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Prognostic Significance of Tumor-associated Stroma in Nasopharyngeal Carcinoma

A Multicenter Study

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Abstract: Assessment of tumor-associated stroma has shown a reliable prognostic value in recent research. We evaluated the prognostic value of tumor-stroma ratio (TSR) in a large multicenter cohort of nasopharyngeal carcinoma (NPC). We used the conventional hematoxylin and eosin–stained slides of 115 cases of NPC to assess TSR as described in recent guidelines. The amount of tumor-associated stroma was assessed as a percentage and then tumors were classified as stroma-high ($>50\%$) or stroma-low ($\leq 50\%$). Kaplan-Meier curves, χ^2 test, and Cox regression univariable and multivariable analyses were carried out. A total of 48 (41.7%) tumors were stroma-high and 67 (58.3%) tumors were stroma-low. In the Cox regression multivariable analysis, the tumors categorized as stroma-high were associated with a worse overall survival with a hazard ratio of 2.30 (95% CI: 1.27-4.15, $P=0.006$) and with poor disease-specific survival (hazard ratio = 1.87, 95% CI: 1.07-3.28, $P=0.029$). The assessment of TSR in NPC is simple and cost-effective, and it has a significant prognostic value. TSR can aid in risk stratification and clinical decision-making in NPC.

Key Words: tumor-stroma ratio (TSR), nasopharyngeal carcinoma (NPC), prognosis, stroma-high, stroma-low

(*Am J Surg Pathol* 2024;48:54–58)

Nasopharyngeal carcinoma (NPC) still constitutes a significant health burden around the world.[1] Despite improvements in treatment strategies, the prognosis of NPC patients remains relatively poor with a high number of cancer-related mortality.[2] The prognostication of NPC in daily practice depends mainly on TNM staging. However, tumors of the same stage may present with very different clinical behaviors. Thus, additional prognostic markers are needed to characterize tumor behavior with more accuracy. This should preferably be based on consideration of both cancer-related and stroma-related properties.

Tumor microenvironment (TME) is a key player during the progression of head and neck cancer and it also plays a role in treatment resistance.[3] TME consists of many cell types including cancer-associated fibroblasts (that have a prominent role in the recruitment of immune cells) and mesenchymal stromal cells.[4] In the ongoing research efforts to target both the cancer cells and the cells of the TME in NPC, however, the prognostic significance of the TME has not yet been resolved. Thus, analyzing stroma-related prognostic biomarkers is necessary to better characterize tumor behavior in NPC.

Tumor-stroma ratio (TSR) is a stroma-related prognostic marker that has been introduced recently as a reliable prognosticator in different tumor types,[5–7] including head and neck squamous cell carcinoma in some subsites.[8] TSR is defined as the percentage of cancer cell component relative to tumor-stroma component in the tumor tissue. TSR is evaluated using histologic analysis of hematoxylin and eosin (HE)-stained slides[5–8] to assess the

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Conflicts of Interest and Source of Funding: Supported by The Finnish Cancer Society, the Turku University Hospital Fund, Finska Läkaresällskapet, Maritza and Reino Salonen Foundation, K. Albin Johansson Foundation, the Finnish Dental Society Apollonia, the Helsinki University Hospital Research Fund, and the Sigrid Jusélius Foundation. The authors have disclosed that they have no significant relationships with, or financial interest in, any commercial companies pertaining to this article.

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amount of the stroma compartment within the tumor.[7] Data on the significance of TSR and tumor-associated stroma in NPC is lacking, especially in patients from nonendemic regions, such as Europe and North America. Studies on NPC in the latter regions are usually based on small cohorts due to paucity of cases. Therefore, we investigated the prognostic significance of TSR in NPC in a large nonendemic multicenter cohort.

MATERIALS AND METHODS

Our study comprised patients with primary NPC treated at one of the 5 Finnish University Central Hospitals (Helsinki, Tampere Turku, Oulu, and Kuopio). A total of 115 cases were eligible to be included as in our previous study.[9] At the end of follow-up, 52 (45.2%) patients had died of NPC, while 24 (20.9%) had died of other causes, and 39 (33.9%) were alive.

For the assessment of TSR, all representative HE-stained diagnostic slides were retrieved. To be considered representative, a biopsy should show invasive growth present in both tumor and stroma compartments. We followed recent guidelines for the evaluation of TSR in colorectal and breast carcinomas,[10,11] and these were applied, as has been reported previously by our group for oral and oropharyngeal squamous cell carcinoma.[12,13] Thus, following the guidelines we first scanned the whole tumor at low magnification (×5 objective) to select an area with the highest amount of tumor-associated stroma. Then, at higher magnification using a ×10 objective we assessed an area of 3 mm^2 for the amount of tumor-associated stroma so that cancer cells were present in all 4 edges of the selected microscopic field.[10,11] Only a stromal area surrounded by cancer cells was assessed to ensure that tumor-associated stroma only was evaluated. In cases of a heterogenous tumor with areas of both high and low amounts of tumor-associated stroma, the stroma-high area was considered decisive for scoring the case, as recommended in the guidelines.[10,11] Areas of necrosis, native lymphoid stroma, preexisting lymphoid tissue, and lymphoid aggregates not constituting tumor tissue were visually excluded from the estimation as recommended in the guidelines since they are not part of response to the tumor.[10,11]

For survival analyses, the tumors were classified based on the amount of tumor-associated stroma (Fig. 1) into stroma-high (> 50% stroma) or stroma-low (≤ 50% stroma) as described in recent guidelines for the assessment of TSR.[10,11] This cutoff point (ie, 50%) has been widely used and has shown a valuable discriminative power for prognostication of many tumor types[5–7] including some subsites of head and neck squamous cell carcinoma.[12–15] Samples were scored by 2 observers experienced in head and neck pathology (A.A. and I.L.), who were blinded to the clinical data. Inter-observer variability was registered to assess the inconsistency between the observers, which was mainly encountered in cases close to the 50% cutoff. For such cases, we arranged a review session to reach agreement between the observers.

Statistical Analyses

We conducted all analyses using IBM SPSS Statistics, version 27, and the significant *P*-value was considered at <0.05. The correlation between TSR and the clinicopathologic parameters including age, sex, TNM stage, T classification, nodal status, histopathology, and Epstein-Barr virus (EBV) status was analyzed using cross-tabulation and the Pearson χ^2 test.

Kaplan-Meier survival curves for TSR categories (ie, stroma-high and stroma-low) were produced for both

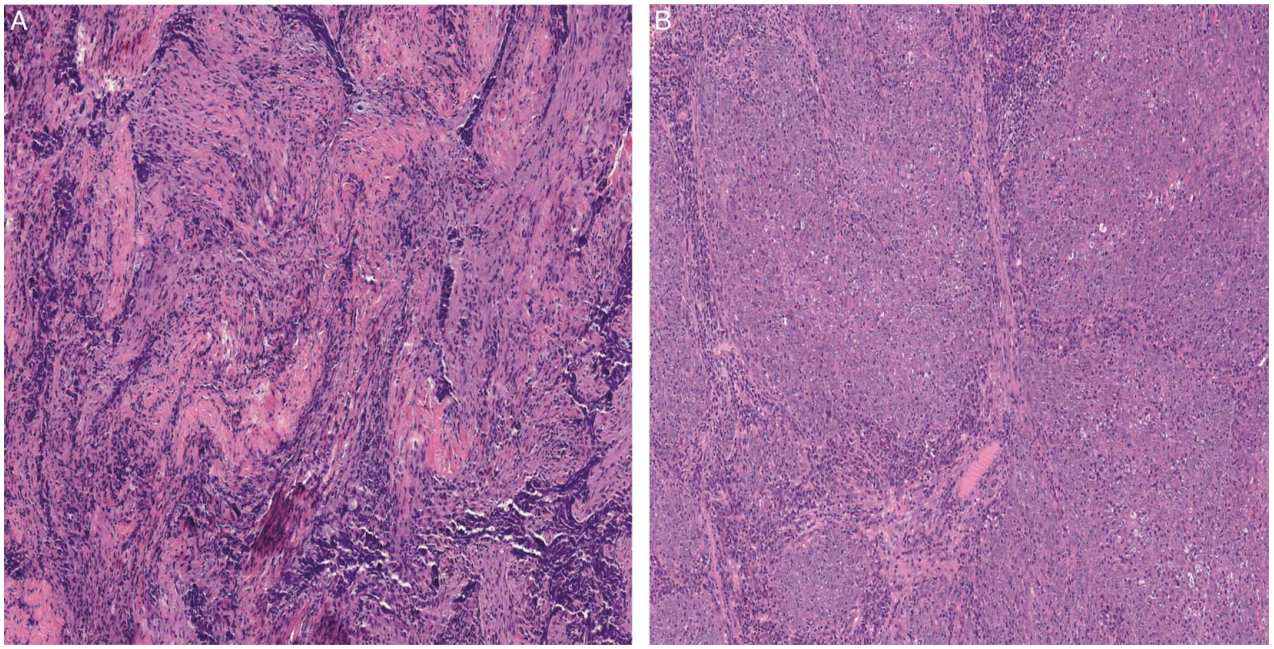

FIGURE 1. HE-stained sections of NPC. A, Stroma-high tumor (> 50% stroma). B, Stroma-low tumor (≤ 50% stroma).

overall survival (OS) and disease-specific survival (DSS). OS was defined as the interval between diagnosis and date of death or the last time of follow-up. DSS was defined as the period from the time of diagnosis to the time of death due to NPC. The log-rank test was used to assess the statistical significance of differences between the survival curves. We conducted univariable and multivariable Cox regression analyses and reported hazard ratios (HRs) with 95% CIs.

RESULTS

There were 67 (58.3%) patients aged 60 years or less, and 48 (41.7%) older patients aged over 60 years. A total of 44 (38.3%) cases were diagnosed at an early stage (I or II), and 71 (61.7%) cases were diagnosed at an advanced stage (III or IV). A total of 28 (24.3%) tumors were keratinizing, 19 (16.5%) were nonkeratinizing differentiated, and 68 (59.1%) were nonkeratinizing undifferentiated tumors. The scoring of TSR showed that 48 (41.7%) tumors were stroma-high and 67 (58.3%) were stroma-low. There was a good agreement between the observers with a κ value of 0.57 ($P < 0.001$).

In cross-tabulation (Table 1), keratinizing histology was associated with TSR as keratinizing tumors had a higher amount of tumor-associated stroma when compared with nonkeratinizing tumors ($P = 0.001$). Similarly, EBV-negative cases were associated with a higher amount of tumor-associated stroma when compared with EBV-positive cases ($P = 0.009$). The other clinicopathologic characteristics (Table 1) including patient age and sex or tumor stage did not have a significant relationship with TSR ($P > 0.05$).

In survival analyses (Tables 2, 3), TSR showed a significant prognostic value in predicting OS with stroma-high cases having a poorer prognosis in the univariable analysis (HR = 2.46, 95% CI: 1.55-3.92, $P < 0.001$) as well as the multivariable analysis (HR = 2.30, 95% CI: 1.27-4.15, $P = 0.006$), when compared with stroma-low cases. Analogously, TSR was associated with DSS as stroma-high tumors were associated with high cancer-related mortality in univariable analysis (HR = 1.90, 95% CI: 1.09-3.30, $P = 0.023$) and in multivariable analysis (HR = 1.87, 95% CI: 1.07-3.28, $P = 0.029$). The multivariable analysis included the following variables: age and sex of patients, tumor stage, histology, EBV status, and TSR. Furthermore, Kaplan-Meier survival curves confirmed that stroma-high cases were associated with a worse survival (Figs. 2A, B). This indicates that TSR can be used as an independent prognostic classifier in NPC. In addition to TSR, EBV status and tumor stage demonstrated significant prognostic performance in the multivariate analyses, while the other parameters were not significantly associated with survival outcome (Tables 2, 3).

TABLE 1. Relationship Between TSR and Clinicopathologic Parameters of NPC

		TSR, n (%)		
Variables	**Total (N = 115)**	**Stroma-low tumors, n = 67 (58.3%)**	**Stroma-high tumors, n = 48 (41.7%)**	***P* (Pearson χ^2)**
Age (y)				0.71
≤ 60	67	40 (59.7)	27 (40.3)	
> 60	48	27 (56.3)	21 (43.8)	
Sex				0.28
Men	80	44 (55)	36 (45)	
Women	35	23 (65.7)	12 (34.3)	
Stage				0.19
I-II	44	29 (65.9)	15 (34.1)	
III-IV	71	38 (53.5)	33 (46.5)	
T classification				0.23
T1	41	29 (70.7)	12 (29.3)	
T2	35	18 (51.4)	17 (48.6)	
T3	18	10 (55.6)	8 (44.4)	
T4	21	10 (47.6)	11 (52.4)	
N classification				0.42
N0	39	26 (66.7)	13 (33.3)	
N1	25	14 (56.0)	11 (44.0)	
N2	41	23 (56.1)	18 (43.9)	
N3a	7	2 (28.6)	5 (71.4)	
N3b	3	2 (66.7)	1 (33.3)	
Histology				0.001
Nonkeratinizing undifferentiated	68	47 (69.1)	21 (30.9)	
Nonkeratinizing differentiated	19	12 (63.2)	7 (36.8)	
Keratinizing	28	8 (28.6)	20 (71.4)	
EBV status				0.009
Positive	69	47 (68.1)	22 (31.9)	
Negative	44	19 (43.2)	25 (56.8)	

TABLE 2. OS Analysis of the Prognostic Significance of TSR and Clinicopathologic Parameters in NPC (N = 115 Patients)

	HR (95% CI), *P*	
Parameters	**Univariable analysis**	**Multivariable analysis**
Age (y)		
≤ 60	Reference	Reference
> 60	1.98 (1.25-3.12), 0.004	2.003 (1.13-3.54), 0.017
Sex		
Men	Reference	Reference
Women	0.89 (0.54-1.46), 0.64	0.99 (0.55-1.78), 0.96
Stage		
I-II	Reference	Reference
III-IV	2.01 (1.22-3.30), 0.006	1.97 (1.12-3.47), 0.019
Histology		
Nonkeratinizing undifferentiated	Reference	Reference
Nonkeratinizing differentiated	2.62 (1.55-4.43), <0.001	1.38 (0.54-3.54), 0.49
Keratinizing	1.64 (0.89-3.04), 0.12	0.83 (0.35-1.97), 0.67
EBV status		
Positive	Reference	Reference
Negative	3.47 (2.15-5.59), <0.001	2.59 (1.53-4.38), <0.001
TSR		
Stroma-low	Reference	Reference
Stroma-high	2.46 (1.55-3.92), <0.001	2.21 (1.24-3.96), 0.008

TABLE 3. DSS Analysis of the Prognostic Significance of TSR and Clinicopathologic Parameters in NPC (N = 115 Patients)

	HR (95% CI), *P*	
Parameters	**Univariable analysis**	**Multivariable analysis**
Age (y)		
≤60	Reference	Reference
>60	1.55 (0.89-2.67), 0.12	1.83 (1.05-3.19), 0.034
Sex		
Male	Reference	Reference
Female	0.99 (0.49-1.65), 0.73	1.08 (0.58-1.98), 0.82
Stage		
I-II	Reference	Reference
III-IV	3.39 (1.69-6.78), <0.001	3.56 (1.76-7.18), <0.001
Histology		
Nonkeratinizing undifferentiated	Reference	Reference
Nonkeratinizing differentiated	2.47 (1.33-4.59), 0.004	2.25 (1.15-4.39), 0.02
Keratinizing	1.48 (0.69-3.18), 0.31	1.46 (0.68-3.14), 0.34
EBV status		
Positive	Reference	Reference
Negative	2.40 (1.37-4.22), 0.002	1.81 (0.99-3.31), 0.06
TSR		
Stroma-low	Reference	Reference
Stroma-high	1.89 (1.09-3.29), 0.023	1.87 (1.07-3.28), 0.029

DISCUSSION

Chemoradiotherapy is a widely applied treatment protocol for NPC but treatment failures occur even at experienced centres. Thus, appropriate prediction and risk stratification (based on multiple prognostic factors) is essential toward a better treatment planning of NPC. The significance of TSR has been studied in different types of epithelial malignancies including oral squamous cell carcinoma,[16] triple-negative breast cancer,[6] non–small cell lung cancer,[17] and urothelial carcinoma.[7] In NPC, one previous study has reported the significance of TSR based on a single institution cohort from an endemic region (China).[14] In this study, we analyzed for the first time the clinical significance of TSR in a large multicenter cohort of NPC from a nonendemic region (Finland). We found that TSR is a valuable prognostic indicator that can be easily assessed.

Evidence from molecular studies has reported on interactions between the stromal cells with neighboring cancer cells and highlighted the role of these interactions in cancer progression and metastasis.[18] Furthermore, stromal cells have a role in resistance to anti-angiogenic therapy.[19] A recent study by Xu et al[7] reported on tumors with high stroma presenting with abundant cancer-associated fibroblasts. These fibroblasts form a key component of tumor-stroma and contribute to tumor progression.[20] In addition, other cells of TME (such as endothelial cells) play roles in tumor progression as well.[21] Of note, growth factors capable of inducing epithelial-mesenchymal transition are produced by stromal cells.[21] Thus, the presence of a high amount of tumor-associated stroma may facilitate the epithelial-mesenchymal transition, which is operative in cancer invasion, metastasis, and drug resistance.[22] Interestingly, EBV-negative cases had a higher amount of tumor-related stroma, concurring with results showing that EBV (and HPV)-negative tumors have a worse prognosis in NPC.[23]

Evaluation of specific elements of stromal tissues, such as cancer-associated fibroblasts using α-smooth muscle actin staining, has been studied previously in NPC.[24]

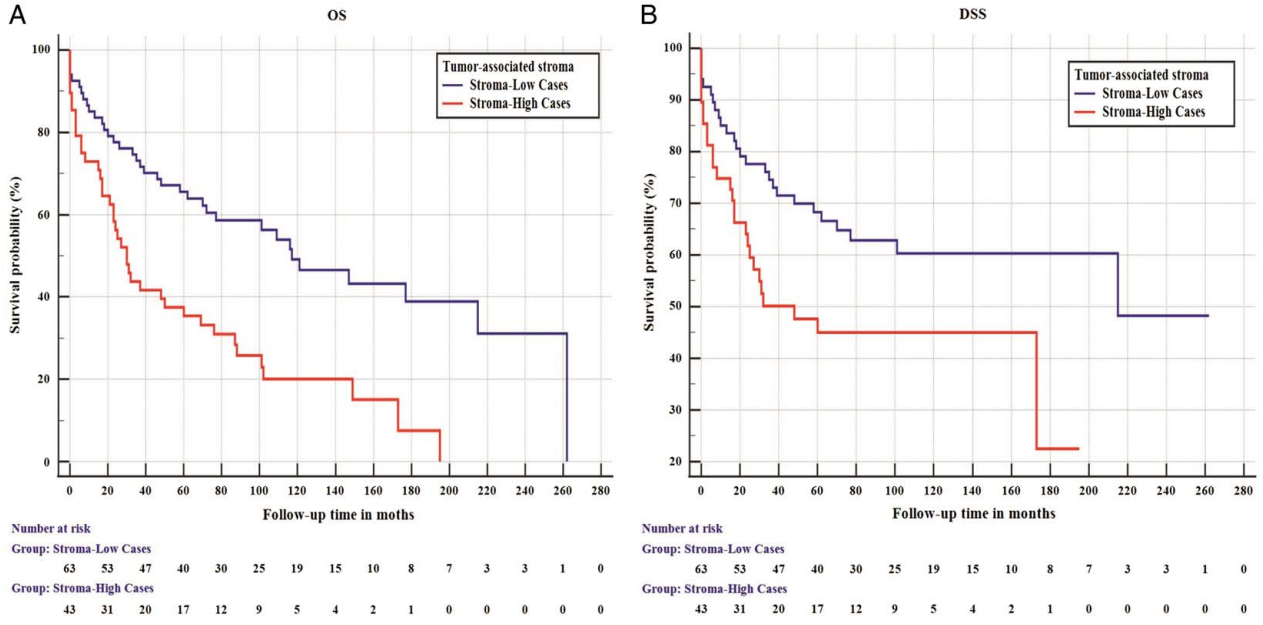

FIGURE 2. Kaplan-Meier survival curves for OS (A, $P < 0.0001$) and DSS (B, $P = 0.020$) of stroma-high and stroma-low tumors. Stroma-high tumors were associated with poor prognosis in both analyses.

However, the use of immunohistochemistry for scoring specific molecules is not necessary for the prognostication benefits. Evaluation of TSR is a simple, fast, cheap, and routinely available prognostic method using conventional HE-stained sections, as also reported widely in many other cancer types.[8,22,25] Furthermore, TSR provides prognostic information based on the stromal compartment of tumors, complementing tumor cell-related prognostic information.

Interestingly, in recent studies of head and neck cancers including laryngeal squamous cell carcinoma[15,26] and oral tongue squamous cell carcinoma[27] the visual estimation of TSR has shown concordance between tissue biopsies and surgical samples. A similar concordance has been reported in esophageal adenocarcinoma[28] and invasive breast cancer.[29] This is important particularly in NPC, as typically only diagnostic biopsies are available before the administration of (chemo)radiotherapy. Furthermore, in recent studies, digital assessment of TSR has shown a promising prognostic significance and a good agreement with the visual assessment by pathologists.[30,31] Possibly in the future, digital methods may be used in the standardization of the assessment of TSR and reducing interobserver variability. Such a standardized assessment of TSR can be a step forward towards personalized treatment based on the assessment of the stroma compartment in addition to currently available tumor-related characteristics. This requires further research including prospective clinical studies to validate the findings of our current study and to allow for the implementation of TSR in clinical decision making.

In conclusion, TSR seems to have a significant prognostic impact on NPC. Integration of a stromal prognostic marker such as TSR to the routine diagnostics of NPC can aid in improving risk stratification and subsequently optimizing the therapeutic strategies. Targeting the stromal compartment of stroma-high tumors might improve survival figures in NPC patients and should be addressed in future research.

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