on Clinical-Pathological Parameters and Preoperative SIRI for mspHNSCC Patients (n=101)

Variables	5-Year OS (%)	*p*	5-Year CSS (%)	*p*
Gender, male/female	49.8/0	0.081	76.1/0	0.614
Habit of smoking, yes/no	46.4/70.0	0.113	73.7/100	0.08
Habit of alcohol consumption, yes/no	49.2/42.9	0.624	75.9/85.7	0.608
ECOG performance status, 0/1/2	50.1/37.5/100	0.451	74.2/84.4/100	0.915
Treatment for fpHNSCC, RT/surgery+RT/RT+CT/surgery+RT+CT	25.0/59.1/30.8/50.0	0.144	75.0/73.7/60.9/81.2	0.614
Age, < 55y/≥ 55y	42.3/55.9	0.313	73.8/78.6	0.749
Sites, oral cavity/oropharynx/others	81.3/28.1/40.9	0.009	81.3/61.3/72.8	0.389
Adjuvant therapy, no/yes	50.3/28.6	0.402	79.7/38.1	0.027
AJCC stage, I–II/III–IV	52.3/43.6	0.143	83.5/65.2	0.010
Histologic differentiation, WD/MD/PD	70.4/42.0/28.6	0.049	83.6/70.7/64.3	0.139
Perineural invasion, no/yes	52.8/34.8	0.110	82.5/55.4	0.011
Lymphovascular invasion, no/yes	53.2/10.0	<0.001	82.6/18.8	<0.001
Extranodal extension, no/yes	50.8/16.7	0.003	80.4/16.7	<0.001
Surgical margin, < 5mm/≧5 mm	36.9/61.1	0.007	64.7/86.6	0.063
Preoperative SIRI, < 1.383/≥ 1.383	60.1/32.9	0.001	83.9/64.7	0.003
Interval from first primary HNSCC to mspHNSCC, < 33.1/≥ 33.1 months	39.2/59.0	0.102	81.8/71.8	0.249

Abbreviations: mspHNSCC, metachronous second primary head and neck squamous cell carcinoma; ECOG: Eastern Cooperative Oncology Group; OS, overall survival; CSS, cancer specific survival; AJCC, American Joint Committee on Cancer staging system, 8th edition; WD, well differentiated; MD, moderately differentiated; PD, poorly differentiated; SIRI, SIRI: systemic inflammation response index (monocyte x neutrophil/lymphocyte); HNSCC, head and neck squamous cell carcinoma; mspHNSCC, metachronous second primary HNSCC.

Table 6 Multivariate Survival Analysis Incorporating Clinical-Pathological Parameters and Preoperative SIRI for mspHNSCC Patients (n=101)

	Overall Survival		Cancer Specific Survival	
Variables	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***
Age, continuous	0.997 (0.968–1.027)	0.152	0.994 (0.948–1.043)	0.817
Sites: others (Ref: oral cavity)	1.418 (0.799–2.518)	0.233	N/A	N/A
Adjuvant treatment: yes (Ref: no)	N/A	N/A	0.408 (0.099–1.676)	0.214
Histologic differentiation: non-WD (Ref: WD)	1.323 (0.668–2.618)	0.422	N/A	N/A
AJCC: stage III–IV (Ref: I–II)	N/A	N/A	1.374 (0.482–3.918)	0.552
Lymphovascular invasion: yes (Ref: no)	2.089 (0.873–4.997)	0.098	6.340 (1.711–23.499)	0.006
Perineural invasion: yes (Ref: no)	N/A	N/A	1.391 (0.460–4.206)	0.559
Extranodal extension: yes (Ref: no)	2.709 (0.948–7.745)	0.063	7.620 (1.690–34.353)	0.008
Surgical margin: < 5mm (Ref: ≥ 5mm)	1.750 (0.988–3.099)	0.055	N/A	N/A
Preoperative SIRI: ≥ 1.383 (Ref: < 1.383)	2.328 (1.356–3.995)	0.002	4.197 (1.645–10.709)	0.003

Abbreviations: mspHNSCC, metachronous second primary head and neck squamous cell carcinoma; HR, hazards ratio; CI, confidence interval; N/A, not applicable; Ref, reference; AJCC, American Joint Committee on Cancer staging system, 8th edition; WD, well differentiated; SIRI, systemic inflammation response index (monocyte x neutrophil/lymphocyte).

Conversely, the 5-year CSS rates were 18.8% and 16.7% for individuals with the presence of LVI and ENE, respectively, in contrast to 82.6% and 80.4% for those without LVI or ENE.

In the Cox model, individuals with a high SIRI had a 2.328 - fold (95% CI: 1.356–3.995, p = 0.002) increased likelihood of overall mortality and a 4.197-fold (95% CI: 1.645–10.709, p=0.003) increased likelihood of cancer-specific mortality compared to those with a low SIRI. Moreover, those with the presence of LVI or ENE had a 6.340-fold (95% CI: 1.711–23.499, p = 0.006) and 7.620-fold (95% CI: 1.690–34.353, p = 0.008) higher likelihood of cancer-specific mortality compared to those without LVI or ENE, respectively.

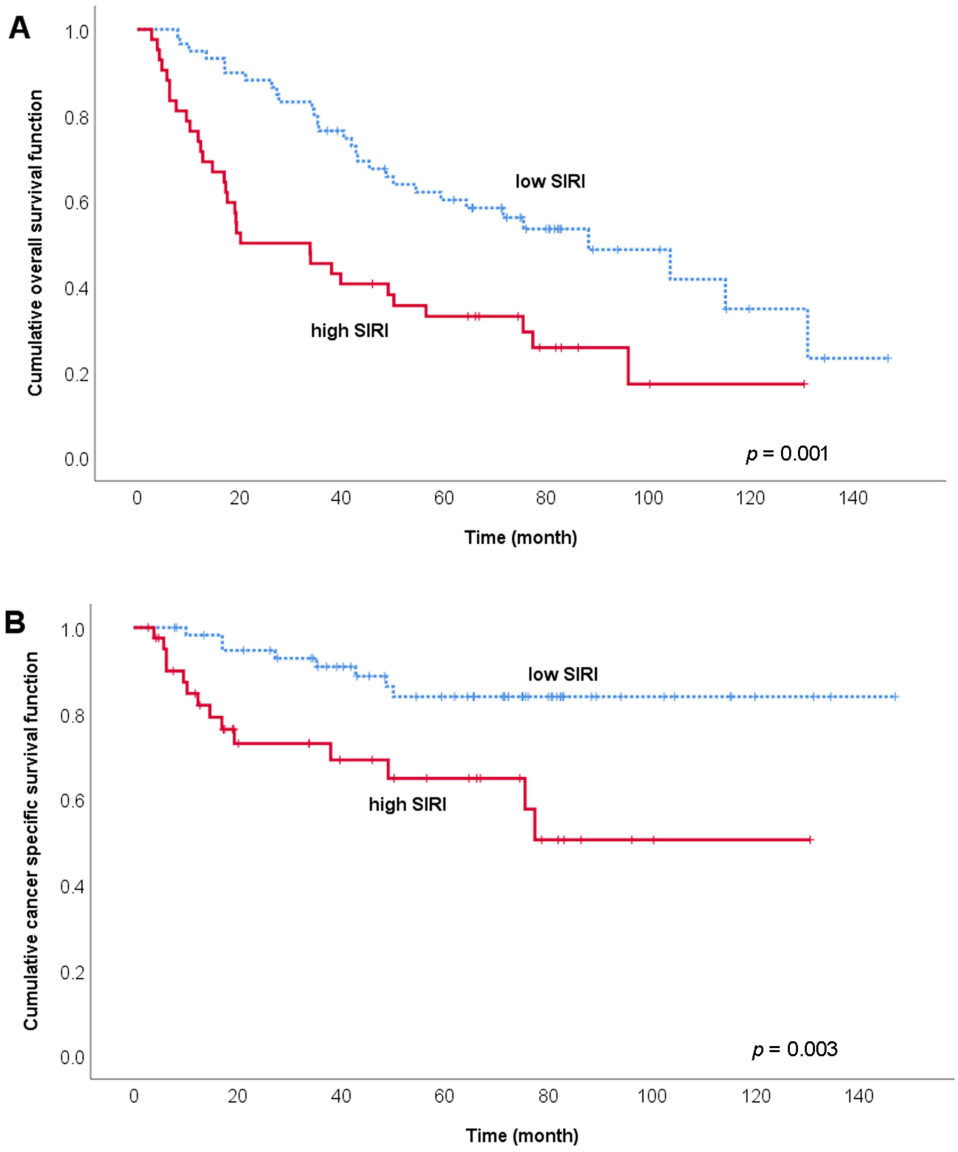

Figure 1 Overall survival curves (**A**) and cancer specific survival curves (**B**) for those with high SIRI (≥ 1.383) versus those with low SIRI (<1.383).

To account for heterogeneity in prior RT dose and field, which may differentially affect bone marrow irradiation and confound SIRI's prognostic value, we performed subgroup analyses by RT dose and primary site. In patients receiving ≥60 Gy (N=80), high SIRI predicted significantly worse 5-year OS (33.7% vs 58.7%, p=0.004) and CSS (66.6% vs 81.5%, p=0.025). Among those with <60 Gy (N=21), high SIRI was associated with inferior CSS (57.1% vs 91.7%, p=0.048), while the OS difference (28.6% vs 64.3%) did not reach significance (p=0.097). By primary site, high SIRI was prognostic in oral cavity cancers (N=75) for both OS (38.2% vs 67.6%, p=0.003) and CSS (72.2% vs 86.4%, p=0.012), whereas in non-oral cancers (N=26) similar trends were observed but without statistical significance. These findings suggest SIRI's prognostic value is consistent across RT doses and sites, though power is limited in smaller subgroups.

Nomogram Performance

For further validation, we established a nomogram, consisting of ENE, LVI and preoperative SIRI, for the prediction of 5-year CSS (Figure 2A). As shown in Figure 2A, ENE was the most influential prognostic factor, followed by LVI, and SIRI. Each variable contributed a specific number of points to the risk score: the absence of ENE was assigned 100

points, the absence of LVI 79.86 points, and low SIRI 66.47 points, whereas the presence of these adverse factors (ENE, LVI, and low SIRI) corresponded to 0 points, and the total score was used to estimate the 5-year CSS probability. The calibration curves showed that the 5-year CSS predicted by the SIRI-based predictive nomogram were consistent with actual observations (Figure 2B). We also created a nomogram model based only on TNM staging, and its c-index was 0.650 (95% CI: 0.531–0.769). However, when assorted clinicopathological factors including the preoperative SIRI were incorporated, the model achieved a higher c-index of 0.773 (95% CI: 0.670–0.867), which had a statistically significant improvement compared to the predictive nomogram constructed solely by the TNM staging system (p = 0.047). This means that the preoperative SIRI-based nomogram had better performance in predicting the CSS of patients with previously irradiated mspHNSCC who underwent radical surgery than the AJCC 8th edition staging system.

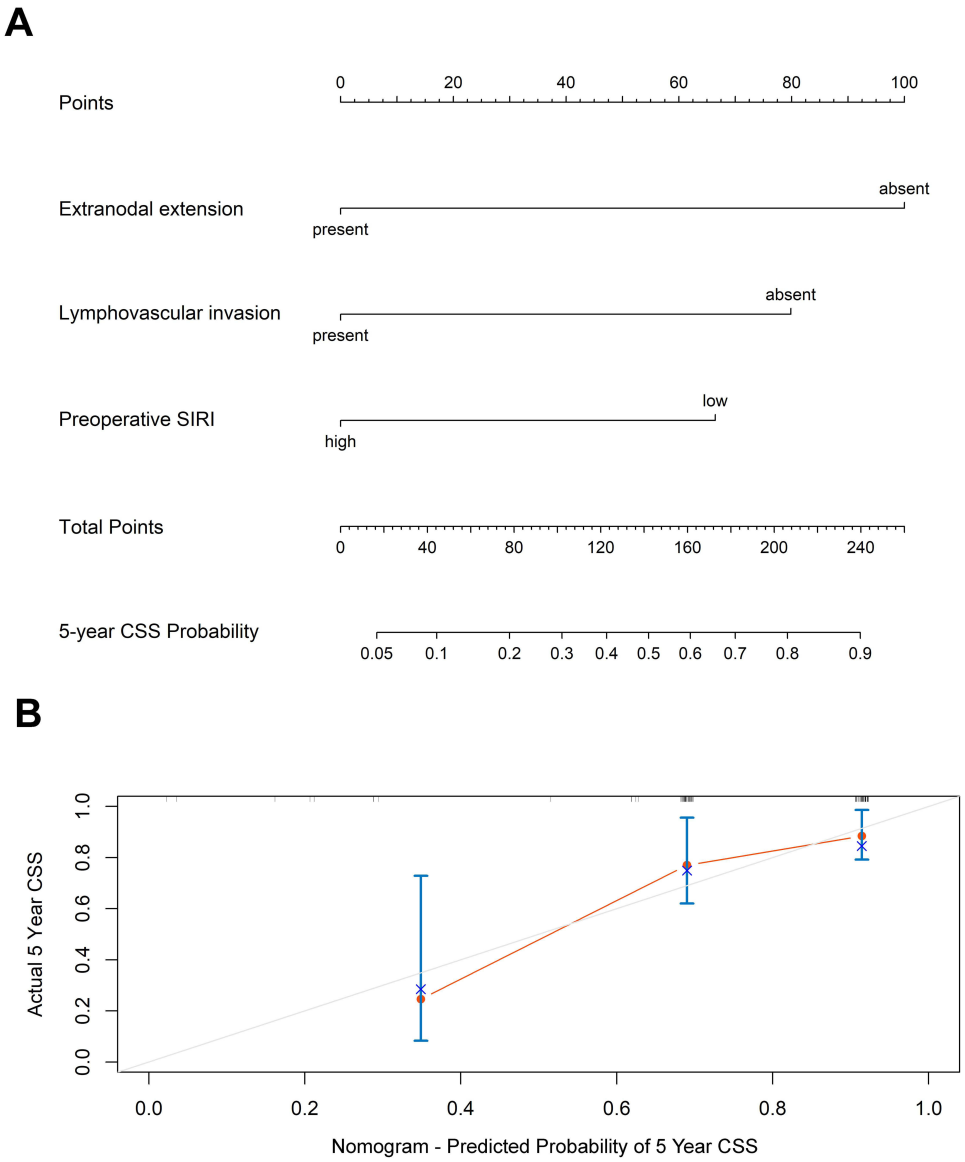

Figure 2 Nomogram and survival predictions. (**A**) nomogram for prediction of 5-year cancer specific survival (CSS). A vertical line is drawn from each factor to the point score. By adding the points from all factors, a total points score is reached, which is translated into 5-year CSS probabilities by drawing a vertical line to its axis. (**B**) Calibration plots of the nomogram to predict 5-year CSS. The 45-degree straight line indicates the ideal prediction, and the Orange line represents the nomogram's performance. Blue dots with bars represent the nomogram's performance with 95% confidence interval when applied to the observed surviving cohorts.

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Discussion

Compared to numerous other prognostic factors, inflammation-based prognostic parameters offer the benefits of simplicity, widespread applicability, and cost-effectiveness for pretreatment assessments through blood tests. To the best of our knowledge, this study represents the first investigation into the clinical significance of preoperative SIRI in mspHNSCC patients. Our results suggest that the preoperative SIRI serves as an independent predictor of OS and CSS in patients with mspHNSCC, and its predictive efficacy surpasses that of other inflammatory markers examined in the study. Moreover, we identified LVI and ENE as the independent adverse pathological features predicting CSS in mspHNSCC patients following surgical intervention.

While radical surgery is the recommended approach for resectable mspHNSCC, the role of postoperative adjuvant therapy in high-risk patients remains a subject of controversy, considering factors such as feasibility, toxicities, and potential survival benefits. A comparative trial investigating re-irradiation combined with chemotherapy versus observation in patients with previously irradiated recurrent HNSCC after complete surgical resection revealed improved local control and disease-free survival in the re-irradiation plus chemotherapy group. However, there was no observed improvement in OS, and a substantial 40% experienced grade 3 or 4 toxicities.[20]

Unlike fpHNSCC, the criteria for defining high-risk features after surgical resection for mspHNSCC remain unclear and poorly established in the literature. Chen et al, utilizing data from the Taiwan Cancer Registry database, analyzed survival prognostic factors in 1,741 mspHNSCC patients.[21] Their findings identified a Charlson Comorbidity Index ≥6, advanced stages of both mspHNSCC and fpHNSCC, and an interval of less than three years from fpHNSCC diagnosis as significant independent risk factors associated with poorer overall survival. Gross residual disease, positive margins, or ENE in resected mspHNSCC were considered adverse features warranting further adjuvant therapy.[22,23] In our series, the presence of LVI and ENE emerged as independent adverse predictors of survival based on clinicopathological parameters. In our cohort, 9 out of 10 patients presenting with LVI died during the follow-up period, with 7 deaths attributed to mspHNSCC. These findings align with emerging evidence suggesting that LVI plays a critical role in tumor progression and metastasis. Increased vascular and lymphatic invasion has been linked to increased nodal metastasis and ENE.[24] Our results highlight the potential clinical utility of SIRI as a stratification tool in mspHNSCC. Because SIRI reflects systemic inflammation and immune competence, it may help identify patients at higher risk of poor outcomes who could benefit from tailored management strategies. For instance, patients with elevated SIRI might warrant closer surveillance, early nutritional and supportive interventions, or prioritization for clinical trials testing immunomodulatory agents, while those with low SIRI may be adequately managed with standard approaches. However, given the retrospective nature of our analysis and lack of external validation, these applications remain exploratory. Prospective, multi-institutional studies are required to determine whether integrating SIRI into clinical workflows can improve treatment selection, optimize supportive care, and ultimately enhance patient outcomes.

In our study, margin status and AJCC stage did not reach statistical significance in the multivariate analysis. The relatively small sample size (only 4 cases with positive margin in the study cohort) and specific characteristics of our study cohort may have limited the statistical power to detect the prognostic impact of margin status and AJCC stage. The inclusion of other strong prognostic factors, such as LVI, ENE, and SIRI, in the multivariate model may attenuate the independent contributions of margin status and AJCC stage due to potential collinearity or overlapping prognostic information. Additionally, the focus on mspHNSCC may introduce unique biological or clinical factors that modify the influence of these variables.

Neutrophils, monocytes, and lymphocytes are key mediators of systemic immunity and inflammation, with established roles in cancer progression.[25] Neutrophils and monocytes promote tumor growth through angiogenesis, reactive oxygen species, and pro-tumor cytokines, whereas lymphocytes reflect antitumor immune competence and are highly radiosensitive, with even low-dose irradiation causing substantial cell loss.[26] In our cohort, prior treatments contributed to lymphopenia and monocytopenia, yet preoperative inflammatory markers, including SIRI, retained prognostic significance in mspHNSCC. The biological rationale lies in SIRI's integration of these leukocyte subsets, capturing the balance between protumor inflammation and antitumor immunity. Prior irradiation can further disrupt this balance through bone marrow alterations, lymphopenia, and myeloid skewing,[11] amplifying the relevance of SIRI as a marker of immune dysregulation and survival outcomes.

SIRI, which integrates the counts of neutrophils, monocytes, and lymphocytes in peripheral blood, has been investigated across diverse cancer types, such as nasopharyngeal carcinoma,[27] HNSCC,[13–18,28] hepatoma,[29] cholangiocarcinoma,[30] lung cancer,[31] renal cell carcinoma,[32] etc. In the context of HNSCC treated through surgical resection, Lin et al investigated the prognostic implications of SIRI in a cohort comprising 535 patients with oral squamous cell carcinoma. Their study unveiled a notable correlation, indicating that individuals with a higher preoperative SIRI encountered a significantly increased risk of mortality in comparison to those with a low SIRI.[14] Similarly, Song et al analyzed the SIRI in 235 patients with early-stage (cT1-2N0) oral squamous cell carcinoma treated with primary tumor resection. Their study demonstrated that individuals with a high preoperative SIRI experienced significantly poorer OS and disease-specific survival than those with a low SIRI.[16] In contrast to these studies focusing on fpHNSCC, our current research extends the understanding of preoperative SIRI's role in predicting survival outcomes for individuals with mspHNSCC. Compared to other inflammatory biomarkers such as ANC, AMC, ALC, NLR, PLR, and MLR, SIRI has been identified as a more powerful survival predictor in the mspHNSCC cohort. However, given the potential for multi-collinearity among these inflammatory markers, SIRI may serve as a surrogate for them. These findings highlight SIRI's potential as a robust prognostic marker, while suggesting that future studies could investigate its integration with other markers to further enhance prognostic accuracy.

The optimal SIRI cutoff for survival prediction has varied across cancer types and cohorts, ranging from 0.84 to 3.26.[13–15,17,18,27–32] In fpHNSCC, values of 1.6 and 1.3 were reported by Lin et al[14] and Song et al[16] respectively. Although prior irradiation may induce leukopenia, our study identified a comparable cutoff of 1.383 for mspHNSCC. At this threshold, preoperative SIRI was the most predictive inflammatory marker, with higher values independently associated with poorer OS and CSS in multivariate analysis. However, several limitations should be noted: (1) the impact of comorbidities such as diabetes and chronic kidney disease on inflammatory markers was not assessed; (2) the SIRI cutoff was data-driven, raising concerns of overfitting and highlighting the need for validation in larger, independent cohorts. Moreover, the absence of immune profiling (eg, CD8+ T-cell infiltration, MDSCs, cytokine activity) limited mechanistic insights, underscoring the need for further translational studies to substantiate its biological rationale; (3) lack of longitudinal blood data precluded analysis of leukocyte recovery or SIRI dynamics; and (4) the retrospective, single-center design without external validation may limit generalizability. Despite these limitations, our findings provide a foundation for future prospective, multi-institutional studies to validate SIRI and refine its clinical utility.

Conclusions

In summary, this study provides the first evidence that preoperative SIRI is a valuable prognostic indicator in previously irradiated mspHNSCC. Combined with adverse pathological features such as LVI and ENE, SIRI may aid risk stratification and guide decisions on adjuvant therapy.

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This paper has been uploaded to SSRN as a preprint: [https://papers.ssrn.com/sol3/papers.cfm?abstract_id=4706992].

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Disclosure

The authors have declared that no competing interest in this work.

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