

Defining Optimum Surgical Margins in Squamous Cell Carcinoma of Oral Cavity

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Description

Squamous cell carcinoma is the commonest cancer in the head neck. Surgical excision is the treatment of choice and this is in form of a wide excision of primary and a neck dissection followed by an appropriate adjuvant therapy as indicated. The prime goal for any surgical resection is achieving optimum surgical margins. The reason margin is of such importance is because it is the only prognostic factor which is under direct control of the operating surgeon. Resection margin is the cuff of normal tissue around the tumor. Margins are not just limited to circumferential margins but also refer to the deep margin in a three-dimensional tumor. The tumor with its free margins measures the completeness of the surgical resection. Having said that, the distance and histopathological and molecular properties of this normal cuff of tissue is a matter of interest for researchers.

The importance of margin on local recurrence and survival had been analyzed by Loree and strong in their seminal paper. The overall survival being 52% in positive margins as compared to 60% in free margins [1]. The margin cut off was considered as >5 mm to be free. The two important landmark randomized trials by EORTC 22931 and RTOG 9501 found positive margins as one of the most important factors warranting adjuvant chemoradiation. Both the trials defined positive margin differently EORTC as <5 mm and RTOG group as tumor at the cut margin [2,3]. A meta-analysis on the subject by Anderson et al showed a reduction in local recurrence by 21%, when margins were 5 mm or more [4]. Now, this leaves us with, several pertinent questions on margins, that remain unanswered. i) What is the distance of adequate margin? ii) How does worst pattern of invasion or microscopic spread of disease beyond tumor be addressed? iii) Does more margin proportionately translates into better survival? Many of these important issues have been dealt in the retrospective analysis by Mishra, et al. [5].

The study had shown that with increasing margin the Local Recurrence Free Survival (LRFS) improves. There is an incremental benefit on LRFS as the margin increases by each milli meter. However, this improvement is seen till 7 mm pathological margins and then the impact plateaus. Beyond this, taking an additional margin was not associated with any significant improvement in LRFS. Another aspect of the margin that is addressed in the study is the worst pattern of invasion or the microscopic spread of disease beyond gross tumor, which may alter the final margin status. The incidence of microscopic spread is shown in around 8.7% of patients and this does alter the final margin status.

Adequacy of margin is further marred by the problem of post excision tissue shrinkage. There is a tissue shrinkage of 20 to 30% post excision. Furthermore, formalin and paraffin cause further margin shrinkage. Hence, to achieve a 7 mm tumor free margin, surgeon

needs to place his knife at 1 to 1.5 cm from the tumor edge to account for tissue shrinkage.

This opens up another debate of utilizing frozen section assessment for intraoperative margin assessment. Frozen section is definitely a very helpful tool for margin assessment intraoperatively. A recent meta-analysis has shown that the frozen section guided revision of a positive margin does not translate into equal local control of an initially negative margin [6]. In another study gross examination of margin has been evaluated as a cost-effective alternative for frozen section. They found that GE and FS have similar rates of detecting inadequate margins 6.63% vs. 6.69% in FS and GE respectively. This was despite, 5.7% incidence of microscopic spread in the tumor. It also showed that taking more than 7 mm gross pathological margin reduced the chances of an inadequate margin in final histopathology report and obviates the need of frozen section [7].

The final margin status on histopathology is utilized for planning of adjuvant therapy. The pooled analysis by Cooper and Bernier showed a benefit of approximately 25% by adding chemoradiotherapy in margin positive patients [8]. Despite adding chemoradiotherapy, the outcome of patients with positive margin remained poor as compared to patients with free margin. This emphasizes an important dictum that adding chemo radiotherapy to close and positive margin improves survival however it does not give an equal survival as compared to free margin. Therefore, achieving a tumor free margin in a resection specimen is of utmost significance.

Even after achieving an adequate three-dimensional margin around the tumor on histopathology, the possibility of failure remains as high as 25%. The local control depends upon several factors like biologic behavior and other adverse factors. This has led to several studies evaluating the field cancerization and molecular changes in the normal tissue and development of novel molecular margin assessment techniques. Expression of several biomarkers like p53, Loss of heterozygosity (LOH) eukaryotic translation initiation factor 4E (eIF4e) could be causative of local failures. However, the routine use of molecular assessment of surgical margins has significant limitations, primarily as it is expensive, labor intensive, cannot be used *in vivo* and can only reveal genetic alterations in the mucosa and not the deep soft tissue margins.

To conclude, a 5 mm margin in final histopathology is the most commonly accepted definition of an “adequate” margin. A 7 mm free margin on final histopathology provides superior LRFS. With each millimeter increment of margin there is an improvement in LRFS. However, there is no added benefit on local control as the margin increases beyond 7 mm. Taking a 7 mm margin might obviate the use of frozen section for margin assessment. Further molecular analysis of margin and tumor host interphase may provide insights towards

understanding the biology and interventions for improving survival in oral cancer.

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