Understanding the Surgical Margin
A Molecular Assessment

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KEYWORDS

• Molecular margins • Head and neck malignancy • p53 mutation • Field cancerization

KEY POINTS

- The theories of minimal residual cancer and field cancerization can help to explain reasons for tumor recurrence despite negative histologic surgical margins.
- Histologically benign tissue adjacent to premalignant lesions have genomic alterations.
- Molecular information can help improve outcomes in surgical margin analysis not able to be detected on hematoxylin and eosin frozen section.
- Human papillomavirus (HPV)-negative tumors display a twofold increase in mutations relative to HPV-positive tumors.

SURGICAL RESECTION OF HEAD AND NECK CANCERS

Head and neck cancer is a broad term for malignancies developing in the epithelial cells lining the oral cavity, pharynx, and larynx. In the United States, there are estimated 59,000 new incidences of head and neck squamous cell carcinoma (HNSCC) diagnosed, with approximately 12,000 related deaths, in 2015 alone.[1] On diagnosis, factors including tumor location, staging, and the patient's age and health status are assessed to determine the best modality of treatment for individual patients, with most treated via surgery.[2] The central tenet of surgical resection in HNSCC is the complete removal of the tumor, wherein, a surgeon will resect the gross tumor in addition to surrounding tissues that may contain invading cancer cells. Histologic assessment by a pathologist is used to determine if cancer cells are detectable at the edge of the resection, which would be indicative of a positive surgical margin (presenting tumor cells). With a correlation between evidence of a positive margin in resected surgical samples and tumor recurrence, as well as a decreased survival, surgeons may elect to remove additional surrounding tissues until a negative margin is obtained.[2,3] A confounding aspect of surgical resection in HNSCC is the limited anatomic area of the head and neck, where aggressive surgical efforts to remove cancerous regions and obtain a negative surgical margin may reduce the functionality of various organs (ie, tongue, larynx), as well as significantly impacting the postoperative quality of life for the patient.

INCORPORATING MOLECULAR SURGICAL MARGINS IN HEAD AND NECK CANCER

Accurate histologic assessment of margins in HNSCC surgical resections is vital; however, the variety of anatomic sites and respective differences in surgical approach results in a lack of standardization regarding the definition of an adequate margin. Resulting from this variability, histopathological examination within HNSCC can be subjective, and the classification of disease severity (ie, moderate dysplasia vs in situ, or

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severe dysplasia) by one pathologist may conflict with another.[4] When members of the American Head and Neck Society were surveyed concerning the classification of margins containing carcinoma in situ or dysplasia, most considered the former to be a positive margin, but not the latter.[5] The lack of uniform criterion in assessing the surgical margin may result in residual disease, which has severe consequences in terms of recurrence and overall patient survival, and it becomes evident that despite efforts to define the adequate surgical margin in HNSCC, histologic examination alone appears to be insufficient.

It has been well-established that cumulative genetic alterations facilitate the progression of premalignant lesions into HNSCC.[6] However, in premalignant lesions, the genetic alterations incurred may not result in morphologic changes, thus histologic examination alone may be inadequate in accurately defining the extent of disease.[7] Furthermore, certain differentiation agents may convert dysplastic lesions to "normal-looking" tissues histologically and therefore masking their underlying genetic alterations.[8] The inclusion of molecular characteristics into surgical margin analysis may not only yield a more sensitive and accurate assessment of the cells in these margins, but may also provide insight into their impacts to patients' postoperative prognosis. This concept of the "molecular surgical margin" (MSM) is advantageous, as it integrates recent advances in our understanding of head and neck carcinogenesis, while also retaining the established methodology of histopathology. This multidisciplinary approach may facilitate the development of a uniform criterion for defining the surgical margin, which will likely result in a reduced recurrence rate and improved overall patient survival.

UNDERSTANDING HEAD AND NECK SQUAMOUS CELL CARCINOMA RECURRENCE

The most significant metric regarding the success of surgical resection in HNSCC is the occurrence of disease relapse. One study reported that patients whose surgical resection met the respective criteria as satisfactory margins experienced a 12% recurrence rate at the primary tumor site, with patients displaying advanced disease having a higher rate of recurrence,[9] whereas others have suggested that despite histologic negative margin, a recurrence rate involving all sites could be as high as 30%.[10] Traditionally, a local recurrence is defined as the occurrence of another carcinoma less than 2 cm from the site of the initial resected carcinoma within a 3-year period. This definition was meant to distinguish local recurrence from second primary tumors (SPT), which were first defined by Warren and Gates[11] in 1932 as being a distinct, nonmetastatic malignancy, with the additional clinical criteria of occurring more than 2 cm from the initial anatomic site and diagnosed at least 3 years later being included.[12]

There are two theoretic explanations regarding the incidence of disease recurrence in HNSCC after surgical intervention. One theory involves the concept of minimal residual cancer (MRC), whereby a small number cancer cells, undetected by the pathologist examination of the surgical margin, remain and develop into a malignancy. A second theory of recurrence involves the concept of "field cancerization" first proposed by Slaughter and colleagues,[13] whereby after extensive histologic examination of oral cancers, the investigators summarized several observations: (1) oral and oropharyngeal cancer develops in multifocal regions of premalignant cells, (2) atypical tissue surrounds the tumor, (3) oral and oropharyngeal cancer is composed of multiple, independent lesions, and (4) the persistence of abnormal tissues gives rise to SPT and local recurrence. These two concepts of disease recurrence not only relate distinct mechanisms of cancer relapse, but may also impact the choice of therapeutic intervention.[14] Recurrences based on MRC theory may be treated by a combination of re-resection and postoperative radiotherapy. In contrast, treatment for recurrences due to field cancerization may be treated as a primary tumor with expanded fields containing premalignant cells. As both concepts relating to recurrence are related to the inadequacy of histologic assessment, additional methods that expand beyond macroscopic-based evidence need to be explored.

Incorporating molecular information into the analysis would not only provide more sensitive and specific determination of residue tumor cells, but also enable the detection of the "defected" field that cannot be histologically defined, and therefore allow a better understanding of disease progression and the basis of tumor recurrence. As observed in other cancer types, the accumulation of genetic alterations facilitates the transforming of a normal squamous epithelial cell into a cancer cell, and this transition is referred to as multistep carcinogenesis.[15,16] As described by Califano and colleagues,[16] the number of genetic alterations observed are in parallel with the level of malignancy presented in histologic examination. Furthermore, it was shown that even histologically benign tissues, adjacent to precancerous lesions, have acquired genomic alterations. In fact, it was revealed that these fields can have a fairly large diameter, with one study observing a

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