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Stroma AReactive invasion Front Areas (SARIFA) in early-stage oral tongue squamous cell carcinoma

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ABSTRACT

Background: Stroma AReactive Invasion Front Areas (SARIFA) has recently been introduced as a prognostic indicator. The prognostic value of SARIFA has not been studied in early-stage oral tongue squamous cell carcinoma (OTSCC).

Material and methods: A total of 287 cases of early-stage OTSCC were included in this multicenter study. SARIFA was defined as direct contact between tumor cells and the adipose tissue, and was assessed in hematoxylin and eosin (HE)-stained sections.

Results: In early-stage OTSCC, SARIFA-positive tumors were associated with worse disease-specific survival with a hazard ratio (HR) of 1.86 (95% CI 1.06–3.28, $P = 0.032$), overall survival (HR 1.52, 95% CI 1.06–2.19, $P = 0.023$) and disease-free survival (HR 1.79, 95% CI 1.09–2.93, $P = 0.021$).

Conclusions: SARIFA is a histomorphology-based prognosticator, that can identify cases with early-stage OTSCC who might benefit from a multimodality treatment protocol.

Introduction

Oral tongue squamous cell carcinoma (OTSCC) is the most common oral cavity cancer and it comprises about 25–40% of all oral cancers [1]. Despite advances in cancer treatment modalities, OTSCC is still associated with high morbidity and mortality [2,3]. The late presentation of OTSCC at advanced stages is well known factor contributing to aggressive tumor behavior and poor outcomes [4]. However, the prognosis of early-stage OTSCC remains highly unpredictable in many cases emphasizing the need for reliable prognostic markers and insight into histopathologic characteristics associated with tumor progression [5]. Such characteristics are typically assessed at the tumor invasive front area which is a biologically dynamic region where cancer-stroma interactions drive tumor aggressiveness and metastatic potential [6].

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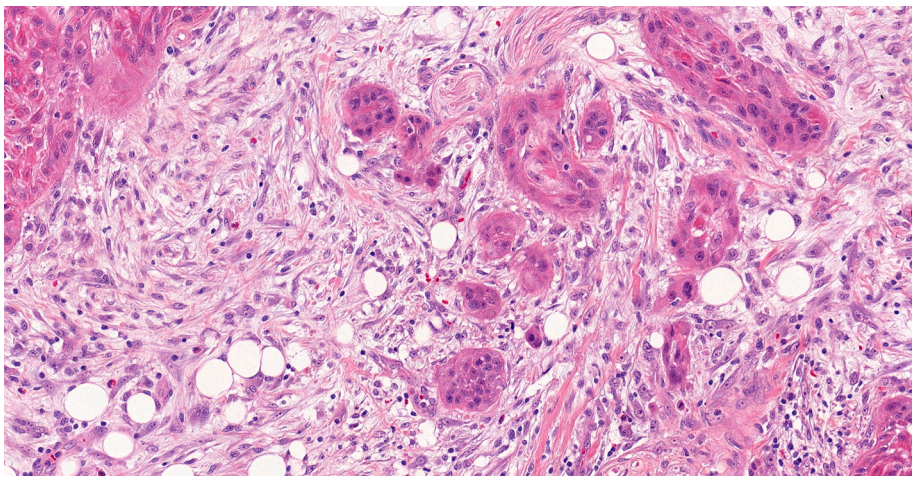

Fig. 1. Presence of Stroma AReactive Invasion Front Area (SARIFA) in hematoxylin-eosin-stained section of early-stage oral tongue squamous cell carcinoma.

The evaluation of histomorphologic characteristics using hematoxylin and eosin (HE) staining is considered the gold standard in routine diagnostics, as no additional staining is required. Recently, the assessment of Stroma AReactive Invasion Front Areas (SARIFA) defined as a direct contact between cancer cells and adipocytes at the invasion front of the main tumor mass has been reported as a promising histopathologic feature associated with worse prognosis in many malignant tumors [7]. This might implicate an interaction between cancer cells and cancer-promoting adipocytes [8]. Notably, histopathologic features that are associated with metabolic changes in cancer cells are not yet available in routine diagnostics [9].

Currently, there is no knowledge about the prognostic significance of SARIFA in OTSCC. Understanding the interplay between SARIFA, immune infiltration at the tumor front, and patient outcome could provide valuable insights into tumor biology and help to refine risk stratification. This will open avenues for integration of histopathological assessment with immunological markers to guide clinical management and to identify patients who might benefit from immunotherapeutic strategies. Therefore, the aim of this study was to evaluate the prognostic value of SARIFA in a large multicenter cohort of early-stage OTSCC.

Material and methods

We included a total of 287 patients treated for early-stage OTSCC at five Finnish university hospitals (Helsinki, Tampere, Turku, Oulu, Kuopio) or at the A.C. Camargo Cancer Center, São Paulo, Brazil. The included cases were diagnosed at cT1-2 N0 stage and reclassified as described in the American Joint Committee on Cancer 8th edition (AJCC 8) staging system [10]. The primary treatment of the included cases was surgical excision of early-stage OTSCC. Ethical permissions were obtained from the included hospitals, from the National Supervisory Authority for Welfare and Health in Finland and from the Brazilian Human Research Ethics Committee.

The assessment of SARIFA was conducted in HE-stained sections as described in previous studies [11–13]. In brief, SARIFA was evaluated at the invasive front area in a representative tumor section. When there was direct tumor cell-adipocyte contact at the invasion front, the case was considered as a SARIFA-positive tumor (Fig. 1). Otherwise, the tumor was considered as SARIFA negative. Even if only one tumor cell cluster (≥5 cells)-adipocyte contact was present, the tumor was classified as SARIFA positive, as described in previous research [11]. Two observers (AA & IL) arranged a training session on the assessment criteria of SARIFA with emphasis on interobserver agreement and variation. The observers were blinded to the patient outcomes.

We evaluated tumor-infiltrating lymphocytes (TILs) in HE-stained specimens as described by the TILs Working Group [14] in incremental percentages (5%, 10%, 20%, 30%, 40%, etc). The intratumoral TILs (i.e. inside the tumor areas) are defined as the percentage of tumor area occupied by infiltrating lymphocytes, and stromal TILs (i.e. within the tumor stroma) are defined as the percentage of stromal

Table 1
Relationship between Stroma AReactive Invasion Front Areas (SARIFA) and clinicopathologic features in early-stage (T1T2N0, AJCC8) oral tongue squamous cell carcinoma.

Parameter	Total	SARIFA		*P* value of chi-square test
		None	Present	
	N = 287	N = 216 N (%)	N = 71 N (%)	
Age (years)				0.64
≤60	120	92 (76.7%)	28 (23.3%)	
>60	167	124 (74.3%)	43 (25.7%)	
cTNM stage				**0.001**
T1N0M0	89	78 (87.6%)	11 (12.4%)	
T2N0M0	198	138 (69.7%)	60 (30.3%)	
Gender				0.092
Men	153	109 (71.2%)	44 (28.8%)	
Women	134	107 (79.9%)	27 (20.1%)	
WHO grade				0.348
Well or Moderately	218	167 (76.6%)	51 (23.4%)	
Poorly differentiated	69	49 (71.0%)	20 (29.0%)	
Immune response				**0.041**
Low	46	29 (63.0%)	17 (37.0%)	
High	238	184 (77.3%)	54 (22.7%)	
Perineural invasion				**< 0.001**
Absent	251	198 (78.9%)	53 (21.1%)	
Present	36	18 (50.0%)	18 (50.0%)	
Depth of invasion				**0.007**
Superficial (≤5 mm)	180	145 (80.6%)	35 (19.4%)	
Deep (>5 mm)	107	71 (66.4%)	36 (33.6%)	

Table 2
Disease-specific survival, overall survival, and disease-free survival analyses of 287 cases of early-stage (AJCC 8) oral tongue squamous cell carcinoma.

Parameter	Disease-specific survival		Overall survival		Disease-free survival	
	Univariable Analysis	Multivariable Analysis	Univariable Analysis	Multivariable Analysis	Univariable Analysis	Multivariable Analysis
	HR (95%CI) *P* value	HR (95%CI) *P* value	HR (95%CI) *P* value	HR (95%CI) *P* value	HR (95%CI) *P* value	HR (95%CI) *P* value
Age						
≤ 60 years	Reference	Reference	Reference	Reference	Reference	Reference
> 60 years	2.14 (1.19–3.83)	2.09 (1.14–3.81)	2.26 (1.58–3.23)	2.33 (1.61–3.36)	1.80 (1.11–2.91)	1.76 (1.07–2.88)
	$P = 0.011$	**$P = 0.017$**	$P < 0.001$	**$P < 0.001$**	**$P = 0.016$**	**$P = 0.026$**
Stage						
T1N0M0	Reference	Reference	Reference	Reference	Reference	Reference
T2N0M0	1.42 (0.76–2.64)	1.38 (0.72–2.64)	1.25 (0.85–1.83)	1.14 (0.77–1.69)	0.69 (0.44–1.11)	0.59 (0.36–0.97)
	$P = 0.272$	$P = 0.330$	$P = 0.256$	$P = 0.523$	$P = 0.126$	**$P = 0.037$**
Gender						
Men	Reference	Reference	Reference	Reference	Reference	Reference
Women	1.35 (0.79–2.29)	1.34 (0.77–2.33)	0.83 (0.59–1.16)	0.75 (0.53–1.06)	1.15 (0.73–1.79)	0.99 (0.62–1.59)
	$P = 0.273$	$P = 0.303$	$P = 0.279$	$P = 0.104$	$P = 0.551$	$P = 0.961$
Perineural invasion						
None	Reference	Reference	Reference	Reference	Reference	Reference
Present	1.29 (0.61–2.73)	1.01 (0.47–2.18)	1.46 (0.94–2.27)	1.21 (0.77–1.89)	1.67 (0.92–3.03)	1.70 (0.91–3.19)
	$P = 0.506$	$P = 0.972$	$P = 0.091$	$P = 0.419$	$P = 0.093$	$P = 0.098$
WHO Grade						
Well or Moderately	Reference	Reference	Reference	Reference	Reference	Reference
Poorly differentiated	1.04 (0.56–1.93)	1.15 (0.61–2.19)	0.87 (0.59–1.29)	0.96 (0.64–1.44)	1.09 (0.65–1.84)	1.18 (0.69–2.01)
	$P = 0.912$	$P = 0.666$	$P = 0.498$	$P = 0.843$	$P = 0.738$	$P = 0.539$
SARIFA*						
None	Reference	Reference	Reference	Reference	Reference	Reference
Present	1.95 (1.13–3.38)	1.86 (1.06–3.28)	1.66 (1.16–2.35)	1.52 (1.06–2.19)	1.79 (1.11–2.87)	1.79 (1.09–2.93)
	$P = 0.017$	**$P = 0.032$**	**$P = 0.005$**	**$P = 0.023$**	**$P = 0.017$**	**$P = 0.021$**

***SARIFA**: Stroma AReactive Invasion Front Areas

areas occupied by infiltrating lymphocytes. Tumor cases were divided into "high TILs" and "low TILs" (Supplementary Figure I) and 20% was deemed as an optimal cutoff point, as described in our previous research [15].

Associations between SARIFA status and clinicopathologic parameters, including age at diagnosis, gender, TNM stage (AJCC 8), histopathologic grade, perineural invasion and immune response based on the overall score of tumor-infiltrating lymphocytes [15], were performed by cross-tabulation and chi-square test. Univariable and multivariable analyses were reported with a hazard ratio (HR) and 95% confidence interval (CI). Kappa statistics were used to measure the interobserver agreement. The SPSS 27 software was used for all statistical analyses, and statistical significance was set at P value of < 0.05.

Results

Of the 287 patients included in this study, 153 (53.3%) were men, and 134 (46.7%) were women. The median age at the time of diagnosis was 63.4 years. There were 77 (26.8%) patients who had experienced a recurrence, and 55 (19.2%) patients had died of the disease. There were 71 (24.7%) SARIFA-positive tumors and 216 (75.3%) SARIFA-negative tumors. In the assessment of SARIFA, there was an excellent agreement (Kappa value = 0.837) between the observers when they independently evaluated 130 randomly selected cases for this calculation.

Cross-tabulation analyses (Table 1) showed that SARIFA-positive tumors were associated significantly with T2N0 tumors ($P = 0.001$), presence of perineural invasion ($P < 0.001$), deep invasion of > 5 mm ($P < 0.001$), and low immune response ($P = 0.041$) as indicated by low infiltration of lymphocytes. No significant association was observed between SARIFA status and patient age, gender or tumor grade ($P > 0.05$).

In prognostic analyses, SARIFA-positive cases were associated significantly with a higher-risk of cancer-related mortality in univariable analysis with an HR of 1.95 (95% CI 1.13–3.38, $P = 0.017$), as also in multivariable analysis (HR 1.86, 95% CI 1.06–3.28, $P = 0.032$) (Table 2). In overall survival analysis, SARIFA-positive cases had worse prognosis in univariable analysis with an HR of 1.66 (95% CI 1.16–2.35, $P = 0.005$), and in multivariable analysis with an HR of 1.52 (95% CI 1.06–2.19, $P = 0.023$). Furthermore, SARIFA-positive cases were associated with worse disease-free survival in univariable analysis with an HR of 1.79 (95% CI 1.11–2.87, $P = 0.017$), and in multivariable analysis with an HR of 1.79 (95% CI 1.09–2.93, $P = 0.021$). Our multivariable analyses (Table 2) for SARIFA status were adjusted by routine prognostic indicators including TNM stage (AJCC 8), tumor grade and perineural invasion, in addition to patient age and gender.

Survival curves (Fig. 2) also showed a significant association between SARIFA-positive cases and worse cancer-related survival ($P = 0.015$), overall survival ($P = 0.005$) and disease-free survival ($P = 0.015$), as presented in Fig. 2 A, 2B and 2C respectively.

Discussion

Prognostication and treatment planning of early-stage OTSCC are among the most challenging tasks for clinicians in daily practice [5]. Such cases are typically expected to have a favorable prognosis and are therefore often treated with tumor resection alone. However, some early OTSCCs behave aggressively and are associated with poor survival [16]. For example, in the study by Xu et al. [17] on early OTSCC, 29% of the cases had a recurrence and 30% of the patients died. Similarly, in the Lee et al. [18] study, 31% of patients with early oral tongue cancer developed a recurrence. That is in line with the current cohort where 26.8% of the patients suffered from a tumor recurrence and 19.2% of them died of OTSCC. Such relatively high recurrence and death rates reveal the aggressive and unpredictable behavior of this cancer although patients were diagnosed at an early-stage of the disease. Identification of histopathologic features that can predict the clinical behavior of early OTSCC is of high clinical relevance. In this study, our findings indicate that SARIFA (Stroma AReactive Invasion Front Areas) status is an eligible prognostic marker for prognostication of early-stage OTSCC.

The clinical significance of SARIFA has been emphasized recently

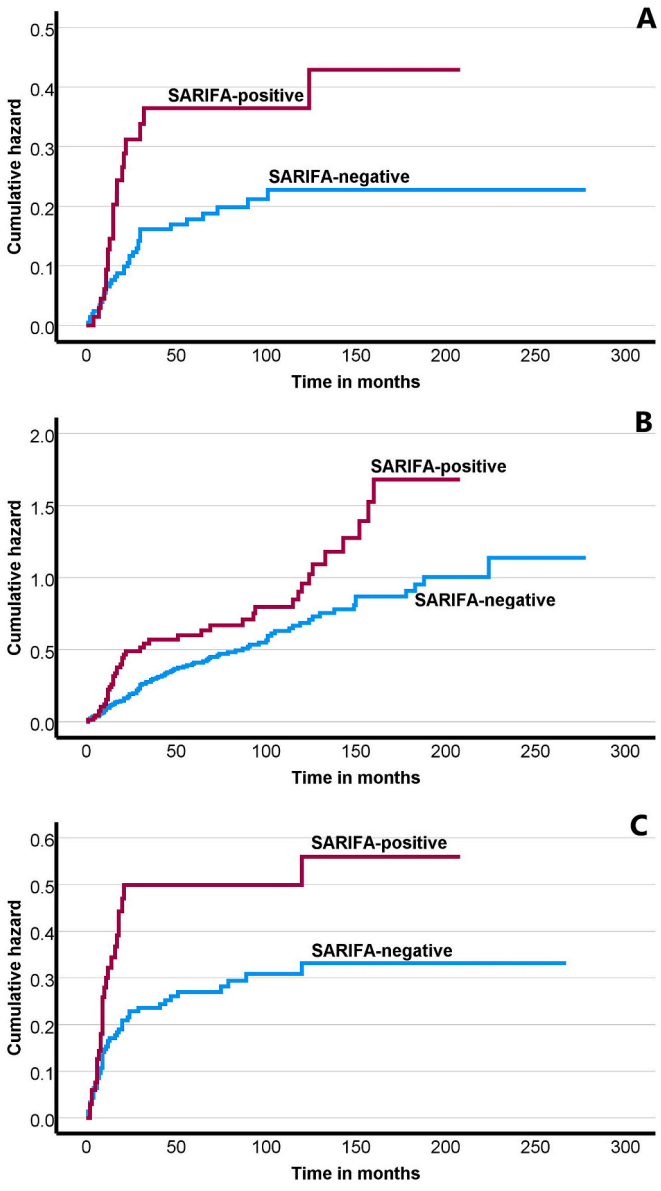

Fig. 2. Survival curves for early-stage oral tongue squamous cell carcinoma patients according to SARIFA status (positive *vs.* negative). **A:** Cancer-related survival ($P = 0.015$). **B:** Overall survival ($P = 0.005$). **C:** Disease-free survival ($P = 0.015$).

due to its powerful prognostic impact in different epithelial tumors including esophageal cancer [19], colorectal cancer [12,13,20], gastric cancer [11,21], pancreatic ductal adenocarcinoma [22] and prostate cancer [23]. Many studies have reported that the assessment of SARIFA in hematoxylin-eosin-stained sections is easy and gives a moderate to excellent agreement between observers [11,13,20,22]. In addition, SARIFA status was an independent prognostic marker in the multivariable analyses regardless the AJCC 8th edition TNM stage (T category including depth of invasion), WHO tumor grade, and perineural invasion, which are routinely reported classifiers in OTSCC.

In this study we noted that the presence of SARIFA was associated with low infiltration of TILs, which in recent research has been considered an indicator of low immune response [24]. Of note, in gastric cancer, an altered immune response has been reported in SARIFA-positive tumors by Grosser et al. [8]. In addition, SARIFA positivity was associated with aggressive tumor characteristics including high depth of invasion ($\geq$ 5 mm) and perineural invasion.

The biological background of SARIFA is not fully understood. However, the role of SARIFA as a prognosticator results from direct interaction between cancer cells and adipocytes. It seems that invasive growth of cancer cells in SARIFA-positive tumors represents a biologically significant form of invasion, where tumors benefit from direct contact with adipocytes [7]. Moreover, it has been speculated that cancer incidence is higher and tumors more aggressive in obese people, but, unfortunately, the relationship between adiposity and cancer is not well-understood [25]. In general, it has been speculated that crosstalk between cancer cells and adipocytes takes place, enhancing the effects of microenvironment in cancer growth [11,26]. Furthermore, upregulation of fatty acid-binding protein 4 (FABP4) has been reported in SARIFA-positive cases of gastric [11] and pancreatic cancer [22]. In addition, higher expression of other proteins associated with fatty acid metabolism, namely fatty acid translocase (known as CD36), has been reported in SARIFA areas of gastric cancer [11].

Although there is lack of studies on the biologic background of SARIFA in oral tongue cancer, a recent study by Peltonen et al. [27] found that adipose tissue is a prominent component of tumor microenvironment of OTSCC. In addition, they reported that adipocytes enhanced the aggressiveness of OTSCC through the secretion of soluble factors that could be transferred by extracellular vesicles [27]. Of note, obese patients with early stage OTSCC have been associated with poor prognosis [28]. In addition, Peltonen et al. [27] reported that adipocytes increase migration and induce proliferation in oral tongue cancer cells. These findings support the adverse prognostic role of SARIFA in OTSCC.

In conclusion, this is the first study to report the clinical significance of SARIFA as an adverse prognostic marker in early-stage OTSCC. Limitations of the current study include that the expression of fatty acid-binding proteins (e.g. FABP4) in SARIFA areas was not investigated here. Another limitation was that pathologic staging of the tumor cases was not available by the participating hospitals. In addition, the number of cases in this cohort was not sufficient to be divided into a test set and a validation set. Thus, further validation studies are warranted. Furthermore, understanding of the mechanisms behind the poor prognosis of SARIFA-positive tumors might aid in opening new therapeutic avenues.

Generative AI and AI-assisted technologies were NOT used in the preparation of this work.

CRediT authorship contribution statement

Alhadi Almangush: Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Muhammad Faisal:** Writing – original draft, Formal analysis. **Caj Haglund:** Writing – review & editing, Project administration, Data curation. **Luiz Paulo Kowalski:** Writing – review & editing, Resources, Project administration, Data curation. **Jaana Hagström:** Writing – review & editing, Resources, Data curation. **Ricardo D. Coletta:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Data curation, Conceptualization. **Antti A. Mäkitie:** Writing – review & editing, Software, Project administration. **Tuula Salo:** Writing – review & editing, Supervision, Project administration, Data curation, Conceptualization. **Ilmo Leivo:** Writing – review & editing, Resources, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.oraloncology.2026.107936.

References

[1] Bello IO, Soini Y, Salo T. Prognostic evaluation of oral tongue cancer: means, markers and perspectives (I). Oral Oncol 2010;46:630–5.
[2] Ng JH, Iyer NG, Tan MH, Edgren G. Changing epidemiology of oral squamous cell carcinoma of the tongue: a global study. Head Neck 2017;39:297–304.
[3] Farhood Z, Simpson M, Ward GM, Walker RJ, Osazuwa-Peters N. Does anatomic subsite influence oral cavity cancer mortality? A SEER database analysis Laryngoscope 2019;129:1400–6.
[4] Almangush A, Pirinen M, Youssef O, Makitie AA, Leivo I. Risk stratification in oral squamous cell carcinoma using staging of the eighth American Joint Committee on Cancer: Systematic review and meta-analysis. Head Neck 2020;42:3002–17.
[5] Rajappa SK, Ram D, Bhakuni YS, Jain A, Kumar R, Dewan AK. Survival benefits of adjuvant radiation in the management of early tongue cancer with depth of invasion as the indication. Head Neck 2018;40:2263–70.
[6] Christofori G. New signals from the invasive front. Nature 2006;441:444–50.
[7] Markl B, Reitsam NG, Grochowski P, Waidhauser J, Grosser B. The SARIFA biomarker in the context of basic research of lipid-driven cancers. npj Precis Oncol 2024;8:165.
[8] Grosser B, Heyer CM, Austgen J, Sipos E, Reitsam NG, Hauser A, et al. Stroma AReactive Invasion Front Areas (SARIFA) proves prognostic relevance in gastric carcinoma and is based on a tumor-adipocyte interaction indicating an altered immune response. Gastric Cancer 2024;27:72–85.
[9] Offermans K, Reitsam NG, Simons C, Grosser B, Zimmermann J, Grabsch HI, et al. The relationship between Stroma AReactive Invasion Front Areas (SARIFA), Warburg-subtype and survival: results from a large prospective series of colorectal cancer patients. Cancer Metab 2024;12:21.
[10] Amin MB, Edge S, Greene F, Byrd DR, Brookland RK, Washington MK, et al. AJCC Cancer Staging Manual. 8th edition. New York: Springer; 2017. p. 2017.
[11] Grosser B, Gluckstein MI, Dhillon C, Schiele S, Dintner S, VanSchoiack A, et al. Stroma AReactive Invasion Front Areas (SARIFA) - a new prognostic biomarker in gastric cancer related to tumor-promoting adipocytes. J Pathol 2022;256:71–82.
[12] Reitsam NG, Offermans K, Simons C, Grosser B, Zimmermann J, Grabsch HI, et al. Prognostic and predictive value of SARIFA-status within Molecular subgroups of colorectal cancer: insights from the netherlands cohort study. Am J Surg Pathol 2025;49:956–69.
[13] Tapiainen VV, Sirnio P, Elomaa H, Karjalainen H, Aijala VK, Kastinen M, et al. Stroma AReactive Invasion Front areas (SARIFA), tumour immune microenvironment, and survival in colorectal cancer. Br J Cancer 2025;132:805–13.
[14] Salgado R, Denkert C, Demaria S, Sirtaine N, Klauschen F, Pruneri G, et al. The evaluation of tumor-infiltrating lymphocytes (TILs) in breast cancer: recommendations by an International TILs Working Group 2014. Ann Oncol 2015;26:259–71.
[15] Heikkinen I, Bello IO, Wahab A, Hagstrom J, Haglund C, Coletta RD, et al. Assessment of tumor-infiltrating lymphocytes predicts the behavior of early-stage oral tongue cancer. Am J Surg Pathol 2019;43:1392–6.
[16] Galli A, Bondi S, Canevari C, Tulli M, Giordano L, Di Santo D, et al. High-risk early-stage oral tongue squamous cell carcinoma, when free margins are not enough: critical review. Head Neck 2021;43:2510–22.
[17] Xu B, Salama AM, Valero C, Yuan A, Khimraj A, Saliba M, et al. The prognostic role of histologic grade, worst pattern of invasion, and tumor budding in early oral tongue squamous cell carcinoma: a comparative study. Virchows Arch 2021;479:597–606.
[18] Lee J, Ding T, Wimbiscus M, Liu D, Hicks MD, Langerman AJ, et al. Neck dissection reduces risk of recurrence in early-stage oral tongue cancer. Head Neck 2026;48:339–45.
[19] Jakab A, Zarandy L, Kocsmar I, Varkonyi T, Kenessey I, Szijarto A, et al. Local invasion patterns characterized by SARIFA and tumor budding differ and have distinct prognostic significance in esophageal adenocarcinoma and squamous cell carcinoma. Cancers (Basel) 2024;16.
[20] Foersch S, Harb N, Litmeyer AS, Roth W, Breus I, Schraml J, et al. Stroma areactive invasion front areas (SARIFA) in 1,298 pT3/pT4 colorectal cancers: a strong prognostic parameter complementing established morphological criteria. Histopathology 2025;87:464–73.
[21] Ulase D, Behrens HM, Rocken C. Stroma AReactive Invasion Front Areas (SARIFA) predict poor survival in adenocarcinomas of the stomach and gastrooesophageal junction: a validation study. Virchows Arch 2024;485:527–34.
[22] Grochowski P, Grosser B, Sommer F, Probst A, Waidhauser J, Schenkirsch G, et al. The Concept of Stroma AReactive Invasion Front Areas (SARIFA) as a new prognostic biomarker for lipid-driven cancers holds true in pancreatic ductal adenocarcinoma. BMC Cancer 2024;24:768.
[23] Enke JS, Gross M, Grosser B, Sipos E, Steinestel J, Lohr P, et al. SARIFA as a new histopathological biomarker is associated with adverse clinicopathological characteristics, tumor-promoting fatty-acid metabolism, and might predict a metastatic pattern in pT3a prostate cancer. BMC Cancer 2024;24:65.
[24] Peled M, Onn A, Herbst RS. Tumor-infiltrating lymphocytes-location for prognostic evaluation. Clin Cancer Res 2019;25:1449–51.
[25] Renehan AG, Zwahlen M, Egger M. Adiposity and cancer risk: new mechanistic insights from epidemiology. Nat Rev Cancer 2015;15:484–98.
[26] Mukherjee A, Bilecz AJ, Lengyel E. The adipocyte microenvironment and cancer. Cancer Metastasis Rev 2022;41:575–87.
[27] Peltonen J, Tiikkaja R, Ketomaki L, Taivaanlahti S, Kaakkuriniemi T, Kokkonen S, et al. Adipocytes enhance tongue cancer progression potentially via IL-6 and extracellular vesicles. Sci Rep 2025;15:41191.
[28] Iyengar NM, Kochhar A, Morris PG, Morris LG, Zhou XK, Ghossein RA, et al. Impact of obesity on the survival of patients with early-stage squamous cell carcinoma of the oral tongue. Cancer 2014;120:983–91.