Review Article

Surveillance or resection after chemoradiation in esophageal cancer

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Abstract: The treatment of locally advanced esophageal cancer continues to evolve. Previously, surgery was considered the foundation of treatment, but chemoradiation (CRT) has taken on a larger role both in the neoadjuvant setting and as definitive treatment. It has become clear that although some patients benefit from esophagectomy after CRT, a large subset of patients likely derive no benefit, and may be harmed by surgery. Some patients are cured from CRT alone and therefore do not need surgery. Another group of patients likely have metastatic disease at the time of local therapy that is just undetected on imaging and also do not benefit from surgery. A third group of patients will have persistent locoregional disease only after CRT. This last group is the subset who will actually benefit from surgery, but this likely comprises only a minority of patients with locally advanced disease. A strategy to maximize survival while minimizing unnecessary surgery is a reasonable goal, but present technology does not allow us to do this with certainty. Thus, the decision of whether to pursue resection or surveillance after CRT can be difficult as clinicians and patients try to balance the goal of maximizing the likelihood of cure against the risk of surgery and its impact on quality of life.

Keywords: Esophageal cancer; esophagectomy; definitive chemoradiation (CRT); neoadjuvant chemoradiotherapy (nCRT)

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Introduction

Esophageal cancer is the sixth leading cause of cancer-related mortality worldwide due to its overall poor prognosis (1). The global age-standardized incidence rate of esophageal squamous cell carcinoma (ESCC) is 1.4–13.6 per 100,000 people (2). Esophageal cancer is estimated to be responsible for 15,690 deaths and 16,940 new cases in the United States in 2016 (3). The majority of patients present with locally advanced or systemic disease and outcomes remain poor despite advances in treatment (4,5). Although esophagectomy has traditionally been the mainstay of curative treatment for esophageal cancer, the role of surgery has been evolving. Fewer and fewer patients are being treated with esophagectomy alone. Endoscopic mucosal resection and ablation have achieved excellent results in patients with very early stage disease such as high grade dysplasia or intramucosal tumors. Esophagectomy as monotherapy remains the treatment of choice only for that small subset of patient with local disease not amenable to endoscopic therapy, but not yet considered locally advanced—multifocal T1a tumors, T1b tumors, and some T2 tumors (6-8).

Trimodality therapy with neoadjuvant chemoradiation (nCRT) followed by surgery has become the standard of care for many patients with locally advanced esophageal...
cancer. Multiple randomized studies have demonstrated the advantages of nCRT including tumor down staging, enhanced resectability (R0 resection), better local control, and most importantly, improved overall survival (OS). While trimodality therapy has become increasingly common in the treatment of locally advanced esophageal cancer, evidence has also emerged supporting the use of definitive CRT for some patients. Retrospective studies of definitive CRT for esophageal cancer have reported survival rates comparable to those for trimodality therapy (9). Randomized controlled trials, with predominantly squamous cell patients, have not found a survival benefit for the addition of surgery after CRT, calling into question the necessity of surgery (10,11). Based on the available data, there appears to be only a group of patients who actually derive a survival benefit from esophagectomy after CRT, but identifying that group of patients is problematic (12). Thus, for patients who have a good response to CRT, the decision of whether to undergo surveillance or resection is difficult.

Emergence of nCRT

In the first randomized study investigating nCRT for esophageal carcinoma, performed by Walsh et al., trimodality therapy was associated with a longer median survival (16 vs. 11 months, \(P=0.01\)) and a higher 3-year survival rate (32% vs. 6%, \(P=0.01\)), when compared to surgery alone (13). Since then, additional studies and meta-analyses have demonstrated the superiority of treatment with nCRT plus surgery as compared to surgery alone for locally advanced esophageal cancer (14-17). Over the past 20 years, the use of nCRT has become much more common. As experience with trimodality therapy has increased, there has been greater recognition that some patients have pathologic complete response (pCR) after nCRT with no evidence of residual tumor on final pathology. This appears to be a true reflection of treatment response, rather than a sampling error (18). As opposed to nCRT which rarely leads to pCR, nCRT may lead to pCR in a significant percentage of patients (19).

Importance of pathologic response

Multiple studies have demonstrated the importance of pCR for prognosis. In many studies, the pathologic response to nCRT was the most important factor for OS (20-24). Due to the heterogeneity of patient characteristics and treatment regimens, studies have reported a wide range of pCR rates. In randomized trials of nCRT, pCR rates of 16–43% have been reported (Table 1). In a prospective study, Lee et al. showed that pCR was achieved in 43% [95% confidence interval (CI), 27–59%] of patients who underwent surgery after CRT (24). Samson et al. reported that a pCR rate of 17.2% (30). There is a myriad of factors that likely influence the probability of achieving pCR. Squamous cell histology has generally been thought to be more responsive to radiotherapy than adenocarcinoma (AC). Burmeister et al. reported that the pCR of squamous cell carcinoma (SCC)

<table>
<thead>
<tr>
<th>Study/year</th>
<th>Patients (nCRT + S/S) (n)</th>
<th>Histology (SCC/AC%)</th>
<th>pCR% (CRT + S group)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bosset et al. 1997</td>
<td>143/139</td>
<td>SCC 100%</td>
<td>26</td>
</tr>
<tr>
<td>Walsh et al. 1996</td>
<td>58/55</td>
<td>AC 100%</td>
<td>22</td>
</tr>
<tr>
<td>Urba et al. 2001</td>
<td>50/50</td>
<td>75%/25%</td>
<td>28</td>
</tr>
<tr>
<td>Lee et al. 2004</td>
<td>51/50</td>
<td>SCC 100%</td>
<td>43</td>
</tr>
<tr>
<td>Burmeister et al. 2005</td>
<td>128/128</td>
<td>37%/62%</td>
<td>16</td>
</tr>
<tr>
<td>Tepper et al. 2008</td>
<td>30/26</td>
<td>25%/75%</td>
<td>40</td>
</tr>
<tr>
<td>van Hagen et al. 2012</td>
<td>178/188</td>
<td>23%/75%</td>
<td>29</td>
</tr>
<tr>
<td>Saeki et al. 2013</td>
<td>102/81</td>
<td>SCC</td>
<td>20.1</td>
</tr>
<tr>
<td>Mariette et al. 2014 (FFCD 9901)</td>
<td>98/97</td>
<td>70%/29%</td>
<td>33.3</td>
</tr>
<tr>
<td>van der Woude et al. 2016 (14)</td>
<td>178/188</td>
<td>NA</td>
<td>29</td>
</tr>
</tbody>
</table>

S, surgery alone; CRT + S, chemoradiotherapy and surgery; SCC, squamous cell carcinoma; AC, adenocarcinoma; pCR, pathological complete response; NA, not available.
is higher than AC (27). However, in a review of multiple, heterogeneous studies, Bollschweiler et al. reported that SCC was not consistently associated with improved rates of pCR (31). More recent studies have reported greater response rates in SCC than for AC. In the CROSS trial, patients with squamous histology had more than double the rate of pCR (49%) compared to AC (23%, P=0.008) (16). One study found that patient age, smoking history, and tumor diameter were predictors of pCR (32).

**Definitive CRT**

Definitive CRT has long been the standard treatment for unresectable disease and has been an option for patients with poor physical status or patients who refuse esophagectomy (33,34). The JCOG 9906 trial, reported by Kato et al., reported survival rates after definitive CRT for stage II and III esophageal SCC that were similar to trimplodity therapy (median survival of 29 months, 3- and 5-year survival rates of 44.7% and 36.8%, respectively) (35). Two European randomized trials of CRT vs. trimplodity therapy have also provided evidence to support the use of definitive CRT even for patients who are surgical candidates. Bedenne et al. (FFCD 9102) and Stahl et al. randomized patients to either surgical resection after CRT or definitive CRT. Neither of these studies found a survival benefit for surgery. However, postoperative mortality after esophagectomy was relatively high in both studies and locoregional control was significantly better with surgery in both studies (10,11). These studies were largely performed before more modern staging with positron emission tomography/computed tomography (PET/CT) and endoscopic ultrasound, which probably would have identified additional patients with metastatic disease. Retrospective studies have reported improved survival for treatment that includes surgery, but these studies are obviously limited by selection bias (36). Even if esophagectomy offers some survival benefit, that benefit must be weighed against the potential short-term and long-term harms, including perioperative mortality and morbidity, and adverse effects on long-term quality of life (37).

One important consideration for definitive CRT is the dose of radiation. Evidence from the intergroup (INT) 0123 trial (RTOG 94-05) indicates that the optimal dose for nCRT and definitive CRT are equivalent, and that higher doses beyond 50 Gy of radiation are unwarranted even for definitive CRT (38). In some ways, this eliminates the need to decide on definitive or nCRT prior to therapy. The decision to perform surgery may be made after completion of CRT without compromising the chemotherapy or radiation plan.

**Clinical tools to predict pCR after CRT**

The recognition that many patients have no viable tumor in the resected specimen has naturally led to the question of whether surgery is beneficial for patients with pCR. There has been increased interest in ways to identify which patients have pCR prior to surgery. At present, imaging modalities have suboptimal accuracy in differentiating residual carcinoma from inflammation or fibrotic change after CRT. PET continues to be integrated into treatment decision-making, as well as the prediction of response and survival after CRT. Arnett et al. demonstrated that the rates of pCR in patients with and without radiographic complete response after preoperative CRT were 42% and 31% (P=0.17), respectively. In addition, no predictive correlation was found between pCR and the change in maximum standardized uptake value (SUV) (P=0.25) (39). Likewise, endoscopic ultrasound has limited accuracy in determining pCR after CRT (40).

Recently, there has been some interest in potentially increasing the rate of pCR by increasing the interval between CRT and surgery. The results of a recent meta-analysis indicate that a longer interval (more than the standard 7-8 weeks) between nCRT and surgery likely does increase the mortality or major complication rate (41). However, the longer interval does not appear to significantly improve pCR rates and may be associated with worse OS. Interpretation of these results should be done with caution, given the retrospective nature of the studies included in the analysis and the significant selection bias.

**The role of salvage esophagectomy**

Some patients that choose to have surveillance rather than resection after CRT will have local recurrence. Local recurrence rates following definitive CRT have been reported in up to 40–75% of patients (42,43). If the recurrence is only local, the question then becomes whether salvage resection should be attempted. Recent studies have demonstrated that the postoperative morbidity, mortality, and OS of patients after salvage esophagectomy are comparable to matched patients after planned resection in cases of esophageal AC. One study found that both salvage esophagectomy and planned esophagectomy after nCRT showed good 3-year survival results (63% vs. 71%,
respectively), with low postoperative morbidity and mortality (44). In addition, Marks et al. found no difference in the OS between salvage resection and planned resection after CRT (48% at 3-year and 32% at 5-year vs. 55% at 3-year and 45% at 5-year, respectively) (45) These studies suggest that patients with esophageal AC who fail definitive CRT and have locoregional recurrence should be considered for salvage esophagectomy at experienced surgical centers (45,46). However, in a meta-analysis study by Markar et al., which closely examined esophageal SCC, salvage esophagectomy was shown to have poor short-term outcomes when compared with planned esophagectomy following nCRT. Salvage esophagectomy was associated with a significantly increased incidence of post-operative mortality (9.50% vs. 4.07%; P<0.001), anastomotic site leakage (23.97% vs. 14.47%; P=0.005), pulmonary complications (29.75% vs. 16.99%; P<0.001), and an increased duration of hospital stay (P<0.001) (47).

Selective surgery
Given the combination of the above data (a lack of survival benefit for the addition of surgery after CRT, the equivalent radiation dose for definitive and nCRT, and emerging studies demonstrating the safety of salvage esophagectomy), a compelling argument can be made for a selective approach to surgery after CRT. For patients with complete clinical response after CRT, close observation could be performed. Salvage esophagectomy could be used for recurrent locoregional disease. On the other hand, patients who have clear residual disease after CRT could be offered esophagectomy within the same time frame as traditional trimodality therapy. This type of treatment strategy was investigated in the RTOG-0246 prospective trial of selective surgery for esophageal cancer (48). Patients were treated with induction chemotherapy followed by CRT. Patients were then recommended surgery based on clinical suspicion of residual disease. Nearly half the patients (20/41) avoided esophagectomy. Overall 5-year survival was 37% for the group as a whole and 53% among those with clinical complete response.

Future directions in esophageal cancer treatment
Improved systemic therapies may improve the efficacy of nonoperative treatment. Trastuzumab has been studied in combination with nCRT for HER2-expressing esophageal cancer (49). Immunotherapy, such as pembrolizumab the anti-PD-1 antibody, is also being investigated in combination with CRT (50). Aside from increasing cures for esophageal cancer, improving technology will allow us to determine with confidence who will truly benefit from surgery. Newer imaging technologies have shown promise in detecting response to treatment in pilot studies. Some researchers have found diffusion weighted magnetic resonance imaging (MRI) to be predictive of pCR (51). There has been an explosion of interest in biomarkers to predict and assess response to CRT. In particular, miRNA profiling has the potential to predict response to therapy and detect cancer in the serum (52,53).

Conclusions
The current treatment of esophageal cancer involves multidisciplinary therapies including esophagectomy, CRT, chemotherapy, and endoscopic resection. However, esophagectomy remains a complex surgical procedure with associated high mortality and morbidity rates and has the potential to adversely impact long-term quality of life (54). Much like other areas of cancer care, the treatment of locally advanced esophageal cancer needs to move towards personalized medicine. Treatment plans should be based on the underlying biology of the tumor as well as the preferences of the patient. Such an individualized treatment strategy should also take into account the surgical risk of the particular patient and potential impact on quality of life. An organ preservation strategy will likely be more common as methods to assess response to CRT improve. However, given the limitations of current diagnostic technology, we contend resection should remain the standard of care after nCRT for AC. On the other hand, surgery should be approached more judiciously in patients with esophageal SCC who have a complete response to nCRT, and it should only be done at centers with low operative mortality. Given the poor long-term survival in patients with significant residual nodal disease after CRT, caution should also be exercised in performing surgery in this cohort (55).

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Footnote
Conflicts of Interest: The authors have no conflicts of interest to declare.
References


