

Salvage surgery for head and neck squamous cell carcinoma

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Introduction

Head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer worldwide and fifth most frequent cause of malignancy-related mortality [1, 2]. Despite advances in various treatment modalities, the overall prognosis of HNSCC patients has not improved significantly within the last several decades. About 50 % of patients survive their disease [3]. Advanced tumors have a recurrence rate of around 20–30 % at the primary tumor site and 10–15 % in the neck [3].

Throughout most of the twentieth century, resectable advanced-stage HNSCC was treated by radical surgical approaches and primary radiochemotherapy (pRCT) was reserved for the treatment of locally advanced, unresectable tumors. However, over the past two decades, non-surgical organ-preservation strategies such as primary radiotherapy (pRT) or pRCT have been increasingly applied as treatment

modalities for resectable stage III and IV cancers as an alternative to surgical management. This development has led to an increasing role for salvage surgery in cases of recurrent disease. In HNSCC, salvage surgery is, besides aggressive re-irradiation if applicable, often the only curative option in patients with locoregional recurrence [4].

Among patients with advanced HNSCC treated with definitive pR(C)T or adjuvant R(C)T, locoregional recurrence develops in 18–20 % of cases and in 17–33 % of patients treated with definitive RCT for locally advanced, unresectable tumors [5]. Locally, recurrent tumors may arise from residual neoplastic cells that survive initial treatment—most likely due to biological factors that provide radio- and/or chemoresistance, the existence of cancer stem cells, or insufficiencies in initial treatment parameters such as radiation dose, volume, fractionation and/or treatment duration. Also, secondary tumors following pR(C)T may develop from underlying field cancerization, as a radiation-induced malignancy, or as a de novo process.

For patients with resectable disease recurrence, salvage surgery is considered the standard of care and may provide long-term disease control in up to 45 % of patients with advanced and up to 80 % of patients with early recurrent disease [3, 6]. However, recurrence rates after salvage surgery, even when negative margins have been obtained, are high [7]. The rate of recurrence following salvage surgery has been described as 54.9 % in a retrospective analysis of patients with oropharyngeal cancer and cancer of the oral cavity, with an overall five-year survival rate of 32.3 %. In this study, significant prognostic factors in multivariate analysis were recurrent tumor stage ($p = 0.049$) and disease-free interval ($p = 0.045$) [8]. Rösli et al. [9] showed in a retrospective study of 156 patients with recurrent oropharyngeal tumors that five-year overall survival and disease-specific survival after salvage treatment was 29 and

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40 %. With reference to specific initial treatment modalities, after initial pRT, survivals were 25 and 40 %; after initial surgery followed by radiation therapy, 40 and 40 %; and after initial surgery alone, 20 and 40 %. The authors concluded that despite poor ultimate outcome, salvage treatment should be attempted in patients with resectable disease, good performance status and absence of distant metastases.

The term salvage surgery is not clearly defined and has been used variously to describe a second attempt at cure after definite treatment or the final attempt for cure in case of recurrent disease following previous surgery, previous RT or RCT or a combination of the options mentioned. In HNSCC, salvage surgery is often the only curative option available and is mainly performed as the final curative attempt. The term salvage surgery is currently also used incorrectly for elective surgery following initial treatment and for persistent disease following an initial treatment attempt [10].

In this editorial, we review current applications of salvage surgery in HNSCC patients with a focus on indications for its rational use in different settings.

Challenges in salvage surgery

The tissue toxicity resulting from previous irradiation and chemotherapy produces a higher incidence of complications after salvage surgery than after initial surgery performed on healthy tissue. Acute toxicity is an inflammatory response leading to impaired wound healing and increased risk of infections. Late toxicity, fibrosis and avascularity, also impairs wound healing and repair. Complications of salvage surgery are often multiple and interrelated, including infection, bleeding and formation of pharyngocutaneous fistula (PCF) resulting in complex and prolonged wound healing phases, and often require additional interventions [11, 12]. The frequency of complications is correlated with the clinical stage of the recurrent tumor: >20 % in stage I and II tumors, >30 % in stage III tumors and >35 % in stage IV tumors [13]. Complication rates as high as 40–53 % have been reported in the literature [14]. The key to successful salvage is appropriate patient selection with adequate preoperative measures including correction of co-morbidities, cessation of smoking and alcohol, improvement of nutritional deficits and eradication of methicillin-resistant *Staphylococcus aureus* (MRSA) infection [12, 15, 16].

Specific aspects contributing to complications in salvage surgery include advanced medical co-morbidities, co-morbidities related to prior treatment for HNSCC and prior tracheostomy, age and tumor location outside the larynx [12]. Recurrent tumors of the oropharynx, hypopharynx

and larynx are diagnosed in more advanced disease stages compared with primary tumors [17]. Therefore, a well-experienced surgical team must conduct salvage surgery. An interdisciplinary approach to minimize complications and improve survival and functional outcome is required.

Preventive measures

Patients suspected of recurrent disease should undergo a restaging evaluation prior to a decision on salvage surgery. In addition to evaluation for locoregional disease, distant metastases have to be ruled out as recurrent disease is associated with the existence of distant metastases [18]. The most important diagnostic procedure and standard to screen for distant metastases in HNSCC is a CT scan of the thorax to evaluate for pulmonary and mediastinal lesions [19]. Some authors suggest the use of positron emission tomography to increase sensitivity in screening for distant metastasis [19–21]. However, this technique has not become a routine practice in many centers yet, as clear data on its predominance over conventional methods are pending and its use is cost-intensive and access often limited. The patient's co-morbidities and life expectancy, performance status, speech and swallowing function, nutritional status and severity of current symptoms need to be evaluated and documented. The patient needs to be educated about the often complex surgery with extensive reconstructive procedures.

Preoperative measures may be undertaken for correction of co-morbidities, nutritional deficiencies and hemoglobin levels. Patients should be screened for MRSA, especially in countries with known high MRSA infection rates, e.g., South and North America, Asia and Malta [22], as MRSA positivity has been evident in 80 % of all post-operatively developed fistulae [23]. The same study demonstrated previous radiation and MRSA positivity to be the only predictors for the development of fistula [23]. The incidence of wound infection has been reported to be as high as 87 %. Short regimen antibiotic prophylaxis covering aerobic and anaerobic bacteria has been shown to reduce the risk of infection in clean-contaminated major oncological head and neck surgery, and is also advisable in clean major oncological head and neck surgery [24]. Smoking and alcohol consumption should be discouraged to reduce the respiratory and metabolic problems associated with these agents.

The development of PCF is a frequent and feared complication of salvage surgery, especially salvage laryngectomies with concomitantly performed neck dissections [25]. The rate of development of PCF appears to correlate with the time from primary treatment to salvage surgery, with a mean time of 19.5 months in those who developed a PCF versus 47 months in those who did not ($p = 0.02$) [26]. In a

meta-analysis of 33 studies performed by Sayles and Grant [27], the incidence of PCF was 14.3 % in primary laryngectomy, 27.6 % in salvage laryngectomy and 10.3 % in salvage laryngectomy with flap reconstruction. Reconstruction with either free or pedicled flaps allows restoration of function and provides aid in wound healing by introducing non-irradiated tissue. A meta-analysis performed by Paleri et al. [28] indicated that the use of vascularized tissue from outside the radiation field significantly reduces the rate of PCF formation. The application of a myofascial pectoralis major flap in salvage laryngectomies to enhance the pharyngeal anastomosis has been shown to reduce fistula rates from 50 to 25 %. If applicable, flaps should be considered early in the surgical salvage setting [29].

The use of chemotherapy is associated with an incidence of fistula formation of 34.1 % compared with 22.8 % in patients treated with RT alone [26].

General measures to minimize complications include prevention of deep venous thrombosis prophylaxis and use of anti-emetics to minimize tension to the wound by reducing nausea and vomiting, in addition to stabilization of hemoglobin, blood sugar and electrolyte balance.

Surgical salvage approaches

Salvage surgery especially salvage laryngectomy is associated with high morbidity rates, poor overall and disease-specific survival, prolonged hospital stays and decreased quality of life compared with primary surgery [13, 30, 31]. With respect to survival rates, salvage surgery has been shown to be most effective for recurrent laryngeal cancer and least effective in pharyngeal tumors [32]. Some authors suggest less radical approaches, whereas others promote extensive resection with reconstruction. The question of whether neck dissection is indicated for patients with recurrent primary tumors without evidence of current or previous neck disease remains open, although there is evidence that neck dissection may be beneficial for patients with more advanced RT stages [33].

As an alternative to total laryngectomy, open partial laryngectomies, particularly the supracricoid procedures, may be reliable salvage operations, if suitably indicated [34]. While preserving function, partial laryngectomy affords no survival advantage. In a retrospective analysis of 56 patients with recurrent laryngeal cancer comparing total to partial laryngectomies, patient survival was not affected by the primary treatment or by salvage surgical approach, but was improved by obtaining negative margins [35]. Patients with an early disease relapse appear to have a worse prognosis compared with patients with a delayed relapse [36].

In general, open approaches are associated with a high incidence of major complications and often produce defects

that require microvascular reconstruction, particularly in a radiated field. Recently, transoral approaches using laser or robotic systems have shown great promise in the surgical resection of recurrent early stage HNSCC. In a retrospective analysis, White et al. [37] showed the feasibility of transoral robotic surgery (TORS) in a salvage setting for recurrent oropharyngeal tumors with a significantly lower incidence of tracheostomy and feeding tube use, shorter overall hospital stays, decreased operative time, less blood loss, significantly decreased incidence of positive margins and no post-operative fistula compared with open procedures [37]. The two-year recurrence-free survival rate was significantly higher in the TORS group than in the open approach group (74 and 43 %, respectively) ($p < 0.01$). Transoral laser microsurgery (TLM) for recurrent T1–T3 supraglottic tumors was shown to be feasible, with two- and five-year overall survival rates of 85.7 and 68.6 %, respectively [38]. In another study including 91 patients with recurrent T1–T4 pharyngeal and laryngeal cancer following prior treatment, three-year local control, survival and disease-specific survival were 70, 62 and 64 %, respectively [39]. For recurrent early glottic tumors, treated with salvage TLM, five-year overall survival, disease-specific survival, local control and locoregional control rates have been shown to be 89.9, 97.9, 62.3 and 60.1 %, respectively ($n = 50$). The larynx preservation rate at long-term follow-up was 86 % [40].

Obviously, there is a selection bias when results for tumors suitable for transoral procedures are compared with those that are not. Nevertheless, these data suggest that transoral approaches, when feasible, should be preferred over open approaches as complications, particularly formation of fistula, are significantly reduced with acceptable oncological safety.

In an effort to achieve greater local and regional control in recurrent HNSCC, re-irradiation alone or in combination with chemotherapy can be considered following salvage surgery. A phase III multi-center study of recurrent HNSCC in previously irradiated post-salvage surgery randomized patients to post-operative observation or re-irradiation with concurrent chemotherapy groups. Local disease control and disease-free survival were improved in the patients who received re-irradiation and chemotherapy [41], although there was no significant difference in overall survival compared with those observed after salvage surgery alone. Grade 3 and 4 toxicity was as high as 40 % compared with 10 % in those randomized to post-operative observation.

Palliative chemotherapy is considered the standard of care for patients with unresectable tumors. Multi-agent chemotherapy regimens may have a response rate of up to 35 %, but results are rarely durable and long-term survival is rare [42]. In these patients, re-irradiation, if applicable,

is the only potentially curative treatment modality. With novel technologies to improve external beam irradiation employing new concepts on dose, fractionation, intensity-modulated radiation therapy and stereotactic approach, as well as brachytherapy, increased response with reduced toxicity is the aim. The RTOG[®] has completed two phase-II studies using re-irradiation and chemotherapy in this patient population. RTOG[®]-96-10 used concurrent hydroxyurea and 5-fluorouracil achieving a median survival of 8.5 months and a two-year survival rate of 15.2 % [43]. RTOG[®]-99-11 employed concurrent cisplatin and paclitaxel and achieved a median survival of 12.1 months and a two-year survival rate of 25.9 % [44]. However, acute toxicity was high in both studies with almost 50 % of patients suffering grade 3 toxicity and 23 % grade 4 in RTOG[®]-99-11.

Palliative salvage surgery

Salvage surgery in a palliative setting can be offered and performed to reduce pain and bleeding, or relieve airway and/or esophageal obstruction. However, these procedures are associated with high complication rates. The potential benefits in relation to associated risks for the patients have to be carefully evaluated.

Rehabilitative salvage surgery directed to improve functionality, particularly voice and swallowing, after definitive treatment without evidence of recurrent disease, has been increasingly discussed. Frequent aspiration and frustrating voice rehabilitation can lead the patient to request rehabilitative surgery. The decision to offer such a procedure needs to be carefully evaluated and should be only performed in agreement with the patient when conservative treatment has shown no improvement.

Conclusion

Salvage surgery in patients with recurrent HNSCC following pR(C)T remains a controversial topic and many aspects in this regard lack sufficient evidence as to their benefit. Only a few patients with recurrent disease are good candidates for salvage surgery, as many suffer from co-morbidities related to their previous HNSCC treatment. Therefore, preoperative consultation, patient evaluation and patient education are essential.

Complications of salvage surgery are often multifactorial and interrelated. The indications for and against salvage surgery need to be carefully considered and met by an experienced, interdisciplinary head and neck oncology group, preferably at a tertiary care center. Preoperative evaluation and correction of nutritional deficiencies and

co-morbidities are critical to good outcomes and to minimize complications.

Transoral approaches such as TORS and TLM, which seem to be associated with a reduced complication rate in a salvage setting, can be an alternative to open approaches for selected tumors. Currently, there are only few data on comparing transoral to open surgery. Long-term results, preferably from multi-center studies, should eventually reveal oncological safety, survival rates and functional outcome of these approaches.

Because of advances in extirpative and reconstructive surgical techniques, as well as progress in non-surgical modalities, the treatment of recurrent HNSCC has shifted within the last decades from palliation toward curative therapy employing surgery, R(C)T or a combination of both with improved survival rates, but which are still less than fully satisfactory.

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