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Expression of EMMPRIN as a biomarker in nonodontogenic carcinomas: a histological study

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ABSTRACT

EMMPRIN is a widely distributed cell surface glycoprotein that belongs to the immunoglobulin (Ig) superfamily. It induces the production of extracellular matrix metalloproteinases (MMPs) and plays an important role in angiogenesis via stimulation of vascular endothelial growth factor (VEGF). The aim of the present work was to assess and compare the expression of extracellular matrix metalloproteinase inducer (EMMPRIN) in different oral nonodontogenic carcinomas. Fifty-four diagnosed cases of oral nonodontogenic carcinomas were selected, and biopsies were taken from the tumor tissue, fixed, processed, and cut into sections to be stained with hematoxylin and eosin (H&E) for routine histopathological examination. Immunohistochemistry was performed for EMMPRIN. All cases showed positive EMMPRIN expression with different intensities. The results were recorded and statistically analyzed using student *t*-test, Pearson correlation, test and ANOVA test. This study concluded that elevated EMMPRIN expression is correlated with tumor proliferation, angiogenesis, metastasis, and invasion.

CLINICAL RELEVANCE

EMMPRIN expression is linked to a more aggressive type of cancer. The overexpression of EMMPRIN is a frequent and important event in the clinical behavior of head and neck cancer invasion and metastasis.

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KEYWORDS
Angiogenesis; EMMPRIN; immunohistochemistry; mestastasis; nonodontogenic carcinomas

1 Introduction

Head and neck cancer is a major health problem worldwide; approximately 263,900 new cases are diagnosed annually, and 128,000 deaths out of this malignancy occur worldwide [1]. Oral cancer is a multifactorial process with etiological factors such as tobacco, alcohol, viruses, environmental factors, and accumulation of genetic alterations [2–4]. Tumors of the oral cavity and oropharynx may be either epithelial or mesenchymal. Epithelial tumors may be classified as those originating from the epithelial lining of the oral cavity and oropharynx and those derived from salivary gland tissue. Squamous cell carcinoma (SCC) accounts for 96% of all oral cancers. It is the sixth most common cancer and causes the death of more than 8000 Americans each year. Salivary gland tumors (SGTs) are a group of heterogeneous lesions with complex clinicopathological characteristics and distinct biological behaviors [5]. SGTs are rare and represent less than 3% of all head and neck tumors [6]. Metastatic tumors in the oral region are uncommon and may occur in the jawbones or soft tissues. Approximately 1% of all oral malignancies represent tumors that have metastasized from any part of the body [7]. The most common sites of primary carcinomas are the breast and lung, followed by the kidney, prostate, thyroid, colon, and rectum [8,9]. The lung is the most common source of metastasis to the oral soft tissues, whereas the breast is the most common source for metastatic tumors to the jawbones [10,11].

EMMPRIN (*E*xtracellular *M*atrix *M*etallo*pr*oteinase *In*ducer) is a widely distributed cell surface glycoprotein that belongs to the immunoglobulin (Ig) superfamily [12]. It is expressed in numerous cells, including

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platelets, fibroblasts, T lymphocytes, and especially cancer cells [13]. Various names are used to name the same protein in different species and tissue origins, including M6 and CD147 in humans [14]; Neurothelin, 5A11, and HT7 in chickens [15]; OX-47 and CE9 in rats [16]; and gp42 in humans and mice [17].

The major function of EMMPRIN has been implicated in many biological functions, such as in the developing nervous system [18], embryo implantation, spermatogenesis, retinal development, and immune cell activation [19]. Elevated EMMPRIN expression levels are correlated with tumor proliferation, angiogenesis, metastasis, and invasion [20]. It was shown that the overexpression of EMMPRIN/CD147 in cancer tissues is associated with poor prognosis in patients with several types of solid tumors [21]. Malignant cells express (EMMPRIN/CD147) on their surfaces. It acts as a potent stimulator to produce MMPs (matrix metalloproteinases) by stromal fibroblasts and endothelial cells. This leads to destruction of the extracellular matrix to facilitate cancer cell migration, metastasis, and angiogenesis. EMMPRIN elevates urokinase plasminogen activator (uPA) and the uPA receptor of both endothelial and tumor cells, which are involved with the ECM degradation process [22]. EMMPRIN additionally upregulates VEGF (vascular endothelial growth factor) from tumor cells, which induces the expression of several MMPs in endothelial cells [23].

High expression of EMMPRIN has been observed in various human tumors and is related to cancer aggressiveness. EMMPRIN has been shown to be correlated with the prognosis of various human malignancies, such as pulmonary adenocarcinoma, salivary ductal carcinoma, prostate cancer, bladder cancer, breast cancer, and colorectal cancer [24]. It was found to be expressed in Hodgkin's lymphoma, anaplastic large-cell lymphoma, non-small-cell lung cancer (NSCLC), thyroid carcinoma, and primary cutaneous malignant melanoma [25].

The number of studies focused on EMMPRIN expression in oral carcinomas is limited, so our aim in the present study was to detect the immunohistochemical expression of EMMPRIN in different oral carcinomas and compare it.

2 Materials and methods

2.1 Biopsies

This study was carried out on 54 cases of oral malignancies. Fifteen cases (27.8%) were diagnosed with squamous cell carcinoma (SCC), 29 cases (53.7%) with salivary gland adenocarcinomas, 5 cases (9.25%) with oral melanomas and 5 cases (9.25%) with metastatic oral carcinomas at the Faculty of Dentistry, Alexandria University, and private clinics. The mean age of the recorded SCC cases was 58.1 years, with a wide range from 30 to 76 years. Eight patients (53.4%) were males, and seven patients (46.6%) were females (Table 1). The mean age of the recorded salivary gland tumors in the present study was 43.5 years, with a wide range from 17 to 74 years. Nineteen patients (65.5%) were females, and 10 (34.5%) were males. With respect to location, the most common site of occurrence was the alveolar ridge in 6 cases (40%), followed by the 5 cases of lateral side of the tongue (33.4%), and 3 cases of the buccal mucosa (20%). Among the 29 cases with malignant salivary gland adenocarcinomas, 8 (27.6%) had adenoid cystic carcinoma (ACC), and 5 (17.24%) had mucoepidermoid carcinoma (MEC). Carcinoma ex-pleomorphic adenoma (CXPA),

Table 1. Clinical data of SCC cases according to location.

Diagnosis	Age (y)/sex	Location	Presence of lymph node metastatic deposits
Poorly differentiated squamous cell carcinoma	30/F	Alveolar ridge	x
Well differentiated squamous cell carcinoma	75/M	Alveolar ridge	√
Poorly differentiated squamous cell carcinoma	60/M	Alveolar ridge	x
Moderate differentiated squamous cell carcinoma	72/M	Alveolar ridge	x
Moderate differentiated squamous cell carcinoma	70/M	Alveolar ridge	x
Well differentiated squamous cell carcinoma	73/M	Alveolar ridge	x
Well differentiated squamous cell carcinoma	63/F	Tongue	x
Poorly differentiated squamous cell carcinoma	64//F	Tongue	x
Moderate differentiated squamous cell carcinoma	33/F	Tongue	x
Well differentiated squamous cell carcinoma	51/M	Tongue	x
Moderate differentiated squamous cell carcinoma	35/F	Tongue	x
Poorly differentiated squamous cell carcinoma	76/M	Buccal mucosa	x
Moderate differentiated Squamous cell carcinoma	50/F	Buccal mucosa	√
Moderate differentiated squamous cell carcinoma	59/M	Buccal mucosa	x
Well differentiated squamous cell carcinoma	61/F	Palatal mucosa	x

Table 2. Clinical data of salivary gland adenocarcinomas.

Salivary gland adenocarcinomas	Type	Age (y)/sex	Location/lymph node metastasis if present
Adenoid cystic carcinoma	ACC	42/F	Submandibular
	ACC	61/F	Palate
	ACC	23/F	Palate
	ACC	60/M	Palate
	ACC	51/F	Palate
	ACC	52/F	Palate
	ACC	35/F	sublingual
	ACC	60/F	Palate
Mucoepidermoid carcinoma	High-grade MEC	40/M	Submandibular *(metastatic to submandibular lymph nodes)*
	High-grade MEC	72/F	Palate and alveolar margin
	High-grade MEC	50/F	Cheek
	Low-grade MEC	42/M	Cheek
	Low-grade MEC	42/F	Sublingual
Carcinoma ex pleomorphic adenoma	CXPA	31/M	Submandibular
	CXPA	48/F	Sublingual
	CXPA	25/M	Palate
Myoepithelial carcinoma	MC	44/F	Sublingual
	MC	74/M	Sublingual
	MC	22/F	Cheek
Acinic cell carcinoma	Acinic cell carcinoma	17/F	Palate
	Acinic cell carcinoma	42/M	Palate
	Acinic cell carcinoma	25/F	Palate
Salivary ductal carcinoma	SDC	55/M	Cheek
	SDC	31/F	Submandibular
Polymorphous low-grade adenocarcinoma	PLAC	48/F	Palate
	PLAC	45/M	Palate
Basal cell adenocarcinoma		35/F	Palate
Papillary cyst adenocarcinoma		46/F	Submandibular
Epimyoepithelial carcinoma		45/M	Palate

myoepithelial carcinoma (MC) and acinar cell carcinoma represented 3 cases each (10.34%). Polymorphous adenocarcinoma (PA) and salivary duct carcinoma (SDC) represented 2 cases each (6.9%). Metastatic lymph nodes ($n = 2$) were also included in the study. Finally, epimyroepithelial carcinoma, basal cell adenocarcinoma, and papillary cyst adenocarcinoma were represented by one case (3.44%) each (Table 2). In the present study, 5 cases with oral malignant melanomas were included. The mean age for the recorded cases was 58.5 years, with a wide range from 50 to 70 years. Three patients (60%) were males, and 2 (40%) were females. The most common location was the palate: 3 cases (60%), followed by the gingiva, and the buccal vestibule was presented by one case (20%). Only one case (20%) out of the 5 cases was diagnosed with amelanotic melanoma. The metastatic oral carcinomas included one case (20%) of each of the following: metastatic breast carcinoma, metastatic thyroid carcinoma, metastatic hepatocellular carcinoma, metastatic lung carcinoma, and finally metastatic carcinoma of unknown origin.

The mean age of the patients in this work was 55.8 years, with a wide range from 50 to 70 years. Three patients (60%) were males, and 2 (40%) were females. The anatomical location of the metastatic tumors in this study differed; the most common site was the alveolar mucosa, 3 cases (60%), followed by the mandible, 2 cases (40%).

The clinicopathological features of the studied cases are summarized in Tables 1 and 2. Biopsies were taken from the tumor tissue, fixed in 10% neutral buffered formalin, processed, and embedded in paraffin wax using the conventional procedures. Serial sections of 4–5 µm thickness were placed on glass slides and stained with hematoxylin and eosin (H&E) for routine histopathological examination.

2.2 Immunohistochemical staining of EMMPRIN

To avoid nonspecific staining, the sections were incubated with normal serum (the normal serum of the species in which the secondary antibody was produced) for 1 h at room temperature. The sections were then incubated with the primary rabbit polyclonal antibody EMMPRIN Glut 1 (0.5 ml) (US Biological Life Science, Massachusetts, U.S.A) and left overnight at 4 °C. The next day, all the sections were incubated with the biotinylated immunohistochemical marker of metallothionein primary mouse anti-rabbit monoclonal antibody for 1 h at room temperature, followed by incubation with avidin–biotin–peroxidase complex (ABC)

(dilution 1:100; Vector, California, U.S.A.) for 1 h at room temperature. Two sections were obtained for the positive test slides, and a third one was obtained for the negative control by omitting the primary antibody. All the sections were counterstained with Mayer's hematoxylin solution for 30 s, dehydrated in graded ethanol, cleared in xylene, and mounted in Diatex. Immunoexpression of EMMPRIN was evaluated by using an image analyzer to evaluate both the mean area percent and the mean optical density.

Area percent: This is a standard measuring frame per 10 fields using a magnification ×400 by light microscopy transferred to the monitor's screen. Areas containing the most intensely immunostained tissues were chosen for evaluation with attempts to avoid edge artifacts. These areas were masked by a binary color using the computer system to be measured.

Optical density: This density was used to measure the intensity of immunoreactivity after the image was transformed into gray mode. Areas with the maximum gray color were masked by the blue binary color. Then, the gray intensity was measured in the form of the maximum gray, minimum gray, sum of gray, and average gray values.

The intensity of EMMPRIN immunostaining was calculated in terms of the mean area percentage and mean optical density by the computer image analyzer.

The results were recorded and statistically analyzed using student *t*-test, Pearson correlation test, and ANOVA test.

3 Results

In the present study, routinely formalin fixed, paraffin-embedded 54 oral malignancy biopsies were used. This was done to detect extracellular matrix metalloproteinase inducer (EMMPRIN) expression along with the normal control.

3.1 Patterns of metallothionein immunostaining in normal salivary gland tissue

Normal salivary gland tissue showed positive immunoreactivity for metallothionein in acinar and ductal epithelial cells.

3.2 Pattern of EMMPRIN immunostaining in normal control sections

Both biopsies of normal oral mucosa ($n = 2$) showed positive immunosignals for EMMPRIN and were limited to the basal cell layer. Normal salivary gland tissue ($n = 3$) showed positive immunoreactivity for EMMPRIN in the lining myoepithelial cells.

3.3 Patterns of EMMPRIN immunostaining in SCC

Well-differentiated SCCs ($n = 5$) showed diffuse positive cytoplasmic immunosignals of EMMPRIN in malignant epithelial cells that formed keratin pearls, while the nuclei were devoid of any reaction (Figure 1a). Moderately differentiated SCCs ($n = 6$) showed positive cytoplasmic immunoreaction of EMMPRIN. The anaplastic cells formed epithelial nests, which stained positively in the membranous part and sometimes in the perinuclear areas. The nuclei did not show any staining (Figure 1b). In poorly differentiated SCC cases ($n = 4$), intense cytoplasmic EMMPRIN immunopositivity was detected in highly anaplastic malignant epithelial cells with abnormal mitotic figures (Figure 1c). The metastatic lymph nodes ($n = 2$) of SCC revealed strong positive diffuse immunosignals of EMMPRIN within keratin pearls (Figure 1d).

3.4 Patterns of EMMPRIN immunostaining in salivary gland adenocarcinomas

EMMPRIN expression was analyzed in 29 cases of salivary gland adenocarcinomas. All the cases showed positive cytoplasmic and membranous EMMPRIN immunoexpression with different intensities.

EMMPRIN expression was evident in all the examined cases of adenoid cystic carcinomas ($n = 8$). In the cribriform pattern, positive immunosignals were detected in almost all the malignant basaloid myoepithelial cells, and only a few cells were negative (Figure 2a). Meanwhile, in the tubular–trabecular pattern,

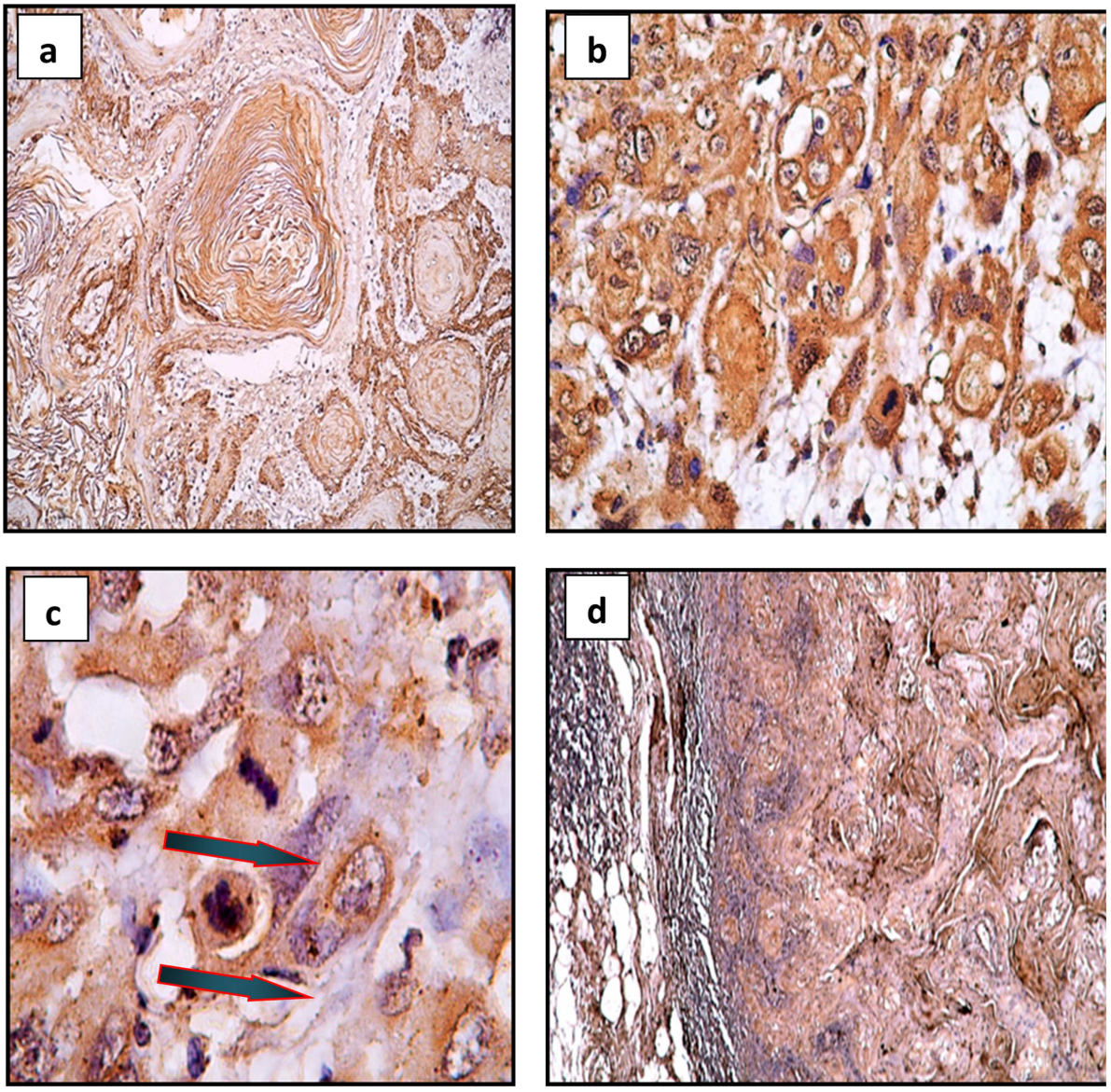


Figure 1. (a) Well differentiated squamous cell carcinoma showing diffuse positive cytoplasmic immunosignals of EMMPRIN in the malignant epithelial cells forming the keratin pearls and epithelial nests (×100); (b) moderately differentiated squamous cell carcinoma demonstrating positive immunoreaction of EMMPRIN in all the malignant cell nests (×400); (c) poorly differentiated squamous cell carcinoma revealing positive intense cytoplasmic immunosignals in the anaplastic epithelial cells. Note the abnormal mitotic figures (arrows) (×1000); and (d) metastatic lymph node of well-differentiated squamous cell carcinoma revealing strong positive diffuse immunosignals of EMMPRIN within keratin pearls (×32).

intense cytoplasmic as well as membranous staining was detected in the ductal epithelial and myoepithelial cells. The solid patterns showed intense and diffuse EMMPRIN expression in the tumor cell nests, which were invading the surrounding bony trabeculae.

Low-grade mucoepidermoid carcinomas ($n = 2$) expressed intense cytoplasmic immunoreactivity of EMMPRIN in intermediate and epidermoid cells, whereas membranous immunosignals were noted in clear and mucous-secreting cells. In high-grade MEC ($n = 3$), EMMPRIN immunopositivity was intense, particularly in all the cytoplasmic and membranous parts of the anaplastic epidermoid cells. However, the nuclei revealed negative immunoreactivity (Figure 2b).

Carcinoma ex-pleomorphic adenoma ($n = 3$) exhibited a positive expression of EMMPRIN in all examined cases. The malignant glandular epithelial cells showed intense cytoplasmic immunosignals, and some cells

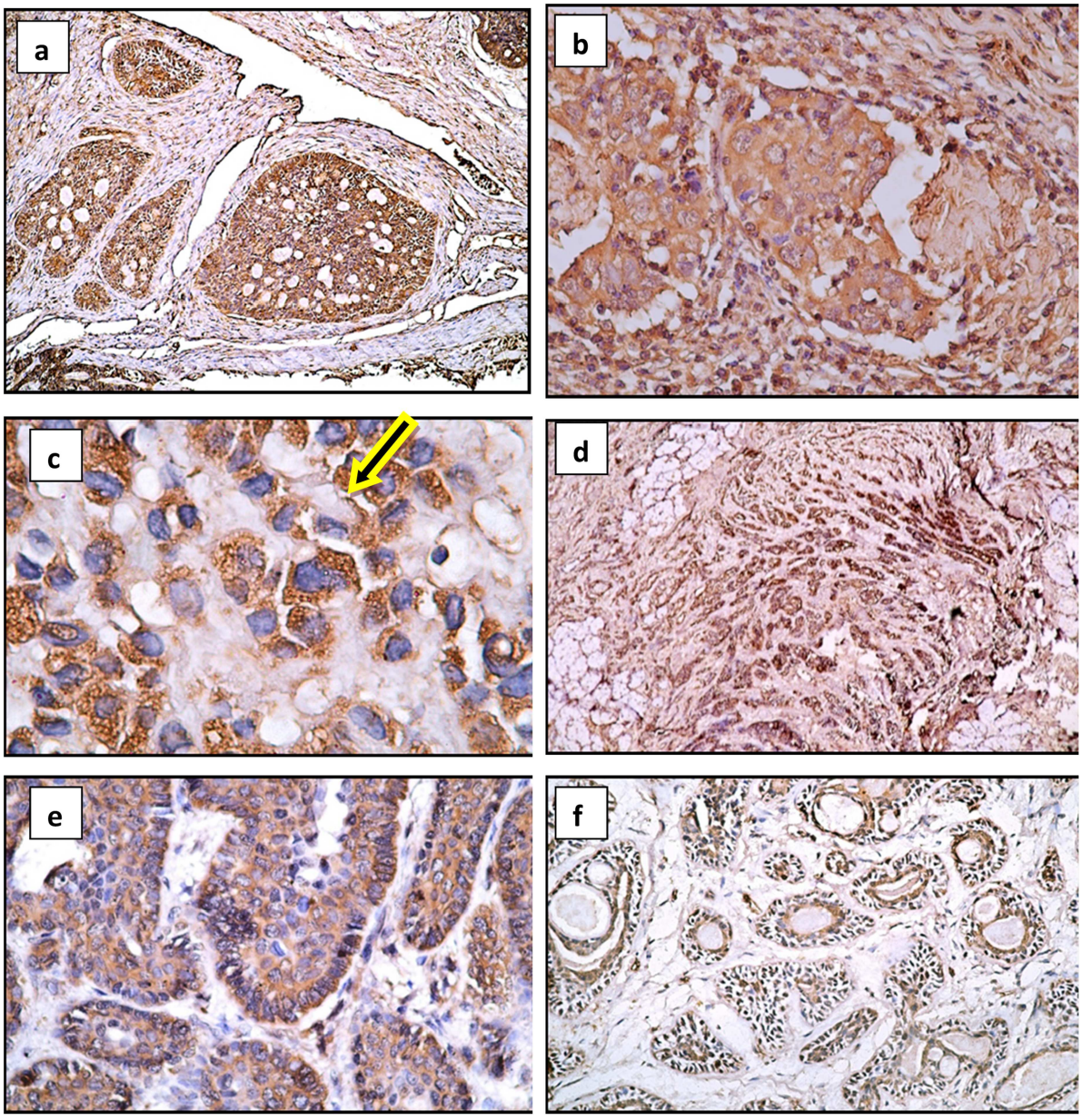


Figure 2. (a) Cribriform pattern of adenoid cystic carcinoma showing a positive EMMPRIN reaction in the cytoplasm of malignant basaloid cells (×100); (b) high-grade mucoepidermoid carcinoma showing cytoplasmic EMMPRIN immunoexpression in anaplastic epidermoid cells (×400); (c) myoepithelial carcinoma showing granular cytoplasmic immunosignals of EMMPRIN in malignant myoepithelial cells. Note that the nuclei are free from any reaction (arrow) (×1000); (d) polymorphous low-grade adenocarcinoma showing a positive reaction of EMMPRIN in malignant glandular epithelial cells (×32); (e) epimyoepithelial carcinoma revealing positive cytoplasmic immunosignals of EMMPRIN in the malignant ductal epithelial cells and clear myoepithelial cells (× 200); and (f) basal cell adenocarcinoma revealing cytoplasmic immunoexpression of EMMPRIN in the malignant glandular epithelial cells (×400).

revealed perinuclear reactions. Sheets of malignant glandular cells also showed membranous reactions, and the nuclei were devoid of any reaction.

Myoepithelial carcinoma ($n = 3$) exhibited cytoplasmic immunosignals of EMMPRIN in clear and spindle myoepithelial cells (Figure 2c).

Acinic cell adenocarcinoma (clear type) ($n = 3$) revealed membranous immunosignals of EMMPRIN in malignant clear vacuolated cells. In the present study, salivary duct carcinomas ($n = 2$) showed intense diffuse positive membranous and cytoplasmic EMMPRIN reactions in ductal epithelial cells. Polymorphous

adenocarcinoma ($n = 2$) showed positive immunoexpression of EMMPRIN in malignant glandular epithelial cells (Figure 2d). The basal cell adenocarcinoma ($n = 1$) revealed diffuse positive cytoplasmic immunoexpression of EMMPRIN in malignant tumor cells (Figure 2e). The papillary cyst adenocarcinoma ($n = 1$) revealed positive EMMPRIN cytoplasmic and membranous immunoreactivity in malignant glandular epithelial cells. The case of epimyoepithelial carcinoma ($n = 1$) showed positive immunosignals of EMMPRIN in malignant ductal epithelial cells and clear myoepithelial cells (Figure 2f).

3.5 Patterns of EMMPRIN immunostaining in oral malignant melanomas

EMMPRIN expression was analyzed in 5 oral malignant melanomas, they all showed intense positive reactions.

Oral malignant melanotic melanoma showed cytoplasmic EMMPRIN expression in the interwoven fascicle and sheets of malignant spindle melanocytes (Figure 3a).

Oral amelanotic melanoma showed positive cytoplasmic immunosignals of EMMPRIN in large bizarre rhabdoid cells and evident membranous reactions in clear malignant melanocytes (Figure 3b).

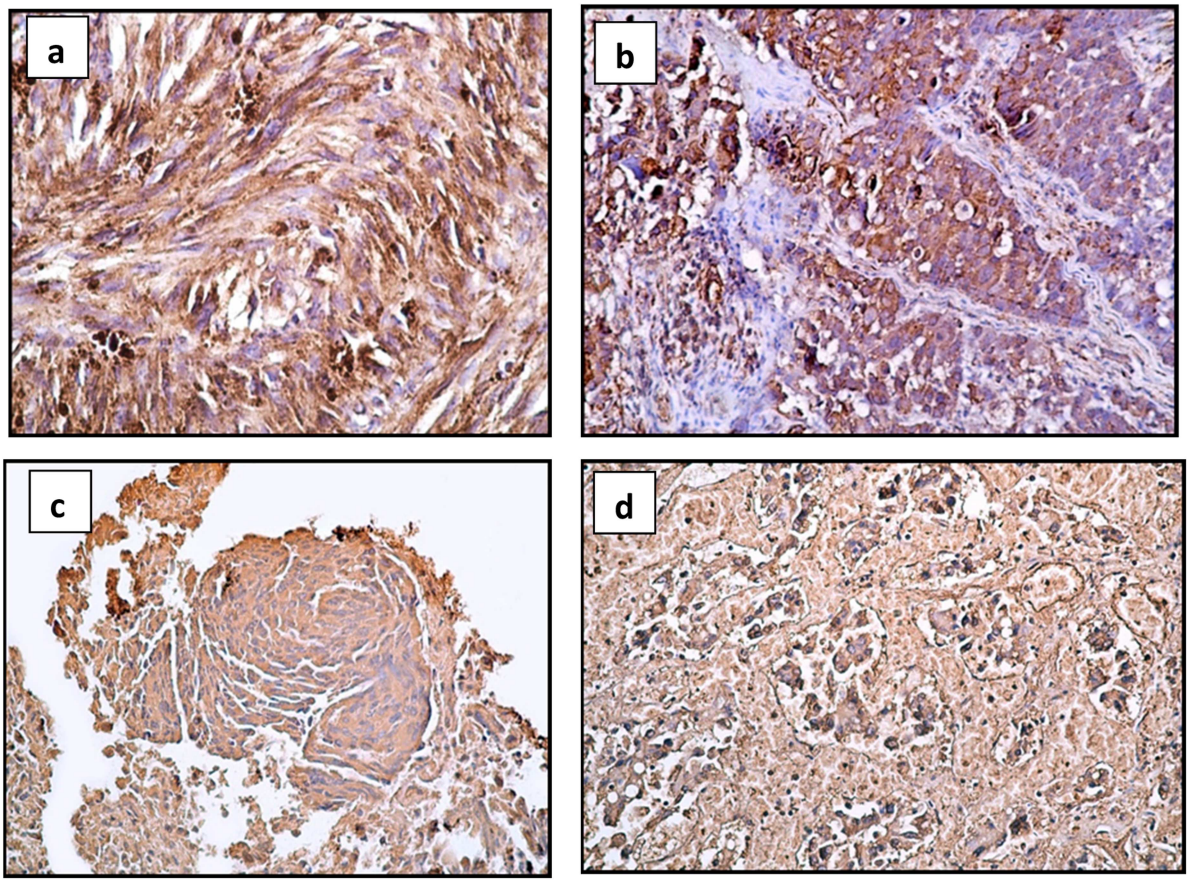


Figure 3. (a) Oral malignant melanoma exhibiting intense positive cytoplasmic EMMPRIN expression in the interwoven fascicles of malignant spindle shaped melanocytes (×400); (b) oral amelanotic melanoma exhibiting positive immunoreactions of EMMPRIN with uneven intensities in the ques of malignant melanocytes (×200); (c) metastatic breast carcinoma showing diffuse intense cytoplasmic immunosignals of EMMPRIN in the malignant glandular epithelial cells (×200); and (d) metastatic hepatocellular carcinoma revealing strong cytoplasmic immunoreaction of EMMPRIN in the malignant glandular epithelial cells enclosed within cystic spaces (×200).

3.6 Patterns of EMMPRIN immunostaining in oral metastatic carcinomas

EMMPRIN expression was analyzed in different types of oral metastatic carcinomas ($n = 5$). They all showed intense positive immunoreactions.

In metastatic breast carcinoma, intense cytoplasmic immunosignals of EMMPRIN were noted in malignant glandular epithelial cells as well as in the cytoplasm of malignant plasmacytoid cells (Figure 3c). The metastatic hepatocellular carcinoma revealed intense cytoplasmic immunoreactions of EMMPRIN in malignant glandular epithelial cells. The nuclei were free from any reaction. Abnormal mitotic figures were evident (Figure 3d). The metastatic lung carcinoma showed diffuse cytoplasmic and membranous immunosignals of EMMPRIN in the anaplastic cells. The nuclei were free from any reaction. The case of metastatic carcinoma of unknown origin showed positive strong cytoplasmic immunoexpression of EMMPRIN in the anaplastic cells.

3.7 Correlating EMMPRIN immunoexpression in different oral malignancies

Both the mean area percentage and the mean optical density of EMMPRIN in all oral malignant cases were correlated using the image analyzer computer system.

The greatest mean area percentage was recorded in the metastatic lung carcinoma (92.18 ± 6.34), whereas the lowest value was recorded in the epimyroepithelial carcinoma (48.04 ± 5.75). Regarding the optical density, the greatest value was recorded in the metastatic thyroid carcinoma (88.67 ± 2.67), while the lowest value was recorded in the basal cell adenocarcinoma (50.33 ± 12.06). Pearson's correlation test revealed a significantly positive correlation between the percentage area and the optical density of the carcinomas studied. A comparison of different nonodontogenic carcinomas (metastatic oral carcinomas, squamous cell carcinomas, and salivary gland adenocarcinomas) according to the percentage area of EMMPRIN immunoexpression revealed that the greatest mean value was in metastatic oral carcinomas (85.13 ± 4.45). The lowest value was in the salivary gland adenocarcinomas (56.96 ± 7.14). ANOVA test revealed a statistically significant difference ($p < 0.00001$). Tukey's post hoc test revealed no significant difference between metastatic oral carcinomas and oral melanoma [Table 3, Graph 1].

Different nonodontogenic carcinomas (metastatic oral carcinomas, oral melanomas, squamous cell carcinomas, and salivary gland adenocarcinomas) were compared according to the optical density of EMMPRIN immunoexpression. The greatest mean value was in oral melanomas (84.98 ± 3.77), and the lowest value was detected in salivary gland adenocarcinomas (56.96 ± 5.48). ANOVA test revealed a statistically significant difference ($p < 0.00001$). Tukey's post hoc test revealed no significant difference between metastatic oral carcinomas and oral melanoma [Table 4, Graph 2].

4 Discussion

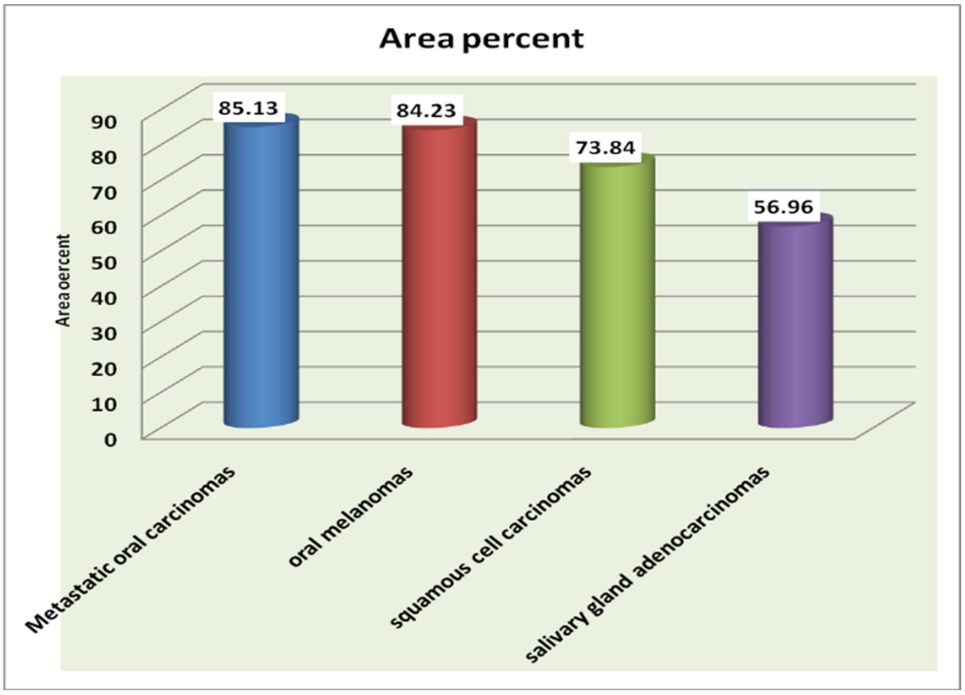
Oral cancer remains a major public health problem, with almost 300,000 new cases worldwide [1,26]. New insights into cancer diagnosis and therapy have not changed significantly; during the last decade, the survival rate of patients with oral cancer is around 50% [26]. Oral tumorigenesis is a multistep process caused by the accumulation of multiple genetic and epigenetic alterations.

The present study included 54 oral malignancies, squamous cell carcinomas, salivary gland adenocarcinomas, oral malignant melanomas, and metastatic oral carcinomas.

Table 3. Comparison between different oral malignancies (metastatic oral carcinomas, oral melanomas and squamous cell carcinomas, and salivary gland adenocarcinomas) according to the area percent of EMMPRIN immunoexpression using ANOVA test.

	Metastatic oral carcinomas (5 cases)	Oral melanomas (5 cases)	Squamous cell carcinomas (15 cases)	Salivary gland adenocarcinomas (29 cases)
Mean ± SD	$85.13^{a} \pm 4.45$	$84.23^{a} \pm 6.8$	$73.84^{b} \pm 8.56$	$56.96^{c} \pm 7.14$
F value			33.258	
p value			<0.00001*	

Tukey's post hoc test: means with different superscript letters are significantly different.
*Statistically significant.



Graph 1. Column chart showing the mean area percentage of EMMPRIN immunoexpression in different oral nonodontogenic carcinomas

Table 4. Comparison between different oral nonodontogenic carcinomas (metastatic oral carcinomas, oral melanomas and squamous cell carcinomas, and salivary gland adenocarcinomas) according to the optical density of EMMPRIN immunoexpression using ANOVA test.

	Metastatic oral carcinomas (5 cases)	Oral melanomas (5 cases)	Squamous cell carcinomas (15 cases)	Salivary gland adenocarcinomas (29 cases)
Mean ± SD	$84.62^{a} \pm 5.15$	$84.98^{a} \pm 3.77$	$73.56^{b} \pm 9.95$	$56.96^{c} \pm 5.48$
F value			46.959	
p value			<0.00001*	

Tukey's post hoc test: means with different superscript letters are significantly different.
*Statistically significant.

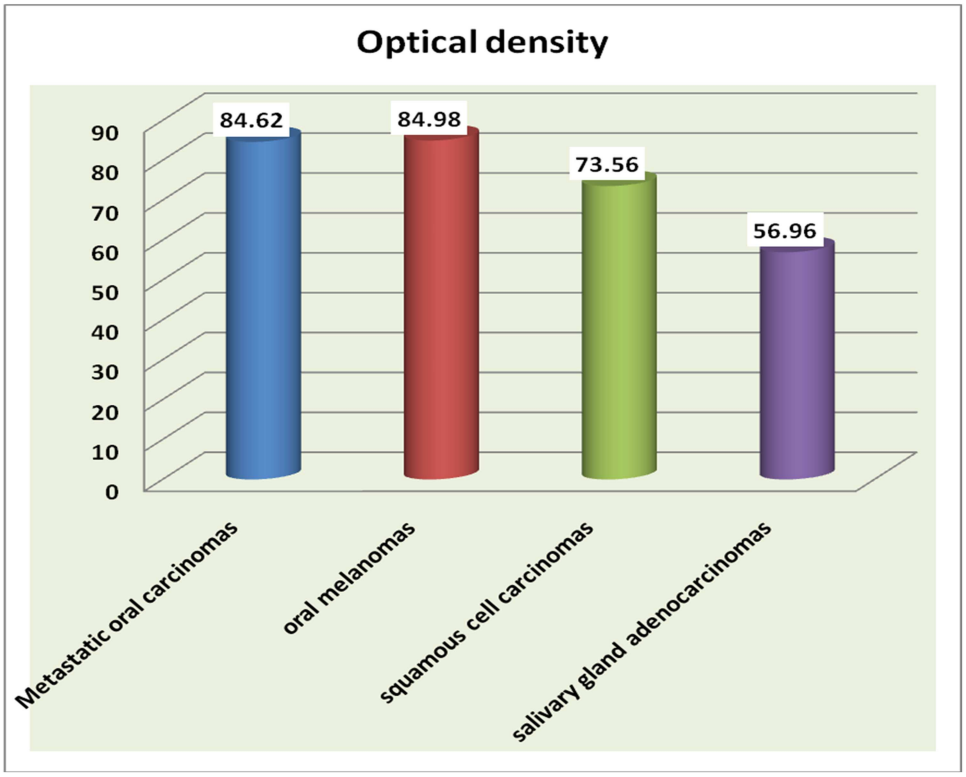
In this research, the encountered squamous cell carcinoma cases showed that the alveolar ridge was the most prevalent site of occurrence, followed by the tongue and the buccal mucosa. This may be due to the poor oral hygiene of the presented cases, as similarly reported by Effiom et al. [27].

Salivary gland adenocarcinomas are rare carcinomas. They account for 5% of all malignancies of the head and neck. They are among the most diverse cancers with different histological subtypes and a wide range of biological behaviors [28].

The clinicopathological results of the present research showed that 65.5% of salivary gland adenocarcinomas affect the minor salivary glands, especially in the palate, while the remainder of these adenocarcinomas are present in the major salivary glands with a predilection to the submandibular gland. These findings are consistent with those of Eveson et al. [29].

The present work encompassed a limited number of metastatic oral carcinomas due to the rarity of these lesions, with most of the lesions affecting the gingiva, while those found in the jaws constituted 40% of the examined cases.

An increasing body of evidence suggests that extracellular matrix metalloproteinase inducer (EMMPRIN), a transmembrane glycoprotein present on the surface of tumor cells, might play a crucial role in the progression of carcinomas [30]. It induces angiogenesis, tumor invasiveness, and multidrug resistance depending on stimulation of VEGF and the ability of MMPs to overcome natural barriers such as the basement membrane and to spread locally and subsequently reach lymphatic and blood vessels and



Graph 2. Column chart showing the mean optical density of EMMPRIN immunoexpression in different oral nonodontogenic carcinoma.

metastasize. It elevates urokinase-type plasminogen activator (uPA), which is important in tumor progression [31].

In the present work, the expression of EMMPRIN was evaluated in oral malignancies such as squamous cell carcinomas, salivary gland adenocarcinomas and malignant oral melanomas, as well as in metastatic carcinomas. EMMPRIN immunoexpression has also been studied in normal salivary gland tissue, normal mucosa, and squamous cell papilloma.

All the examined normal mucosa specimens showed positive cytoplasmic EMMPRIN immunosignals only in the basal cell layer. This is consistent with the findings reported by Siu et al. [32], Ayva et al. [33], and Vigneswaran et al. [34].

In the present study, EMMPRIN immunoexpression was evaluated using the computer image analyzer. All the examined SCC cases revealed high expression of EMMPRIN. The immunopositivity was observed in the cytoplasm and membranes of malignant epithelial cells, in concordance with previous studies [35]. Our examined SCC (moderate and poorly differentiated type) as well as metastatic SCC to lymph nodes showed statistically significant overexpression of EMMPRIN more frequently than the well-differentiated type, as reported by Riethdorf et al. [36]. This finding indicates that EMMPRIN might play an important role in SCC progression and invasion.

A positive association of EMMPRIN expression with histological grade in SCC was found [37], where moderately and poorly differentiated tumors presented with EMMPRIN expression more often than well-differentiated tumors. According to their view, such glycoprotein overexpression occurs during the early steps of oral carcinogenesis and contributes to the process of tumorigenesis, and this marker may serve as a reliable biological marker to identify high-risk subgroups. These findings agree with the findings of the present work. This finding suggests that increased EMMPRIN expression could be a negative prognostic factor in SCC.

Although EMMPRIN expression has been studied in several glandular malignancies [36], very few studies have evaluated EMMPRIN immunoexpression in salivary gland adenocarcinomas. The role of EMMPRIN in these tumors remains to be elucidated.

To the best of our knowledge, this is the first study to evaluate the intensity of EMMPRIN in different types of salivary gland adenocarcinomas using the computer image analyzer, which allows definite comparison between different salivary gland adenocarcinomas. The greatest mean value of the percentage area of EMMPRIN immunoexpression was detected in the high-grade mucoepidermoid carcinoma cases and the lowest value was detected in the epimyoepithelial carcinoma. This agrees with the WHO classification, which clarifies epimyroepithelial carcinoma and mucoepidermoid carcinomas as low-grade and high-grade salivary gland adenocarcinomas, respectively [28].

In the present study, high-grade mucoepidermoid carcinomas showed stronger EMMPRIN immunoexpression than those of low grade. These results were statistically significant according to the area percent, in agreement with the work of Seethala et al. [38].

Histologically, adenoid cystic carcinomas are categorized into three types: cribriform, tubular, and solid. The solid pattern is known to be much more aggressive than the other two types [28]. In the present study, the solid pattern showed the highest EMMPRIN immunoexpression, representing a more aggressive behavior of the solid type than the other two types, a finding that is consistent with that of Yang et al. [39].

Salivary ductal carcinoma is one of the most aggressive types of salivary gland adenocarcinoma, with a marked tendency toward distant metastases and local recurrence [40]. In our study, all the salivary ductal carcinoma cases showed intense cytoplasmic and membranous EMMPRIN immunoexpression whether *de novo* or on top of the pleomorphic adenoma. Surfing the literature revealed only one study, performed by Piao et al. [41], that investigated the immunoexpression of this protein in salivary ductal carcinomas. They found strong expression of EMMPRIN in all *de novo* SDC cases. This finding is in accordance with the results of the present research.

Once more, to the best of our knowledge, no previous studies have evaluated EMMPRIN expression in various salivary gland adenocarcinomas, polymorphous adenocarcinoma as well as myoepithelial carcinomas. In these tumors, EMMPRIN immunoexpression was evaluated using the computer image analyzer. They differ in their expression because of their significantly different biological behaviors, and polymorphous adenocarcinomas showed relatively lower expression than carcinomas ex pleomorphic adenomas and myoepithelial carcinomas.

In the present study, all the examined cases of acinic cell carcinoma showed positive EMMPRIN immunoexpression agreeing with Riethdorf et al. [36].

Epimyoepithelial carcinoma and basal cell adenocarcinoma showed relatively lower immunoexpression than the other salivary gland adenocarcinomas. They are considered low-grade salivary gland adenocarcinomas [38]. However, papillary cyst adenocarcinoma showed higher EMMPRIN immunoexpression than other salivary gland adenocarcinomas because of its aggressive nature [28].

In this study, high-grade mucoepidermoid carcinomas showed the highest percentage area of EMMPRIN expression, followed by salivary ductal carcinomas and finally solid AC, indicating the aggressive nature of these tumors [40].

All the examined cases of oral malignant melanoma showed intense cytoplasmic and membranous immunoexpression when compared with other types of nonmalignant tumors. This finding accords with those of Kanekura et al. [42] study on cutaneous malignant melanomas, and several other studies that have demonstrated that EMMPRIN plays an important role in the invasion and metastasis of several types of glandular malignancies [36].

Although EMMPRIN has been widely studied in various human carcinomas, its immunoexpression has not been studied before in metastatic oral carcinomas. In the present work, expression of EMMPRIN was intensely expressed in metastatic carcinomas to the oral cavity, such as metastatic thyroid, lung, breast, hepatocellular, and metastatic carcinomas of unknown origin. This finding is similar to the results of several investigators who studied EMMPRIN immunoexpression in metastatic thyroid [43], lung [44], breast, and hepatocellular carcinomas [45]. Our results are similar to the findings of Feng et al. [46], who studied malignant tumors, including esophageal cancer, cervical cancer, lung cancer, ovarian cancer, and hepatocellular carcinoma. They reported that EMMPRIN expression was significantly higher in tissues of poorly differentiated and lymph node metastasis. These findings indicate that EMMPRIN may be a prognostic indicator for highly malignant tumors.

In summary, a correlation study of EMMPRIN immunoexpression in different oral malignancies (squamous cell carcinomas, salivary gland adenocarcinomas, oral malignant melanomas, and metastatic oral

carcinomas) was performed. There was an interesting difference in both intensity and distribution among different oral carcinomas. A statistically significant positive correlation was identified between the EMMPRIN immunostaining scores in different oral nonodontogenic carcinomas. The greatest immunoexpression of this protein was detected in metastatic oral carcinomas and oral melanomas. The lowest value was detected in the salivary gland adenocarcinomas. However, no significant difference between metastatic oral carcinomas and oral melanomas was found.

Recent literature continues to support the role of EMMPRIN as a key facilitator of tumor progression in oral malignancies. A comprehensive review by Khan et al. emphasized that EMMPRIN is not only overexpressed in oral squamous cell carcinomas but also actively contributes to extracellular matrix degradation, angiogenesis, and tumor cell invasion through the upregulation of the matrix metalloproteinases (MMPs) and VEGF pathways [47]. This aligns with our findings, particularly the elevated expression observed in high-grade and metastatic oral carcinomas, reinforcing the hypothesis that EMMPRIN may serve as a reliable biomarker for tumor aggressiveness and metastatic potential in nonodontogenic oral cancers.

The limitations of our study are the relatively small sample size, besides the descriptive nature of the study.

5 Conclusion

The main message of our study was that EMMPRIN expression is linked to a more aggressive type of cancer. The overexpression of EMMPRIN is a frequent and important event in head and neck cancer invasion and metastasis; therefore, its use as a biomarker might prove useful for confirming the clinical diagnosis of oral cancer as well as the classification and staging of cancerous behavior in oral tissues.

Author contributions

The manuscript has been read and approved by all the authors, the requirements for authorship have been met, and each author believes that the manuscript represents honest work. (The first author conducted the lab experiments, the second author designed the study, third author analyzed the data, the fourth author supervised the work and revised the manuscript).

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Compliance with ethical standards

We certify that our study and experiments were performed in compliance with the highest standards of research ethics.

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