



ORIGINAL ARTICLE

# Lymphangiogenesis and angiogenesis in oral cavity and lower lip squamous cell carcinoma<sup>☆</sup>



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## KEYWORDS

Pathological neovascularization; Lymphangiogenesis; Lip; Mouth; Squamous cell carcinoma

## Abstract

**Introduction:** Tumors of the lip and oral cavity differ in various aspects; therefore a clarification of the distinctions among these sites may help to better understand the biologic behavior of neoplasms occurring in these locations.

**Objective:** Considering that angiogenesis and lymphangiogenesis are two major elements that can influence various aspects of tumor biology, we aimed to compare these factors between squamous cell carcinoma of the lower lip and oral cavity.

**Methods:** A total of 84 primary squamous cell carcinomas including 45 oral and 39 lower lip tumors were selected and immunohistochemically stained with monoclonal antibody against D2-40 and CD105. Mean microvessel density was assessed in tumoral tissue, while lymphatic vessel density was calculated in both neoplastic tissue and invasion front. Data were statistically analyzed using *t*-test and *p*-values of <0.05 were considered significant.

**Results:** We found a mean microvessel density  $\pm$  standard deviation of  $31.94 \pm 18.9$  in oral cavity and  $27.54 \pm 20.8$  in lower lip squamous cell carcinomas, with no significant difference ( $p = 0.32$ ). Mean lymphatic vessel density  $\pm$  standard deviation was  $13.05 \pm 8.2$  and  $16.57 \pm 10.79$  in of oral cavity and lower lip neoplastic tissue, respectively. The corresponding values were  $9.94 \pm 5.59$  and  $12.50 \pm 7.8$  in the invasive front. Significant differences were not observed in either of the lymphatic vessel density variables between the two sites.

**Conclusion:** According to our results, it seems that the search for additional factors other than those related to the vasculature should continue, to help clarify the differences in biologic behavior between lower lip and oral cavity squamous cell carcinomas.

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**PALAVRAS-CHAVE**

Neovascularização  
patológica;  
Linfangiogênese;  
Lábio;  
Boca;  
Carcinoma de células  
escamosas

**Linfangiogênese e angiogênese em carcinomas de células escamosas de lábio inferior e da cavidade oral****Resumo**

**Introdução:** Os tumores de lábio e da cavidade oral diferem em vários aspectos; portanto, o conhecimento das diferenças entre eles pode ajudar na melhor compreensão do comportamento biológico das neoplasias que ocorrem nesses locais.

**Objetivo:** Considerando que a angiogênese e a linfangiogênese são dois elementos importantes que podem influenciar diversos aspectos da biologia dos tumores, objetivamos comparar esses fatores entre o carcinoma de células escamosas (CCE) de lábio inferior e da cavidade oral.

**Método:** No total, foram selecionados 84 CCEs primários (45 tumores da cavidade oral e 39 tumores de lábio). Esses tumores foram corados por processo imuno-histoquímico com anti-corpo monoclonal anti-D2-40 e CD105. Avaliamos a densidade média de microvasos (DMV) no tecido tumoral, enquanto que a densidade vascular linfática (DVL) foi calculada tanto no tecido neoplásico como no *front* de invasão. Os dados foram estatisticamente analisados com o uso do teste *t* e valores de  $p < 0,05$  foram considerados significantes.

**Resultados:** Chegamos a uma média para DMV  $\pm$  DP de  $31,94 \pm 18,9$  para CCEs na cavidade oral e de  $27,54 \pm 20,8$  no lábio inferior, sem diferença significativa ( $p = 0,32$ ). As médias para DVL  $\pm$  DP foram de  $13,05 \pm 8,2$  e  $16,57 \pm 10,79$  no tecido neoplásico da cavidade oral e lábio inferior, respectivamente. Os valores correspondentes foram  $9,94 \pm 5,59$  e  $12,50 \pm 7,8$  no *front* invasivo. Não foram observadas diferenças significantes nas duas variáveis DVL entre os dois locais.

**Conclusão:** De acordo com os nossos resultados, a pesquisa por fatores adicionais, além daqueles relacionados à vasculatura, deve ter continuidade, para auxiliar no esclarecimento das diferenças do comportamento biológico entre CCEs no lábio inferior e na cavidade oral.

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**Introduction**

Squamous cell carcinomas (SCCs) originate from epithelial cells of various organs and their biologic behavior depends on different factors, one of which is the anatomic location of the tumor.<sup>1</sup> A good example of this fact is the considerable etiologic and prognostic differences between SCCs of the lip and oral cavity, with lip neoplasms demonstrating a lower tendency toward regional lymph-node metastasis and a higher survival rate of approximately 90%.<sup>2,3</sup>

Many factors are involved in the etiopathogenesis of SCC. Contrary to SCC of the oral cavity where tobacco use is the most well-known etiologic factor, chronic exposure to sunlight has been suggested as an important element in SCC of the lower lip, which is known to receive more ultraviolet radiation than the upper lip.<sup>2,4,5</sup> Recent studies have shown that the expression of some markers related to tumor microenvironment and neoplastic cells of lip SCCs are different from those of the oral cavity.<sup>2,3</sup> Therefore, it seems that the differences between these sites are not limited to etiology and prognosis, but may also be related to molecular factors associated with their stroma and cellular structures.<sup>2,3</sup> Consequently, a number of investigators believe that SCC of the lip should be regarded as a separate entity and be evaluated as such. On the other hand, some cellular-molecular studies on these locations have not shown any biological difference in the evaluated markers.<sup>6,7</sup>

Angiogenesis is an important and fundamental process in the progression and metastasis of malignancies. Before

1960, researchers believed that nutrition and blood supply of neoplastic tissues were simply provided through dilation of blood vessels available in the tumor. Subsequent studies revealed that angiogenesis, the formation of new blood vessels, is vital to the growth and propagation of malignancies.<sup>8</sup> Development of a network of new blood vessels in the tumor is essential to provide nutrients and oxygen and remove waste products. For the initiation of angiogenesis, various molecules are released from malignant cells, which send signals to the surrounding host tissues. This may result in the activation of certain genes, followed by protein production, leading to the induction of angiogenesis.<sup>9,10</sup>

Lymphangiogenesis is the formation of new lymphatic vessels from pre-existing vasculature and similar to angiogenesis has several induction mechanisms.<sup>11</sup> The growth of lymphatic vessels occurs in a variety of normal and pathologic processes like wound healing, inflammation, and progression of malignancies.<sup>12,13</sup>

SCC of the oral cavity and lip have been separately evaluated in terms of angiogenesis and lymphangiogenesis, and various reports exist on the association of these processes with the prognosis and invasion of SCC.<sup>14–16</sup> However, a limited number of studies with conflicting results have compared angiogenesis and lymphangiogenesis between these sites.<sup>17,18</sup> It is noteworthy that in these investigations, SCC of both upper and lower lips have been grouped together and evaluated as a single entity. Considering that the lower lip SCC has not been exclusively evaluated in comparison with SCC of the oral cavity and the important differences between upper and lower lip tumors,<sup>19</sup> we aimed to

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