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Pattern of invasion of oral squamous cell carcinoma and its relation to the presence of nodal metastases – a review

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Summary

Squamous cell carcinomas of the oral cavity represent the largest group of malignancies in this area. Currently, there are many prognostic histopathological factors, according to which the maxillofacial surgeon in collaboration with the oncologist is able to determine the prognosis and subsequently also set an appropriate therapy. Nowadays, the squamous cell carcinoma invasion pattern in the area of the "invasive tumor front" seems to be a very important prognostic factor. The invasion pattern is connected to metastatic potential (and to the presence of subclinical microscopic metastases) and may well be the answer to why even early-stage tumors do not respond to standard therapy. That is to say, based on varying invasion pattern, oral cavity squamous cell carcinomas with identical TNM manifest varying clinical behavior and growth tendencies and a varying metastatic potential.

Key words

squamous cell carcinoma of the oral cavity – pattern of invasion – metastatic potential – submicroscopic metastases – invasive front – prognosis – worst pattern of invasion (WPOI)

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Introduction

Oral cavity tumors represent 2% of all malignancies and they are the cause of nearly 180,000 deaths per year worldwide [1]. However, their incidence manifests a significant geographical variability. In Papua New Guinea, and Central and South Asia, oral cavity tumors are actually the most common cause of death in general, which can be explained by the consumption of betel nut, which is highly popular among the local population. In these geographical latitudes, oral cavity carcinomas account for up to 1/3 of all cancers [2,3]. In European countries, these carcinomas are the most prevalent in France and Hungary and they even represent the second most common type of cancer in the male population [4].

Squamous cell carcinoma is the most common of all malignant tumors of the oral cavity [5]. Squamous cell carcinoma accounts for up to 95% of all head and neck cancers, and its 5-year survival rate ranges from 50 to 60% [6].

The prognosis and treatment type depends on many factors, the most important being the staging, i.e. the TNM classification, which can be determined preoperatively on the basis of a combination of clinical examination and imaging methods that can predict 60–70% of nodal metastases, which are frequent metastases for this type of tumor [7,8]. If the oral cavity and oropharyngeal squamous cell carcinomas metastasize, the cervical lymph nodes are affected most often [9]. The presence or absence of lymph node metastases is an important factor that determines the survival and prognosis of patients suffering from oral cavity and oropharyngeal squamous cell carcinomas [10–13]. The presence of nodal metastases reportedly reduces the overall survival by up to 50% [12,14,15].

In the case of early-stage squamous cell carcinomas of the oral cavity (T1-T2N0M0), the presence of nodal metastases is not expected; the distance of the tumor from the resection margins, which determines the necessity of postoperative adjuvant therapy (radiotherapy, chemotherapy or their combination) is the decisive factor. Ideally, the surgeon is trying to reach a free margins resection (R0) so that the distance between the tumor mass margin and the healthy tissue is > 5 mm in squamous cell carcinomas of the oral cavity (Fig. 1).

Extirpation of the tumor into macroscopically healthy tissue, often accompanied by an elective cervical dissection,

Fig. 1. Resected tumor of the floor of the oral cavity. A surgeon is trying to reach free margins of resection (R0) so that the distance between the tumor mass margin and the healthy tissue is > 5 mm.

is the main type of therapy for these carcinomas [10,11]. However, in the case of some tumors (T1-T2N0), standard treatment may not be successful depending on the pattern of the invasive tumor front [16,17].

One of the reasons for this treatment failure is the fact that a certain percentage of patients (5–40%) develop occult (sometimes also referred to as subclinical) nodal metastases already in the early stages of the oral cavity carcinoma (T1-2N0M0) [10,12,18,19]. These metastases are impossible to detect clinically or radiologically due to their very small size. The only way to detect them is to use light microscopy, i.e. detection is only possible postoperatively after a block neck dissection [12,18,20]. However, some occult metastases may also be "submicroscopic" in size, i.e. they remain unseen even to a light microscope during standard hematoxylin and eosin staining. Their largest dimension usually ranges from 0.2 to 2 mm, and submicroscopic metastases < 0.2 mm in the largest dimension are then referred to as isolated tumor cells (ITC) [21,22]. These can be detected immunohistochemically and/or using molecular analysis, but these methods are not routinely used in common practice [12,18–20,22]. Determination of the invasion pattern by a pathologist may be a definite and a rather important clue to the presence of nodal metastases in early stages of cancer [23,24]. On the basis of the available information, the pattern of invasion seems to be closely related to the very presence or absence of nodal metastases [8,16,17,23–25]. In contrast to submicroscopic occult metastases, the pattern of invasion can also be determined from excision biopsy specimen stained with hematoxylin and eosin [18].

Fig. 2. A patient with oral squamous cell carcinoma of the floor of the mouth, cT2-3.

The sources for this manuscript were mainly searched in Medline database, specifically from the articles published between 1989 and 2021. Key words for searching were oral squamous cell carcinoma and pattern of invasion. Articles that did not address the issue were excluded. Additional published sources were retrieved by searching the bibliography of major articles on the topic (Fig. 2).

Discussion

An invasion pattern refers to the way in which the tumor tissue infiltrates the surrounding tissue [26]. When assessing the pattern of invasion, the histopathologist focuses on the "invasive front" of the tumor, which may have the following appearance:

1) "broad" tumor front – when viewed under microscope, the tumor is quite clearly separated from the host's tissue, it pushes the tumor margin "broadly";
2) finger-like protrusions – the invasive tumor front invades the surrounding tissue in the form of finger-like protrusions;
3) tumor cell islets with >15 cells per islet;
4) tumor cell islets with <15 cells or individual tumor cells;

5) satellite tumor cells separated from the invasive tumor front by a distance of > 1 mm.

These five patterns of invasion can be classified into three groups: cohesive (invasion patterns 1–3), non-cohesive (invasion pattern 4), and widely dispersed (pattern 5), referred to as the "worst pattern of invasion" in English literature [26,27].

In the course of determination of the subsequent therapy in bulky oral cavity and oropharyngeal squamous cell carcinomas, tumor staging, which is nowadays essential despite the available histopathological, biochemical or immunochemical markers, is of the utmost importance [13,25]. On the other hand, in early stages of oral cavity and oropharyngeal tumors (T1-2N0M0), it is advisable to focus on other criteria (especially the histopathological ones) as well. These other criteria include the aforementioned invasion pattern – it is the criterion which is the best in predicting the metastatic potential of oral cavity squamous cell carcinomas [8,16,17,23–26, 29]. The advantage of this histopathological marker lies in its possible detection already from a biopsy specimen stained only with hematoxylin and eosin [25]. In these cases, classical staging is often insufficient to determine the prognosis of the disease, because in these early stages, some patients have already developed occult neck metastases that cannot be detected by any clinical or radiological examination [12,18,20]. Sometimes, it is even impossible to detect them in a standard biopsy specimen stained with hematoxylin and eosin; in such cases, these metastases are referred to as submicroscopic [18,19,22,30]. We can learn information about the metastatic potential (the ability and willingness of a tumor to metastasize, even submicroscopic ones) of a tumor just from the very area of the invasive tumor front. For this, the invasion pattern needs to be determined by a histopathologist. Based on the pattern, a clinician is then able to modify, and, if necessary, radicalize the therapy [17,24]. In effect, this means that squamous cell carcinomas with identical staging can and often do exhibit different clinical behaviors and growth patterns [24,28,29].

To determine the prognosis of oral cavity squamous cell carcinomas, a number of markers have been identified in the past, which were referred to as prognostic factors (depth of invasion, perineural invasion, distance of the tumor from the excision margins), but none of them has been completely reliable [28,29,31,32]. According to more recent findings, when assessing the pattern of tumor invasion and thus its aggressiveness, the histopathologist focuses on the "invasive front" of the tumor (from which the invasion pattern can be determined). On the basis of the available information, it seems that the most relevant information regarding the aggressiveness of the tumor and thus also the likely presence of nodal metastases, which is closely related to prognosis, can be acquired from the invasive front of the tumor [17,23,27,31,33–35] The invasive tumor front consists of 3–6 layers of cells or several islands or clusters of tumor cells at the tumor margin [36]. The most aggressive cells are located here, and the tumor is less differentiated than its other parts [32,36–40]. At the area of the invasive front, a histopathologist can detect other characteristics besides the pattern of invasion, including the degree of keratinization, the presence and extent of lymphocytic-plasmocytic infiltration, and nuclear polymorphism. Even though these characteristics can also be learned from the central parts of the tumor, they once again (similarly to the invasion pattern) have the greatest informative value in the area of the invasive front and they can also be connected to the prognosis of the cancer [27–29, 34,41].

Changes at the cellular level can be detected in the area of the invasive front of the tumor, which then lead to easier metastases of squamous cell carcinomas. The most important of these changes include loss of tumor cell adhesion (classified by invasion pattern – cohesive, non-cohesive or widely dispersed – see above), followed by a secretion of proteolytic enzymes, increased cell proliferation, and angiogenesis [38,39]. Multiple invasion patterns may be represented in the invasive front – the worst of these

Fig. 3. Oral squamous cell carcinoma of the floor of the mouth.

patterns is always considered in the classification [17].

In the invasive front of the tumor, we encounter increased secretion of the laminin glycoprotein, for example. On the surface of oral cavity squamous cell carcinoma cells, there are receptors for laminin, which trigger the secretion of enzymes upon binding of this protein. These enzymes then induce a rupture of the basement membrane by destruction of collagen IV and degradation of the aforementioned laminin. This process facilitates the invasion of tumor cells into the surrounding tissue [42]. Disruption of basement membrane integrity is essential for tumor invasion into the surrounding area and for metastatic spread (Fig. 3).

Secretion of the tenascin protein may also be increased at the invasive tumor front [24,43]. Increased tenascin production occurs physiologically during embryogenesis at the junction of epithelium and mesenchyme. At the time of embryogenesis, it is important for proper cell differentiation, motility, and cell proliferation [43]. If it is produced by tumor cells, the tumor is less differentiated, the tumor cells adhere to each other less (tenascin has "anti-adhesive effects"), thus a non-cohesive or widely dispersed invasion pattern in the invasive tumor front is more common when the expression of tenascin is increased [8,24,43,44].

Other changes at the molecular level in the invasive front include decreased synthesis of syndecan-1. It belongs to a group of proteoglycans found on the surface of cells. Syndecan-1 is mainly involved in cell adhesion. In a number of tumors (including oral cavity squamous cell carcinomas), we may encounter decreased expression of syndecan-1. Decreased expression of this glycoprotein correlates with the invasion pattern and thus with tumor prognosis. The lower the expression of syndecan-1, the lower the cell adhesion and the worse the invasion pattern. Therefore, tumors with lower syndecan-1 expression have a worse prognosis – they metastasize more frequently and more willingly [8,24,45].

Cortactin synthesis is another change at the molecular level that correlates with prognosis. Cortactin is a protein which plays a role in cell motility and invasion. Its increased expression means higher tumor aggressiveness, higher metastatic potential and therefore a worse prognosis [24,46]. Decreased expression of fibronectin is also common; fibronectin belongs among high-molecular-weight glycoproteins and it is involved in a number of processes at the cellular level – cell adhesion and migration. Its decreased expression in the cells of the invasive tumor front allows easier spreading of tumor cells, which once again results in a higher metastatic potential [24,47].

For this very reason, it is important to focus on the invasive front of the tumor; based on the front, we are able to determine the metastatic potential and adapt the therapy correspondingly [8,17,48].

Conclusion

The TNM classification is important in determination of the prognosis of oral cavity and oropharyngeal squamous cell carcinomas. However, the classification itself does not provide a lot of information about the prognosis of the tumor, as it has been shown recently. Therefore, it is advisable to take several markers into consideration – the invasion pattern belongs among the most important ones. The advantage of this marker lies in its easy detection by the histopathologist even from a sample commonly stained with hematoxylin and eosin. On the basis of this marker, we can predict the metastatic potential of squamous cell carcinomas of the oral cavity and oropharynx with relatively high probability. The metastatic potential may be high even in early stages (T1-T2N0M0). In these stages, occult (subclinical) metastases in the cervical lymph nodes may already be present.

When determining the invasion pattern, the histopathologist focuses on the areas in the "invasive front" of the tumor, in which the least differentiated tumor cells can be found. If more than one invasion patterns are present in the invasive tumor front, the worst of them is considered to be the decisive one. Therefore, it is advisable to include the deepest possible part of the tumor into the sample already at the time of diagnostic excision. From such a sample, a pathologist is already able to make a preoperative statement on the area of the invasive tumor front. Diagnostic excision from suspicious tumorous tissue should be biopsied with first signs of a malignant lesion. Many changes at the molecular level occur in the area of the invasive front of squamous cell carcinomas of the oral cavity and oropharynx. However, these do not need to be identified and defined in order to determine prognosis because most of them will be reflected in the very invasion pattern. This means that unfavorable changes at the molecular level (such as the increased laminin production, decreased syndecan-1 expression, increased cortactin synthesis, etc.) will be reflected in an unfavorable invasion pattern and vice versa, i.e. by a lower tumor cell cohesion and easier spread of tumor cells. The unfavorable pattern of invasion (widely dispersed pattern, non-cohesive) is then manifested by a higher metastatic potential of oral cavity squamous cell carcinomas. In such a case, it is advisable to radicalize the therapy even in early stages (T1-T2N0M0) of squamous cell carcinomas of the oral cavity and oropharynx.

Whether it is necessary to increase the distance of the resection margins from healthy tissue in patients with unfavourable invasion type is still unclear. Currently, the minimum distance of tumour margins from healthy tissue is recommended to be 5mm in oral squamous cell carcinomas. Further research is needed in this area. However, based

on the findings presented in this article, we anticipate that these patients will require more radicality in both surgical and subsequent oncologic treatment.

Roles of authors

Kateřina Kopecká – first author, performed majority of literature research, and wrote the whole manuscript;
Richard Pink – a co-author, designed the whole conception of this article, performed literature research and critically reviewed the article.

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