Chapter 16
Salvage Surgery in Head and Neck Cancer

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Introduction

Salvage surgery (SS) for head and neck cancer is a much-addressed issue due to its complexity and high stakes for the individual patient. Since the introduction of organ preservation strategies and the rise of concomitant chemoradiation (CCRT) in advanced disease, challenges in SS have grown substantially due to toxicity and a tendency to poor healing. Radicality, which greatly determines success, is often difficult to foresee after previous treatment. Major complications postoperatively have to be anticipated and dealt with.

Realistic expectations should be discussed with the patient as well as the best treatment strategy in each individual patient. Salvage surgery should not be considered a fallback option as the outcome is significantly worse than after primary surgery regardless of adjuvant therapy. Active physician driven surveillance is paramount in early detection of residual or recurrent disease to increase salvage rates.

The dynamic field of head and neck cancer treatment, with developments as increasing incidence of HPV- positive oropharyngeal carcinoma (OPSCC) and related treatment paradigm shifts, has a significant impact on the role of SS [1–6].

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Evolution of Salvage Surgery

Since the emergence of organ preservation in advanced head and neck cancer there has been an increase in need for salvage surgery with various results. The addition of chemotherapy (CT) to primary radiotherapy (RT) has a reported survival benefit of 4–8% but also increases toxicity leading to a more complication prone course if SS is needed. Goodwin in 2000 commented on salvage surgery as—"the double-edged sword"—in the head and neck addressing these issues posing the key question whether the ends justify the means [7]. Despite the use of modern techniques and the increased use of free tissue transfer, the 5-year overall survival after SS does not exceed 40% [8].

Cisplatin (CP) is widely used as radio sensitizer in combined modality treatment in patients with head and neck squamous cell carcinoma (HNSCC).

Bonner et al. recommended cetuximab (an epidermal growth factor receptor inhibitor) as an alternative for CP in patients in whom CP was contra-indicated and its use grew substantially [9]. The side effects were different from those caused by CP and were mainly a cutaneous rash. In the event of residual disease after cetuximab/RT, so called "bioradiation", SS seemed to meet the same setbacks as in combined modality treatment with CP. In clinical practice, cetuximab also significantly added to toxicity and poorer healing tendency in SS [10]. More recently de-escalation trials have shown that cetuximab/RT results in poorer survival outcome in treating HPV-positive OPSCC as compared to CP/RT and has thus been abandoned in this setting. The focus in de-escalation of HPV-positive disease is now on lowerRT or CCRTdoses, induction chemotherapy with definitive treatment based on the response and on up-front minimally invasive surgery with tailored adjuvant treatments [6]. All of these novel approaches will likely influence the field of SS.

History has shown that any non-surgical treatment prior to salvage surgery is associated with a degree of toxicity, determined by the type of treatment as well as individual patient variation. SS may be needed not only for residual or recurrent disease but also for toxicity related functional loss of the aerodigestive tract. The latter is usually seen in advanced hypopharyngeal or laryngeal cancers. These patients may need a (mostly total) laryngectomy due to recurrent aspiration and pneumonia, dyspnea and cartilage necrosis.

Tumor Factors

The surgeon performing SS in HNSCC has to consider both the tumor stage and site. Early stage tumors are obviously better salvageable than advanced stage tumors. Laryngeal recurrence has the best outcome after SS, in contrast to an isolated neck recurrence with adverse features in the previously treated neck, which is on the other end of the spectrum [7, 11], ·(Table 16.1) Goodwin also showed that the 2- year DFS after SS was 24–55% in recurrent neck disease compared to 58% in

Table 16.1 Survival rate per site [7]

Site (all stages)	Survival (%)
Oral cavity	26
Pharynx	47
Larynx	58
Neck	25
Total	44

Goodwin WJ Jr. Salvage surgery for patients with recurrent squamous cell carcinoma of the upper aerodigestive tract: when do the ends justify the means?. *Laryngoscope*. 2000;110(3 Pt 2 Suppl 93):1–18

Table 16.2 Stage related outcome [7]

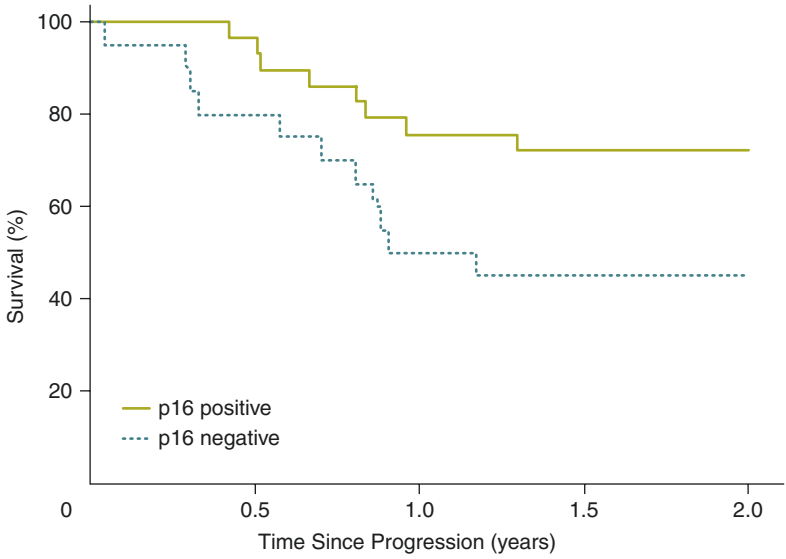
Stage (initial)	I&II	III	IV
2-year survival (%)	70	33	<25
Good QoL(%)	60–85	40	30
Surgical complications	6	30	30
Death related to surgery	Rare	<2%	<2%

Goodwin WJ Jr. Salvage surgery for patients with recurrent squamous cell carcinoma of the upper aerodigestive tract: when do the ends justify the means?. *Laryngoscope*. 2000;110(3 Pt 2 Suppl 93):1–18

recurrent laryngeal carcinoma [7]. Stage is of critical importance as illustrated by a dramatic drop in 2-year post salvage DFS with increasing initial stage (I-II vs. III and IV: 70% vs. 33% and < 25% respectively). Advanced stage disease has a negative impact on quality of life, surgical complications and surgery related death [7]. (Table 16.2) Primary advanced stage disease makes up for the majority of salvage candidates as these tumors show a higher incidence of primary treatment failure. These stage III-IV tumors have a relatively high complication rate with SS. Besides advanced stage disease and positive margins, a short disease-free interval and previous chemotherapy have a negative impact on outcome [12]. Lymph node metastasis at the time of SS and in particular the presence of multiple nodes and/or extracapsular spread (ECS) should be considered as a negative prognostic indicator whereas regional, non- extracapsular single node recurrence outside the previously treated field may result in 5- year disease free survival (DFS) up to 60% [13, 14].

An important factor to consider is the role of HPV in salvage treatment. A 3-year 25% recurrence rate has been reported by different authors. Both Fakhry et al. and Zenga et al. showed that outcome of SS in HPV-positive OPSCC was superior to other sites of HNSCC recurrences. Recurrences in HPV-positive OPSCCs can currently often be treated non-surgically because more patients with HPV(+) OPSCC are being treated nowadays with primary surgery, without adjuvant therapy. Although both HPV+ and HPV- patients benefit from SS with improved overall survival (OS), the outcome of HPV+ patients is superior. (Fig. 16.1) [17–19].

The only independent prognosticator on multivariate analysis is surgical margins. However, achieving clear margins in SS is demanding and extensive



No. at risk					
p16 positive	29	28	22	21	21
p16 negative	20	16	10	9	9

Fig. 16.1 Survival after salvage surgery relative to p16- status [15]. Fakhry C, Zhang Q, Nguyen-Tan PF, et al. Human papillomavirus and overall survival after progression of oropharyngeal squamous cell carcinoma. *J Clin Oncol*. 2014;32 [16]:3365–3373. Reprinted with permission©

submucosal growth makes the delineation of proper margins difficult. This in turn may lead to disappointing histopathological results with only limited (due to previous (chemo) radiation) adjuvant treatment options being available [7, 12, 18].

The best salvageable HNSCC recurrence is laryngeal cancer (2-year DFS 58%, Goodwin) and is the commonest surgically salvaged tumor [20]. Early stage laryngeal cancer is often irradiated or operated on by transoral laser surgery (TLM) as an initial treatment with good results. While the majority of laryngeal SCCs are so called "in the (voice)box" tumors and so surgical margins are relatively easy to achieve in cases of recurrence by performing a laryngectomy (usually total but partial laryngectomy may be feasible in select cases). Van der Putten et al. analyzed outcome of salvage laryngectomy after primary CCRT treatment failure and found a 5- year OS of 27%- Fig. 16.2- and a disease specific survival of 35% [22]. In contrast, advanced OPSCC and hypopharyngeal carcinoma show the poorest outcome in SS. Previous systematic reviews conclude however, that the predominant subsite in head and neck SS is the larynx rendering these subsite differences questionable because of scarce data on advanced non-laryngeal salvaged patients [20]. In oral cavity cancer, primary treatment is essentially surgical. In case of no adverse features after primary surgery adjuvant (chemo) radiation can be avoided. This would leave room for adjuvant treatment in case SS is needed.

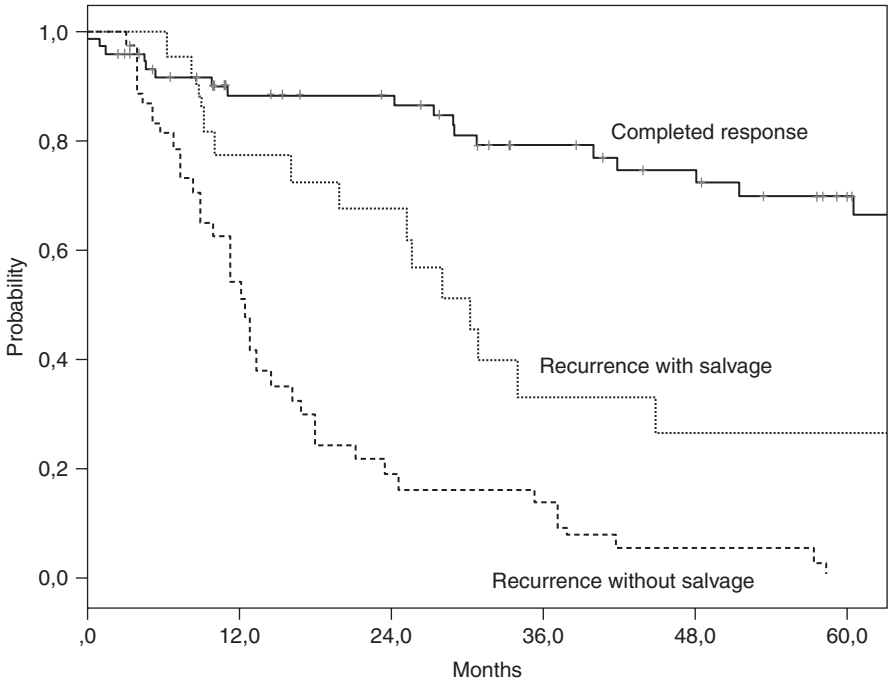


Fig. 16.2 Overall survival after most recent treatment for advanced laryngeal cancer [21]. Putten L, Bree R, Doornaert PA, et al. Salvage surgery in post-chemoradiation laryngeal and hypopharyngeal carcinoma: outcome and review. *Acta Otorhinolaryngol Ital*. 2015;35 [3]:162–172

The key tumor factors thus determining a more favorable course after SS for HNSCC are early stage disease of the tumor, low tumor burden in the neck, no ECS, clear surgical margins, laryngeal site, HPV positivity in OPSCC, no previous chemotherapy and a long disease free interval after initial treatment (>6 months) (Table 16.1) [7, 12–14, 18].

Patient Factors

Patient performance status is equally important for eventual outcome in SS. If considering SS, each case has to be considered individually and be discussed in a multidisciplinary team (MDT). Previous reports have shown irrefutable evidence that MDT discussion leads to an optimal treatment proposition [23, 24]. The definitive decision should not be made by the treating surgeon individually. The patient wishes should be paramount provided that the patient has been thoroughly informed and has a complete understanding of the options available.

Functional status presalvage is a strong indicator for postsalvage outcome. If patients have a relatively poor quality of life (QoL) after primary treatment with

regards to speech and swallowing, further deterioration of these vital functions after SS is likely. Patients should be informed about possible long-term complications like permanent feeding tube dependency and tracheostomy [25–28]. In salvage laryngectomy for toxicity induced sequalae the intention is to restore swallowing and the airway by tracheostomy for improvement of QoL. Whether this expected QoL is accurately predictable and acceptable for the patient will differ in each individual case. Shared decision making is key in this respect and has been more highlighted over the past years with growing attention to value based healthcare [29].

Comorbidities play an important role in the expected outcomes of SS. Is the patient safely able to undergo extensive surgery and is his/her vascular status sufficient for possible use of free flaps? Is the feeding status sufficient to minimize post-operative wound healing problems and other complications? If adjuvant systemic treatment is expected then there should be no medical contra-indication for that (e.g. poorly controlled diabetes or extensive cardiovascular disease). There should at least be a realistic aim to optimize the patient's condition prior to SS to allow for a non-eventful recovery. Kim et al. have advocated the use of the Charlson-Age Comorbidity Index (CACI) as prognostic model for outcome prediction in SS [15, 16, 30–32].

Lastly, the patient's family should not be overlooked. The impact of head and neck cancer on family life is significant and patients considered for SS have been in this situation with their relatives already during the course of their primary treatment. Residual or recurrence of a tumor is devastating and SS brings uncertainties and anxiety for everyone involved. It is of utmost importance to involve the patient's network and offer psychosocial support for those in need [21].

Reconstructive Surgery after Resection for Salvage

The use of pedicled flaps such as the pectoralis major myo(cutaneous) (PMM(C)) flap and the latissimus dorsi (LD) flap have been reported since decades. Ariyan was the first (1979) to describe the PMMC flap in head and neck reconstruction [33]. Today, the PMM(C) is still considered one of the more versatile flaps for reconstruction as well as a preventive measure for wound healing problems such as wound dehiscence or pharyngocutaneous fistula after laryngectomy.

While pedicled flaps are still very useful, free flaps have gained a predominant place in SS over the last decades. It is advantageous to bring healthy, well vascularized tissue in an irradiated environment without having to use local tissue with potential limited geometry.

In SS, the neck is invariably vessel depleted due to sacrifice of the vessels at the time of previous surgery or due to the effects of chemoradiotherapy. Scarring may make identification and isolation of vessels difficult. These factors make reconstructive and in particular free flap surgery a challenge. Pre-operative assessment in terms of reviewing previous operation notes and imaging is essential. A dual phase CT-scan or MR angiogram will predict what neck vasculature may be used for reconstruction

and thus aid planning of the surgery. Vessels within the radiation field, especially after 60–70 Gy, have been shown to have significant intimal changes in arteries [34]. Thus it may be advisable to avoid the use of vessels exposed to high levels of radiation. Previous radiation may also adversely affect the success of microvascular reconstruction [35, 36]. Other studies showed equivalent free flap success rates but an increased incidence of complications [37, 38]. Care must be taken to choose the correct flap for reconstruction and ensure that the flap has adequate pedicle length. Soft tissue flaps with good pedicle length are the radial forearm, anterolateral thigh, latissimus dorsi and rectus abdominis flaps. Composite flaps with good pedicle lengths are the fibula and tip of scapula. (Fig. 16.3) Flaps with poor pedicle length are the Deep circumflex iliac artery and the scapula flap. (Fig. 16.4).

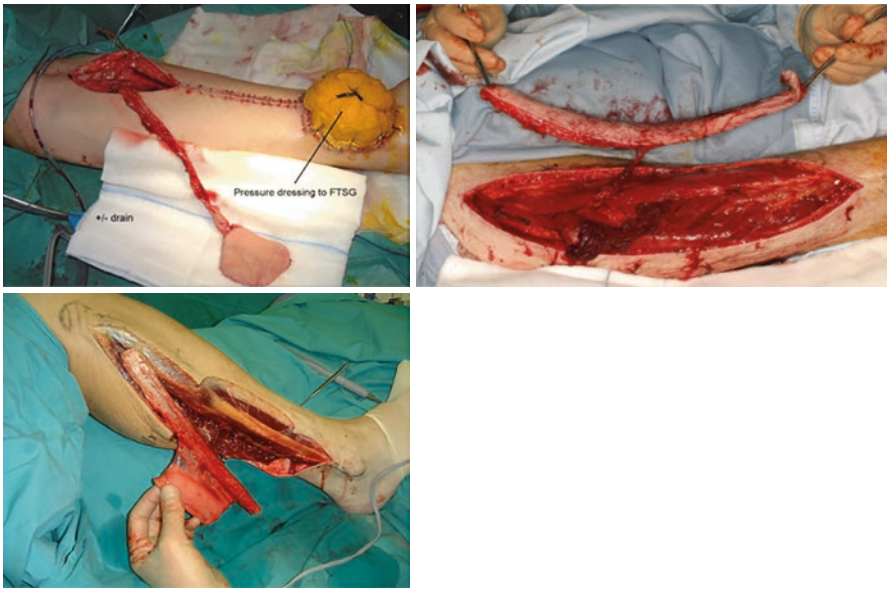


Fig. 16.3 Flaps with adequate pedicle length—radial, anterolateral thigh and fibula

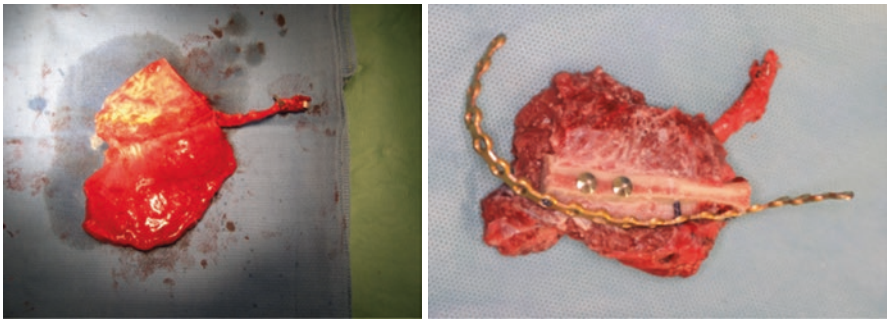


Fig. 16.4 Flaps with poor pedicle length- Deep Circumflex Iliac Artery bone flap and Scapula flaps

Arterial and Venous Options for Reconstruction in a Salvage Neck

Normally branches of the external carotid artery are used if found and patent. If no branches are found the external carotid artery can be harvested at its distal end and end to end anastomosis carried out but there is often a discrepancy in vessel size.

Arteries from the contra-lateral neck can be used but require the flap pedicle length to be long or need vein grafts. End to side anastomosis on the carotid artery has also been described, with no neurological deficit. The transverse cervical artery and vein are vessels located at the base of level IV. They have a reasonable calibre but a flap with a long pedicle is often required. The artery is more reliable then the vein. The Internal mammary vessels are located on the under surface of the upper 6 ribs just lateral to the sternum. Studies show that with careful dissection 85% of internal mammary pedicles can reach the mandibular angle [39]. A corlett loop uses the cephalic vein that is mobilised and detached distally and this is anastomosed to an artery in the contra-lateral neck to create a fistula. This is then divided and provides a longer artery and vein for anastomosis to the flap. Vein grafts can be utilised to lengthen the pedicle length for both arteries and veins. However, vein grafts require two anastomoses for each vessel and thus have a higher rate of failure in several studies [40].

Venous Options for Reconstruction in a Salvage Neck

The use of vein grafts, transverse cervical vessels, the corlett loop and internal mammary vessels have already been described above. The cephalic vein can be harvested, detached distally and rotated into the neck for the venous anastomosis. The vein can be easily found in the deltopectoral groove, detached distally and rotated either under or above the clavicle (Figs. 16.5 and 16.6).

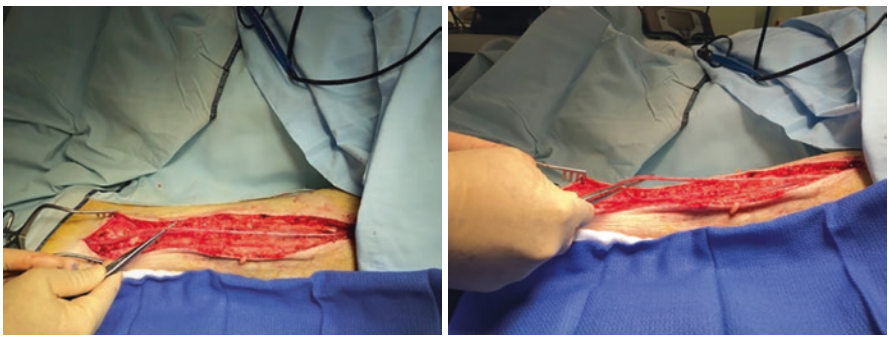


Fig. 16.5 Harvest of long saphenous vein

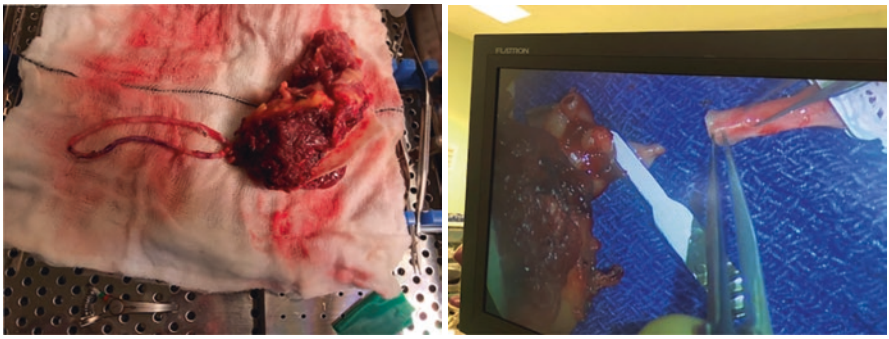


Fig. 16.6 Vein grafts anastomosed to a scapula flap to lengthen the pedicle

Advanced Options for Reconstruction in a Salvage Neck

The pedicle from a previous reconstruction may be used for a new reconstruction but makes the assumption that the former flap has developed an alternate vascularisation. Extracorporeal perfusion of microvascular reconstruction has been described by Wolff for reconstruction in vessel depleted necks. They were able to use the devices for up to two weeks to allow flap autonomization and become independent of the ECMO (Extracorporeal Membrane Oxygenation) machine [41].

Complications in Salvage Surgery

The reported complication rates in SS for recurrent HNSCC can be 67% illustrating that SS is not easily embarked on [16]. In order to improve uniformity and reproducibility in reporting surgical complications, the use of the Clavien Dindo classification for head and neck surgical oncology has been adopted [42]. The addition of neck dissection (ND) to SS for the primary tumor site increases the risk of complications [43–45]. Complications after SS after primary CCRT have been identified as an independent predictor for poor prognosis [46]. Besides the perioperative complications, long term complications as progressive fibrosis, feeding tube dependency and permanent tracheostomy are frequently observed after SS [25–28].

Ideal Candidates

The crucial question to be posed is which patients are amenable for SS with realistic chances of cure and acceptable functional outcome. Ideally, these would be non-smoking and non- drinking young patients with no comorbidities and where initial treatment was for an early stage head and neck cancer. In the past these types of

patients were rare but since the increase in HPV-positive OPSCC they are regularly seen. Primary treatment may be transoral robotic surgery (TORS) combined with ND in case of nodal disease and CCRT in advanced cases of OPSCC or in the presence of ECS. De-escalation of primary and adjuvant treatment is an ongoing subject of multiple trials on the brink of reporting like PATHOS and ECOG E-3311 [3, 47]. Fakhry et al. reported on a significantly better outcome in SS for p16 positive OPSCC (72% 2-y OS) than for p16 negative OPSCC (45% 2-y OS) [28].

In practice, ideal candidates are however seldom encountered as described by Zafereo et al. [32]. They concluded that 3-and 5 year- OS in SS for recurrent OPSCC is only 42% and 28% respectively. Young patients (representing a mere 7% of the total group of recurrent OPSCC) with a prolonged disease free interval and small recurrent tumors had 3- and 5-year OS were 74% and 44% respectively. This poses the question whether prognostic modelling could be of help in decision making. Since several prognosticators have been identified, tools are available for guidance in treatment strategy. Hamoir and Tan for example have proposed a decision model based on comorbidity index, local recurrence vs. loco-regional recurrence, larynx vs. non- larynx and early vs. advanced stage disease. In cases of an early stage laryngeal local recurrence, 2- year DFS up to 96% may be possible. However, as soon as one negative prognosticator was added, the rate dropped dramatically to around 60% and even to 28.6% in cases of an advanced, non-larynx loco-regional recurrence [37, 38]. Other studies have proven that young age as a positive factor and that the presalvage Charlson-Age Comorbidity Index (CACI) can be applied in prognostic modelling [36, 40].

There should be a realistic chance of achieving a R0 resection before proceeding with SS since positive margins in SS have been reported in up to 22% of cases due to reasons already mentioned (submucosal spread, perineural invasion). Positive but even close margins have been identified as an independent factor for re-recurrence. This should be put in perspective since 5- year OS is reportedly around 40% even in cases of clear margins [34, 40, 41]. Positive margins status and/or ECS after SS should be an incentive for enrolment in clinical trials for adjuvant treatment with chemo- or immunotherapy. Table 16.3 summarizes the prognosticators in head and neck salvage surgery.

Table 16.3 Prognosticators in salvage surgery

Positive prognosticators	Negative prognosticators
Early stage disease	Advanced stage disease
Clear surgical margins	Positive surgical margins
Laryngeal site	Non- laryngeal site
HPV positive in OPSCC	HPV negative in OPSCC
No previous chemotherapy	Previous chemotherapy
>6 months DFS	<6 months DFS
N0–1 without ECS	N > 1 or ECS present

Conclusion

SS is the preferred rescue modality after primary treatment failure in HNSCC. Despite the evolution in surgical techniques, improvement of pre- and postoperative care, treatment in designated head and neck centers, an increasing incidence of HPV-associated OPSCC, improved patient selection and an ongoing understanding of prognosticators, 5- year OS is in the range of 30–50% to date [48].

The decision to proceed with SS should therefore not be taken lightly and always in careful discussion with the patient and in the MDT meeting after meticulous analysis of the tumor and patient factors. Expectations should be realistic and communicated in that manner with everyone involved.

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