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Salvage surgery for squamous cell carcinoma of the head and neck in the era of immunotherapy; is it time to clarify our guidelines?

Running title: revisiting salvage surgery

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Precis: Is salvage surgery a one size fits all approach, and more importantly, in the era of improved systemic therapy what are the criteria based on which salvage surgery for SCCHN should be the uncontested modality of choice

Treatment for recurrent squamous cell carcinoma of the head and neck (SCCHN) remains a challenge and the disease carries significant burden for patients and families. While the overall survival of patients with locally advanced SCCHN has improved with the addition of platinum based chemotherapy to definitive radiation [1], significant numbers of patients continue to fail [2, 3]. It is estimated that 30-40 % of patients treated with definitive therapy will recur, the majority loco-regionally [4, 5]. Patients with recurrent disease are faced with few curative options and are

desperate for modalities that prolong life expectancy while preserving key functions and quality of life.

While salvage surgery (SS) has been advocated as the modality of choice to achieve these goals, its indication remains poorly defined, with a significant risk of complications of up to 67% [2, 6, 7]. It is clear that while patients may benefit from SS, the outcome of a number who are offered this modality remains poor [7]. Even though age and performance status are important predictors of patient outcome[8, 9], clear guidelines determining eligibility are lacking [7]. SS has not been compared directly to re-irradiation given the obvious challenges to implement such a trial, and the difficulty interpreting non-randomized data given the lack of uniformity and inherent selection biases.

In the locally recurrent and metastatic setting, we witnessed improvements with the addition of cetuximab to the platinum backbone leading to the adoption of the EXTREME regimen as a new standard of care a decade or so ago [10]; yet despite these advances, practices and recommendations for SS continued to be untested.. It is noteworthy in that respect, that patients are enrolled on systemic therapy trials often based on exclusion of SS, thereby introducing inherent bias rendering retrospective comparisons impossible to perform.

Recently, as immunotherapy has evolved in a relatively short time into a new standard for patients with advanced incurable heavily pre-treated SCCHN with two immune check–point inhibitors (ICPI) approved in 2016 [11, 12], we believe it is time to look at our long held practices in a new light [13]. Historically while induction chemotherapy has failed to produce significant improvement in patient survival, pre-operative single doses of ICPI have produced impressive responses with little toxicity in different tumor types including SCCHN [14]. Chemoresponders consistently show improved survival and increased responses to subsequent radiation. Of significance as well, is that bio-selection with induction chemotherapy has achieved impressive cure rates in laryngeal cancers[15]. While the picture remains unclear as far as the best way to use ICPI in the definitive setting, there is every reason to believe the standard of care for locally advanced SCCHN will soon change. As single agent ICPI can result in long term progression free and overall survival for some heavily pretreated patients, it is legitimate to ask whether combination ICPI approaches may result in this much desired outcome for at least a percentage of patients currently offered SS who continue to fare poorly despite aggressive surgery. A plausible innovative strategy here would be induction immunotherapy for bio selection and subsequent decision regarding the need for SS versus continued systemic

therapy. It is worth noting that current trials are already exploring the impact of induction immunotherapy in the locally advanced settings and can inform similar designs of future SS trials. Of importance as well is that HPV status appears to influence the rate of pathologic remissions noted with SS, pointing to the fact that future trials or guidelines will need to account for HPV [16]. In addition, the effect center volume and expertise has on outcome of patients treated on such trials need to be accounted for [17].

The difficult questions that need to persist are: 1) is salvage surgery a one size fits all approach, and more importantly, 2) in the era of immune-oncology, what are the criteria based on which SS should be the uncontested modality of choice? Getting closer to clarity will require taking courageous steps. The first step would be to consider clinical trial designs targeting patients where clear indications for SS have not been established. Getting there will require a meeting of the leading experts in the various therapeutic disciplines. Lessons from the not too distant past are worth remembering; those include but are not limited to the lack of improvement in larynx cancer mortality despite the increase in the non-surgical management of this disease; Needless to say that factors such as side effects expected from immunotherapy, the rare but concerning phenomenon of hyper-progression, the cost of ICPI, as well as surgical and center expertise, need to be taken into consideration when evaluating ICPI in the context of SS and must be factored in the outcome measure designs of such studies.

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