Worst Pattern of Invasion: An Emerging Trend

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Although we have experienced great deal of advancement in technology and guidelines, the 5year disease-specific survival has remained unchanged in early head & neck squamous cell carcinoma (SCC). When local surgery is used alone, up to 25% (stage I) and 37% (stage II) of patients with low-stage tumors develop local recurrence and/or regional lymph node metastasis during follow-up, associated with disease-related mortality[1].Upwards of 30% such early-stage diseases have a high risk of regional metastasis[2,3]. This portends the problem of whether to proceed with an elective neck dissection, which can amount to overtreatment for many patients. According to D'Cruz et al[3], 8 patients would need to be treated with elective neck dissection to prevent one death, and four patients would need to be treated to prevent one nodal relapse. Elective nodal radiotherapy (RT) in undissected cases can be considered but this also comes along with its own long term toxicity and morbidity. Moreover, regardless of a clear margin, the treatment failure rate for early-stage oral cavity squamous cell carcinoma is in the range of 10–40%[4]. These numbers force us to ponder about some parameter which could redefine guidelines and optimize them further. Amongst the emerging factors are tumor budding, lymphocytic interface and pattern of invasion at the tumor front.

Despite the inherent differences in tumor biology, contemporary practices for early-stage oral cavity squamous cell carcinoma continues to be surgical resection and often with no adjuvant therapy5. The definitive indications for adjuvant RT are close/positive margins and positive lymphnode status. Various other "soft" criteria are considered to judge the aggressiveness of tumor biology and include lymphovascular embolism (LVE), perineural invasion (PNI), grade of the tumor and depth of Invasion (DOI) to mention among the few. Traditionally, the grade of the tumor was considered to be the most predominant parameter defining treatment approach. However, the histologic grading of the deep invasive front of oral carcinomas had been shown to correlate more accurately with survival6,7.

Pattern of invasion (POI) is of 5 types out of which POI 1,2 & 3 comes under non-aggressive category and POI 4 & 5 are defined as aggressive. Brandwein-Gansler et al, proposed a scoring system (HRS) comprising of the sum of the specimen Lymphocytic Host Response (LHR), Worst Pattern of Invasion (WPOI) and PNI8,9. Various studies have validated and corroborated the impact of HRS score in prognostication. However, certain contrasting studies have failed to correlate HRS as a prognostic index but have validated WPOI as an independent prognostic marker for locoregional recurrence and death10,11. Suresh at al12 reported that oral SCCs with poorly differentiated invasive fronts showed localized low levels of expression of E-cadherin and increased incidence of lymph node metastases. The histologic pattern of invasion, a reflection of cell cohesion, correlates with in vitro markers of malignancy such as loss of contact inhibition, tumor cell motility, and secretion of proteolytic enzymes13.Worst POI has been found to be strongly associated with mortality14 and several studies have previously confirmed the relationship of unfavorable WPOI with poor prognosis in oral SCC15,16,17.Recently, a correlation between worst pattern of invasion type 5 (WPOI-5) and occult cervical metastases has been demonstrated18. Extratumoral PNI, and angiolymphatic invasion also count as WPOI-519. WPOI has been validated on multivariate analysis in oral tumors, specifically in low stage tumors20. It is an emerging trend amongst the researchers and looks promising. Even AJCC Cancer Staging Manual, 8th edition, guidelines have emphasized for the reporting of WPOI-5.

WPOI appears to be significant if DOI<4mm21. For DOI >/=4mm, there is a significant risk of locoregional failure and death and is more likely to be associated with other high risk factors like WPOI=5, PNI etc. As such, these patients are often considered for adjuvant treatment irrespective of margin and nodal status. Lastly, there may be a correlation between Biopsy pattern of invasion (BPOI) and the subsequent histological WPOI and DOI. Whether, BPOI can predict WPOI and DOI >/= 4mm and modify surgical decision making while addressing the primary tumor surgically needs to be further explored and validated.

To conclude, as it is well known that most aggressive cells reside at the invasive front of tumors, pattern of invasion could serve as an individual prognostic marker. WPOI alone or in combination with other histological factors it may justify the adjuvant radiotherapy/chemoradiotherapy in early as well as advanced oral cavity squamous cell carcinoma. Moreover, it can be a guide to select patient for neck dissection in early-stage tongue carcinoma with depth of invasion <4mm and therefore may not need to do neck dissections on each and every patient decreasing the morbidity of the treatment. Additionally, at this point of time we need to find out what could be the best possible course of action for patients with worst pattern of invasion 4 and 5 and no other high-risk factors. Whether such patients could benefit simply from addition of adjuvant radiotherapy to treatment protocol, or could this disease be so aggressive that adjuvant radiotherapy will have no impact on outcome and we may need to consider for adjuvant chemo-radiotherapy or even a change in surgical approach altogether. It also needs to be explored in tumors with DOI>/= 4mm, whether WPOI contributes to additional biological aggressiveness and affects the outcomes, thereby building the case for escalating adjuvant treatment. The logical next step would be to take all these points into consideration and conduct a multi-arm prospective randomized controlled trial.

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