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EDITORIAL

When is reoperative surgery not indicated for recurrent head and neck squamous cell carcinoma?

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Many head and neck squamous cell carcinomas (HNSCCs) are treated initially by surgical resection, followed by (chemo-)radiotherapy when indicated. Despite aggressive treatment, locoregional recurrence represents the most frequent cause of failure, and occurs in up to 50 % of the patients with advanced stage tumors [1–3]. For patients previously treated with radiotherapy, salvage surgery is the best curative alternative as costs and complications of re-irradiation (with or without concomitant chemotherapy) are high and usually associated with low cure rates. Chemotherapy, as a single therapeutic modality is essentially palliative in the re-treatment setting, with expected survival of just a few months for most tumors. However, whether initial treatment was surgical, non-surgical or a combination of both, salvage surgery is often limited by extensive tumor involvement, high-risk resection and limitations to reconstruction after previous surgery. Poor general health of the patients at the time of recurrence, and in some circumstances, unavailability of multidisciplinary facilities or experienced surgeons also impose limitations on the feasibility of reoperation. Nevertheless, a significant number of patients with resectable isolated local or regional recurrence have no significant comorbidities and are motivated to undergo aggressive salvage treatment. In these cases, surgical salvage is the treatment of choice, as surgery offers the best chance of achieving locoregional control and prolonged survival [4, 5]. However, surgical management of recurrence after prior surgical resection is technically challenging and demands multidisciplinary treatment. Satisfactory results require adequate resection of all gross tumors with negative margins. This may be difficult to achieve in previously irradiated patients as the extent of disease may be difficult to evaluate even with "state of the art" imaging studies. Although recent advances in reconstructive procedures have increased the feasibility of larger resections for recurrent HNSCCs, these procedures are associated with significant morbidity [1, 6, 7] and economic costs [1, 8]. These issues

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are important in consideration of cost-effectiveness. Moreover, as the prognosis of patients undergoing salvage treatment is often poor, outcomes such as poor speech and swallowing function, tracheostomy, feeding tube dependence, other perioperative complications and prolonged hospital stay, are important quality of life parameters. In these circumstances quality of life issues usually become the patient's main primary concerns. Quality of life often declines precipitously immediately after major surgery for treatment of HNSCC, and frequently takes a full year to recover to preoperative level [1, 6, 9]. In patients with limited life expectancy, these issues should be considered in the decisions on treatment so as to restrict reoperative procedures to patients who may achieve meaningful survival.

Despite frequent presentation of these situations in clinical practice, few studies have addressed the results of surgical salvage for locoregional recurrences in patients who have been previously treated surgically, and there is no consensus in the literature in how to manage these patients. There is a general agreement that findings like carotid artery encasement, prevertebral fascia invasion, major skull base invasion, regional cancer recurrence within the field of a prior modified radical or radical neck dissection, and the presence of dermal lymphatic metastases indicate unresectable disease. In the remaining cases, therapeutic decisions are usually based on individual experience. However, these decisions could be biased by the desire to offer the patient one more opportunity to control the disease. It is, therefore, useful to identify some limits to the indications for surgical salvage: to identify the patients for whom the results, cost and morbidity of these procedures would not justify a new surgical intervention and would perhaps benefit from aggressive re-irradiation with or without concomitant systemic therapy, or are simply candidates for palliative systemic therapy or best supportive care. The factors that predict a low probability of success of a new surgery are discussed below.

The stage of the recurrence is of substantial importance in predicting the success of reoperative surgery, perhaps even more than the stage of the initial primary tumor. Recurrent disease differs from primary tumor as it typically has an infiltrative and multifocal growth pattern, spreading in microscopic deposits beyond the initial tumor boundaries. A high degree of perineural invasion is also commonly identified [10]. Thus, extensive (rT4) recurrences, even when technically resectable, often preclude adequate resection with free margins, and new recurrences usually appear. The fact that the tumor has recurred after previous (multimodality) treatment may in itself be considered a sign of aggressive disease and resistance to treatment. In the meta-analysis of Goodwin [1], patients with rT4 recurrence had median cancer-specific survival of 9.3 months and median disease-free survival after salvage surgery of just 5.5 months. Similarly, in the study of Kim et al. [6] the average disease-free time interval was 7 months in patients with advanced T classifications (T3–T4). These findings demonstrate the poor outcomes for the majority of these individuals, although many studies do not distinguish between types of previous treatment.

The site of recurrence also has a considerable impact on outcome. The surgical salvage rate was higher in primary laryngeal and oral cavity tumors, possibly because of the easier and, therefore, earlier clinical detection of recurrences in these areas, and the increased feasibility of further resection and reconstruction [11]. Recurrent laryngeal carcinoma has been successfully treated for a long time, especially when total laryngectomy has not been previously performed, since most recurrent tumors are confined to the laryngeal compartments. If the recurrent disease is only endolaryngeal, resection is quite satisfactory. However, when there is gross extralaryngeal disease, surgical resection may not be satisfactory. Some of the patients with advanced recurrent laryngeal cancer may require partial or total resection of the pharynx necessitating appropriate reconstruction. The recurrences of oropharyngeal and hypopharyngeal tumors are usually detected late and salvage resection and reconstruction after prior pharyngectomy is difficult. Although surgical reconstruction of large pharyngeal defects has become increasingly possible over the past several decades because of advances in microvascular reconstructive techniques, the results of surgical salvage for pharyngeal carcinomas have remained poor. Approximately two-thirds of patients develop a second recurrence on average 9 months after salvage resection [6, 8]. Moreover, tissue damage induced by previous therapy with intense fibrosis and reduced vascularity may interfere with subsequent salvage surgery and repair of tissue defects, leading to a high incidence of perioperative

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morbidity. In addition, salvage surgery in the oropharynx often results in significant morbidities, including dysarthria, dysphagia and aspiration, sometimes requiring total laryngectomy to restore swallowing and stop aspiration [8]. Hypopharyngeal recurrences have been reported to be technically resectable in only a third of recurrent cases [12, 13]. These factors underscore the need to realistically consider the potentially severe consequences of surgical salvage in oro- and hypopharyngeal recurrences in light of the low rate of cure.

Although it is technically easier to perform neck dissection for nodal recurrence in a previously undissected neck than to resect a recurrent primary tumor, neck recurrences may signal a greater likelihood of distant metastases and consequently worse prognosis [14]. In addition, recurrent neck disease significantly increased the probability of a second recurrence after salvage surgery [8], and the prognosis is even more dismal after previous neck dissection [11]. Recurrent cervical tumor in the field of a previous modified radical or radical neck dissection is often unresectable.

The disease-free interval (DFI) from the first surgery has also been shown to have a significant impact on prognosis. A short (<6 months) or absent DFI is a predictor of poor outcome, probably reflecting a more aggressive tumor phenotype. Some authors consider short DFI to be perhaps the most important factor in predicting a poor outcome, independent of tumor site or original treatment modality [5, 8, 15–17]. They suggest that most patients with early recurrences (<6 months) should be referred for palliative treatment or best supportive care.

The nature of prior treatment should also be considered. Successful salvage is less likely if the patient had been initially treated with both surgery and postoperative radiotherapy or chemoradiotherapy. Not only does previous irradiation limit the possibilities of re-irradiation but recurrence after more aggressive primary treatment implies more resistant disease. In the study of Gleich et al. [13], only one of the 12 patients initially treated with surgery plus radiotherapy were successfully salvaged. Moreover, patients who received adjuvant or neoadjuvant radiotherapy in addition to surgical resection for the previous cancer had a higher probability of surgical complications and morbidity [17]. Prior chemotherapy is also considered a poor prognostic factor among patients with recurrent HNSCC. There is no clear explanation for this, although intensive chemoradiotherapy regimens may result in a more pronounced proliferation of fibrous tissue in the treated area which would compromise subsequent treatment or may select for particularly resistant and aggressive recurrent tumor cells. Also, the fact that chemotherapy was added to the regimen may simply be indicative of initial advanced stage disease, requiring treatment intensification at the time of index treatment, and therefore portending worse outcome at recurrence [1, 4, 18].

Finally, patient performance status is one of the most important factors in determining prognosis. Patients with poor performance status may be unable to endure salvage surgery and subsequent morbidity, even if their tumors are technically curable. In addition, the presence of comorbidities, preexisting organ dysfunction, poor cognitive function, lack of social support, low reported quality of life, and continued tobacco/alcohol use are adverse prognostic factors [1, 4, 6, 8, 17].

Patients presenting with recurrent tumors should undergo careful restaging evaluation before committing to re-treatment. In addition to computed tomography (CT) or magnetic resonance imaging (MRI) to evaluate the extent of the recurrent tumor, positron emission tomography (PET) should be strongly considered to evaluate for metastatic disease, in combination with a CT scan of the chest [19]. The history and physical examination should include an assessment of the patient's comorbidities and life expectancy, performance status, speech and swallowing function, nutritional status, severity of current symptoms, expectations, and documentation of sequelae of prior treatment, such as fibrosis, carotid stenosis, dysphagia, xerostomia, or osteoradionecrosis [20].

Given the poor chance of survival, the potentially high associated morbidity, and the economic costs of treatment associated with salvage treatment, multidisciplinary head and neck oncology teams must carefully weigh harm versus benefit when considering re-treatment options. The selection of patients for second surgical resection must be careful, and the recommendation for these procedures must be made individually. Candidates for reoperation should be motivated and conscious of the risks of the procedure. In addition to relatively good general health, it is preferable for the patient to have a small resectable recurrent tumor for which it is possible to obtain negative surgical margins, and the possibility of adequate reconstruction and rehabilitation. It is also preferable that they do not have recurrent disease in the neck (or only limited recurrence in a previously undissected neck), and that they have not received previous radiotherapy or chemotherapy. Optimal candidates are those with DFI >6 months from the first treatment. In other circumstances, the risks of the procedure in terms of morbidity and quality of life often outweigh the benefits, and other alternatives should be considered.

The aim of reoperative surgery is often improvement of quality of life and changing the mode of eventual mortality, rather than cure. Palliative resection may be employed to avoid uncontrolled fungation of the recurrent tumor. However, we need to recognize palliation as a state of the mind of the patient, family and the treating physician.

These decisions are very complex and must be made with a clear understanding of the goal to be achieved. The patient and the family need to accept the potential risk of serious complications including mortality.

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