Review Article

Salvage surgery after definitive chemoradiotherapy for esophageal cancer

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Abstract: Salvage esophageal resection after chemoradiation is an increasingly recognized clinical challenge, especially in the context of esophageal squamous cell carcinoma. Despite that, there have been varying definitions of salvage in the literature, leading to difficulties in interpreting data. This is further complicated by the limitations in assessing clinical complete response after chemoradiation. At the same time, salvage esophagectomy has classically been approached with reservation because of the associated morbidity and mortality, especially that definitive chemoradiation is sometimes the preferred choice of treatment for borderline-operable and borderline-resectable patients. While some reports have shown good survival outcomes, others have shown the opposite. Yet, the morbidity rate remains relatively high. From a surgical point of view, borderline-operable patients can be further optimized with specialized prehabilitation programs, which have been demonstrated to be useful in gastroesophageal cancers. Intraoperatively, there are important technical modifications that need to be taken into consideration. A special consideration should also be given to patients with limited airway involvement. In this review, we explore the different definitions of salvage and discuss clinical complete response after chemoradiation. We also discuss the postoperative and survival outcomes of salvage esophagectomy. A special focus is given to preoperative optimization and intraoperative technical aspects, including airway resection. Finally, the ongoing clinical trials looking into this subject are discussed.

Keywords: Esophagus; esophageal cancer; salvage esophagectomy; chemoradiation

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Introduction

Esophagectomy after definitive chemoradiotherapy for esophageal cancer presents with many challenges. To begin with, there is paucity of good-quality evidence in the literature that can assist the provider in navigating this clinical problem, as most of the current data is derived from retrospective studies. These data are hampered by a clear definition of salvage esophagectomy, variably described as resection for a persistent disease after a surgery exclusive curative intent treatment (e.g., chemoradiation), resection of recurrent disease after clinical complete response, or resection after a certain defined time period after chemoradiation irrespective of initial treatment intent. This absence of a uniform definition of "salvage" complicates accurate analysis of the literature. This is further complicated by the fact that many patients who undergo definitive chemoradiation have borderline resectability (e.g., cT4 lesions) or operability characteristics (poor performance status or co-morbidities) that prevent

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them from undergoing curative-intent surgery in the first place. Finally, salvage surgery after induction therapy, particularly radiation, can be technically challenging and may be associated with significant post-operative morbidity and mortality. The aim of this review is to shed light on the outcomes of salvage esophagectomy.

Definition of "salvage" esophagectomy

The definition of salvage esophagectomy in the literature entails a number of clinical scenarios. These include resection after clinical complete response with neo-adjuvant therapy in good surgical candidates, resection for *recurrent* disease after clinical complete response with neo-adjuvant therapy, or resection for recurrent/persistent disease after *definitive* chemoradiation. Patients with proximal/middle squamous cell carcinoma of the esophagus treated with chemoradiation represent a unique subset given the common use of such treatment strategy in this patient population. In addition to these treatment- and response-based definitions, "salvage esophagectomy" has also been considered in patients with borderline-resectable lesions or lesions that are resectable but within borderline-operable candidates. Given all that, a more inclusive definition of salvage is surgical resection after surgery exclusive curative-intent therapy.

As can be observed, the aforementioned clinical scenarios are not the same. Each one represents a special patient population who differ in terms of initial treatment, underlying pathology, response to treatment, and operability. In most centers, definitive chemoradiation entails a radiation dose of at least 50 Gy, whilst the doses used in the neo-adjuvant setting are lower (30–41.4 Gy) (1,2). These differences in treatment intent are of higher clinical significance than the actual timing of surgery in defining "salvage". This variation has made the interpretation of data in the literature challenging. Along these lines, it is imperative to reach a consensus with regards to the accurate definition of "salvage" in clinical studies.

What does clinical complete response mean?

In the CROSS trial, it was observed that one third of patients had pathological complete response (pCR) in their resected specimens (1). The rate of pCR was higher in the squamous cell carcinoma group compared to the adenocarcinoma one, which is likely a reflection of the higher response rate of the former to chemoradiation. It was hypothesized that surgical resection may be of no clinical benefit in this subset of patients (3). Another group that will, theoretically, not benefit from surgery are those with subclinical micrometastasis at the time of initial presentation or at the time of neo-adjuvant treatment (3). These patients will likely develop "recurrent" distant metastasis irrespective of the locoregional treatment received (3).

One of the main challenges in defining "salvage" is the ability to clinically confirm disease eradication after induction chemotherapy or chemoradiotherapy. Unfortunately, although the currently available investigations modalities can guide that, these are unreliable (4). Regular endoscopic biopsies have been shown to have a false-negative rate of 31% compared to 11% with bite-on-bite biopsies (5). The false negative rate of PET-CT after neo-adjuvant chemoradiation is also high, being in the range of 12–54% (3). Finally, the false negative rate of endoscopic ultrasound is around 29% (5,6). As a result, a large proportion of patients who are labelled as complete clinical responders end up having residual disease on final pathological analysis (7).

All this highlight the importance of adopting a standardized, active surveillance protocol for patients undergoing non-surgical treatment of esophageal cancer. This is clearly advantageous in terms of management, reporting, and research. The aim of this "active" surveillance is to detect disease when it is still curable. It should mainly focus on the first 2 years after surgery, as this is when the vast majority of recurrences occur (3).

Results of definitive chemoradiation and salvage esophagectomy

Several retrospective studies have evaluated the rates and patterns of disease recurrence after definitive chemoradiation. In a retrospective review by Munch and colleagues (8), patients with squamous cell carcinoma who underwent definitive chemoradiation had 38%, 13%, and 16% rates of local, regional, and distant failures, respectively. Despite that, the difference in overall survival when compared to the neo-adjuvant therapy followed by surgery group was not statistically significant. Similar locoregional recurrence patterns were observed by Barbetta and colleagues: 38%, 19%, and 38% local, regional, and distant 5-year recurrences (9).

These studies demonstrate the fact that the majority of treatment failures were locoregional, highlighting the importance of optimal local control, which can be achieved with surgery. This has been demonstrated in

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the two randomized controlled trials that compared definitive chemoradiation to neo-adjuvant chemoradiation followed by surgery in esophageal SCC (10,11). Both trials showed that surgery may be associated with improved local recurrence rate. Nevertheless, this did not lead to a difference in overall survival, which is likely related to the exceptionally high operative mortality in these trials.

Salvage esophagectomy has been received with skepticism because of the perceived morbidity it carries. In the retrospective review of the Memorial Sloan Kettering Cancer Center's (MSKCC) experience by Barbetta and colleagues, 17 out of 124 patients underwent salvage surgery after definitive chemoradiation for esophageal squamous cell carcinoma (9). The rate of grade 3 and above pulmonary complications and anastomotic leaks were 29% and 18%, respectively. Overall, the rate of all grade 3 and above complications was 53%. Similarly, a meta-analysis of 28 studies by Faiz and colleagues (12) reported 30% pulmonary complications and 19% anastomotic leaks in patients who underwent salvage esophagectomy after definitive chemoradiation. These results seem to be comparable to the CROSS trial, which reported a 46% rate of pulmonary complications and 22% rate of anastomotic leaks in the neo-adjuvant chemoradiation followed by surgery group (1). With regards to perioperative mortality, the reported 30- and 90-day mortality rates are 2.6% and 8%, respectively (12).

Data regarding overall survival has been inconsistent (13). The MSKCC group reported worse 5-year overall survival amongst patients undergoing definitive chemoradiation followed by salvage esophagectomy compared to those undergoing planned surgery (29% *vs.* 45%) (9). These were consistent with the pooled 5-year overall survival rate reported in the meta-analysis by Faiz and colleagues (24%) (12). On the other hand, the MD Anderson group reported no difference in the 3-year overall survival between the two groups (48% *vs.* 57%) (14). When compared to systemic therapy and/or boost radiotherapy, salvage esophagectomy for recurrent/persistent may be associated with superior oncological outcomes in patients with locoregional failure after chemoradiation (15).

In summary, while the morbidity of salvage esophagectomy has been consistently demonstrated in the literature, the reported survival outcomes are conflicting. *Table 1* summarizes the results of the surgical series published between 2018 and 2020, which included patients who underwent salvage esophagectomy.

Special considerations

Patient selection, pre-habilitation, and timing of surgery

As mentioned, salvage esophagectomy can be associated with significant morbidity. This may partly be attributed to the performance status of patients after a relatively intense chemoradiotherapy course. In fact, one of the indications for adopting a surgery exclusive curative intent treatment plan in patients with resectable disease is their borderline operability based on co-morbidities and performance status. In addition to that, it has previously been shown that neo-adjuvant chemotherapy in esophageal and gastric cancer patients is associated with decline in physical fitness, evident by reduction in the oxygen uptake levels at peak exercise (25). Moreover, radiation therapy can make surgery technically challenging because of radiation-related mediastinal fibrosis. Radiation may also lead to declined pulmonary function secondary to radiation-induced pneumonitis as well as impaired wound-healing. Given that surgery in this group of patients offers the only chance for overall survival (26,27), it is imperative to enroll borderline candidates into structured pre-habilitation programs that aim at optimizing their cardiopulmonary and nutritional reserves. Although it is difficult to extract this specific patient population from the retrospective datasets in the literature, they most certainly exist. Our group has previously shown that preoperative exercise and nutrition optimization in patients with esophagogastric junction cancers is associated with improved perioperative functional capacity, reflected by improvement in 6-minute walk test scores (28).

The timing of salvage surgery is a crucial variable to take into account. Longer interval between chemoradiation and surgery may be associated with more intense mediastinal fibrosis and hypervascularity, which in turn increase the technical complexity of the surgery. As expected, this can be influenced by whether the locoregional failure is secondary to recurrence or persistent disease. As mentioned earlier, it is imperative to enroll patients who receive definitive chemoradiation into vigorous surveillance programs, especially during the first 2 years of treatment in order to plan any possible salvage esophagectomy in a timely fashion.

Technical modifications

There are a number of important technical modifications that must be taken into consideration with regards to salvage esophagectomy. To begin with, anastomosis in irradiated

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Table 1 Outcomes of surgical series, published between 2018 and 2020, that included patients who underwent salvage esophagectomy

Study	N	Histology	Stage	Indications	Chemoradiation	Surgery	R0	Complications	Mortality	Survival
Barbetta, 2018 (9)	17	SCC	II and III	16 local and 1 regional recurrence after dCRT	5,040 cGy	–	–	Overall grade ≥3: 53%. Grade ≥3 leak: 18%	30-day mortality 18%	5-year OS 29% for dCRT group
Cohen, 2018 (16)	308	ADC and SCC	64% with stage III–IV	Persistent (within 90 days) or recurrent disease after dCRT	5-FU + cisplatin or oxaliplatin with 50.4 Gy radiation	Transthoracic (94%)	87.3%	Overall: 34.7%. Leak: 12.7%	30-day mortality 6.2% (in-hospital 8.4%)	5-year OS 34%
Hayami, 2018 (17)	70	SCC	I–IV (50% unresectable)	Persistent (within 90 days) in 46 patients and recurrent disease in 24	81.4% CRT. 77% 5-FU + cisplatin. Radiation dose: 50–70 Gy	Transthoracic 95.7%	72.9%	Overall: 60%. Leak 12.9%	–	5-year OS with and without pulmonary complications 11.7% and 28.5%, respectively
Kiyozumi, 2018 (18)	50	SCC	0–IV	Persistent or recurrent disease after dCRT	5-FU + cisplatin +/– docetaxel. 50.4 Gy radiation.	3-incision (80%)	–	Grade ≥II: 58%.	None	–
Levinsky, 2020 (19)	667	ADC	II–III	Esophagectomy ≥90 days after CRT	45 Gy radiation + multiagent chemotherapy	44% open surgery, 22% laparoscopic	95.9%	–	30-day mortality 4%; 90-day 10.4%	Median OS 30.2 months
Mitchell, 2020 (20)	35	SCC	cT3-4 (77%) cN0 (51.4%)	Failure of bimodality therapy	5FU + platinum or taxane. Radiation: 50.4 Gy (in 57%)	3-field 57.1%; 2-field 42.9%	91.4%	Overall grade ≥3: 54%; Grade ≥3 leak: 5.7%	30-day mortality 8.6%; 90-day 17.1%	5-year OS 24%
Sugawara, 2020 (21)	31	SCC	cT4	Clinical partial response after dCRT (at least 30% decrease in greatest tumor dimension)	Platinum-based chemotherapy. Radiation 50.4–65.4 Gy	Ivor Lewis or McKeown esophagectomy (done in 27/31 patients)	71%	Overall grade ≥3: 29%	In-hospital deaths: 10%	3-year OS 59% for R0 resections
Sugimura, 2020 (22)	73	SCC	III–IV (59%)	Persistent or recurrent disease after dCRT	5FU + cisplatin. Radiation: 50–70 Gy	2-field esophagectomy (63%)	86%	Overall complications: 47%. Leak: 19%.	In-hospital mortality 7%	5-year OS 42%
Nagai, 2020 (23)	11	SCC	cT1 (72%), cN0 (91%)	Superficial local failure after dCRT	–	–	–	Overall grade ≥3: 82%	–	3-year OS 72%
Anderegg, 2020 (24)	11	SCC and ADC	T4b	Absence of preoperative airway invasion to the epithelium and no intraoperative need for airway, cardiac, aortic, or vertebral resection	Carboplatin + paclitaxel. Radiation: 50.4 Gy	–	81.8%	Overall: 81.8%, leak: 18.2%, conduit necrosis: 9.1%	In-hospital mortality 18.2%	3-year OS 37.5%

ADC, adenocarcinoma; SCC, squamous cell carcinoma; dCRT, definitive chemoradiation; CRT, chemoradiation; OS, overall survival.

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fields should be avoided, which usually requires fashioning a cervical anastomosis. A pharyngolaryngoesophagectomy may be required, especially that a significant proportion of patients who undergo definitive chemoradiation have proximal squamous cell cancers (8). Previous irradiation to the posterior mediastinum may require the conduit to be placed retrosternally. In the case of significant gastric irradiation, a colon interposition may be a safer option. Extensive dissection around the airways should be avoided to reduce the risk of airway stenosis. In addition, the use of omental buttress to cover the anastomosis should be strongly considered. In malnourished patients, fashioning a feeding jejunostomy may prove to be valuable. Postoperatively, the use of stents in the management of anastomotic leaks should be avoided, as these can easily erode through previously irradiated tissues. In the event of airway invasion, induction chemotherapy is preferred over radiation to mitigate the risk of a tracheoesophageal fistula.

"Inoperable" (cT4) patients

Patients with borderline-resectable esophageal cancer represent a unique subgroup in whom "salvage" esophagectomy may be considered if there is evidence of downstaging of the persistent disease to resectability. The COSMOS group prospectively investigated survival after salvage surgery in patients with stage 3C and cT4b esophageal cancers that became resectable after induction chemotherapy (29) and have demonstrated in their follow-up analysis a 46.6% 3-year overall survival rate (30). Miyata and colleagues (27) retrospectively reviewed 169 patients with cT4, of whom 63% had tracheal invasion, 18% had aortic invasion, and 6% had both. After confirming resectability, 98 patients underwent surgical resection after neo-adjuvant therapy. The 5-year OS in this group was 39.8% compared to 3.5% in those who did not undergo surgery (27). More recently, Anderegg and colleagues (24) analyzed the outcomes of 15 patients with cT4b disease who underwent "extended" neo-adjuvant chemoradiation: 10 with invasion of the aorta, 4 with invasion of the tracheobronchial tree, and one with liver invasion. Of those, 4 patients developed metastatic disease before surgery, and one declined it. Eventually, the remaining 11 patients underwent surgical resection. Although the intraoperative need for aortic, vertebral, cardiac, or tracheobronchial tree resection was considered a contraindication, all patients underwent esophagectomy with an R0 rate of 81.8% (9/11). Nine patients developed postoperative complications (81.8%), 2 had an anastomotic leak (18.2%), and one developed conduit necrosis (9.1%). The rate of in-hospital mortality was 18.2% (2/11) and the 3-year OS was 37.5% (24). Again, this data shows that overall survival can be achieved with cT4 tumors that become resectable after neo-adjuvant therapy but at the cost of increased morbidity and in-hospital mortality.

Patients with airway invasion require special attention. Unlike aortic and spinal invasion, definitive chemoradiation has been generally avoided in these cases because of the risk of tracheoesophageal fistula formation, committing this group of patients to dismal outcomes (31). Therefore, the best chance for survival is with surgical resection where feasible. Concurrent, limited airway resection potentially requires complex reconstruction, such as with pectoralis muscle flap, or bovine pericardium in the event of membranous airway involvement. We have recently published our experience in esophagectomy with en bloc airway resection and reconstruction for cT4b-(airway) esophageal cancers after induction therapy (32). Out of the 14 patients identified, 7 were reconstructed with bovine pericardium, 3 with pectoralis major muscle flap, and 4 with mediastinal tracheostomy. One patient required a pneumonectomy. The 3-year overall survival of this highly selected group of patients was 34% (32). Possession of such armamentarium within an advanced esophageal surgery program is key to achieving success with these kinds of extended resections. As expected, the main aim in salvage surgery is to achieve a complete R0 resection, as this is associated with superior overall survival (15,30).

Future trials

There are a number of currently enrolling trials that will help provide additional information with regards to salvage esophagectomy. These include the NEEDS trial (NCT04460352), which is a phase III randomized clinical trial comparing neo-adjuvant chemoradiotherapy followed by planned surgery versus definitive chemoradiotherapy followed by surgery only when needed for persistent or recurrent disease in esophageal squamous cell carcinoma. In addition, the SANO trial is a multi-center phase III non-inferior randomized controlled trial that is comparing surgery to active surveillance and delayed resection (33); whether this constitutes "salvage" is a matter of debate. Finally, the ESOSTRATE trial is a randomized controlled that is comparing systematic surgery to surveillance and rescue surgery in patient with complete clinical response

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after chemoradiation (NCT02551458).

Conclusions

To summarize, salvage esophagectomy may be the sole option of cure for patients with persistent/recurrent disease after chemoradiation and is associated with a relatively high morbidity and postoperative mortality rates. The data regarding survival outcomes are conflicting. Important technical modifications must be taken into consideration, which may require extensive surgery to achieve a complete R0 resection. Currently enrolling randomized controlled trials will shed further light on this complex clinical problem and will hopefully provide more robust evidence to guide shared decision-making.

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