Surveillance versus esophagectomy in esophageal cancer patients with a clinical complete response after induction chemoradiation

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Abstract: There currently exists an area of controversy in treatment of esophageal cancer for patients who have an apparent clinical complete response (cCR) after induction chemoradiation. A standard treatment is to offer these patients an esophagectomy, but increasingly there is interest from both the patient and provider for active surveillance with so-called “salvage” esophagectomies for local recurrence as an alternative treatment paradigm. In this article, we review the existing evidence that stakeholders should consider for clinical decision-making in this specific patient population, including: the accuracy of post-induction clinical restaging, the reliability of operative risk assessment, the feasibility and adherence to surveillance strategies, and the observed outcomes in these patients after salvage esophagectomy or continued active surveillance. We also briefly discuss quality of life and future directions for this field.

Keywords: Esophageal cancer; complete response; surveillance

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Introduction

The treatment of thoracic esophageal or gastroesophageal junction cancer varies by stage. The earliest stage cancers are treated with surgery (1): either endoscopic resection if the tumor is confined to the mucosa, or esophagectomy if there is evidence of deeper invasion. Patients with locally advanced cancers or evidence of regional lymph node spread have been shown in randomized controlled trials to benefit from induction chemoradiation followed by an esophagectomy as compared to esophagectomy alone (2). Patients with inoperable or unresectable cancers are palliated with definitive chemotherapy or chemoradiation. This typical treatment paradigm, outlined in Figure 1, is well-established for adenocarcinoma patients who are good operative candidates and is supported by esophageal cancer management guidelines from multiple major oncologic groups (3,4). Details may differ for some squamous cell cancer patients, particularly those with cervical esophageal cancer for whom chemoradiation alone is often preferred. New areas of controversy have emerged as chemotherapy and radiation treatments have improved and our field focuses more on individualized medicine. The standard pathway is commonly debated for those Siewert I and II adenocarcinoma patients who have an apparent complete response to induction chemoradiation.

High-level evidence supports restaging following neoadjuvant therapy to rule out interval development of distant metastases prior to committing to the more risky and morbid surgical resection. As a result, preferred restaging strategies often include clinical re-evaluation, CT or PET/CT scanning, and possibly endoscopy to assess the response of the primary tumor to treatment. The Society of Thoracic Surgeons (STS) and National Comprehensive Cancer Network (NCCN) recommendations are to proceed with esophagectomy as long as: there is no evidence of
distant metastatic spread, the cancer remains locoregionally resectable, and the patient remains a favorable operative candidate (3,4). For individuals with evidence of persistent localized disease on post-induction restaging who will tolerate an esophagectomy, these recommendations are not controversial: the standard treatment pathway is likely to improve their long-term survival (5). In recent years, however, the role of universal surgery following chemoradiation for locally advanced esophageal cancer has been called into question, especially for patients who are loosely defined as “marginal” operative candidates at diagnosis or those in whom residual cancer cannot be demonstrated on restaging. For patients who meet both conditions: high risk and apparent clinical complete response, the appeal of a “watch and wait” strategy seems obvious.

This consideration for active surveillance after induction therapy has been influenced by the treatment protocols for cervical esophageal squamous cancers, for which the tide has shifted and the standard of care has become definitive chemoradiation, followed by resection if there is evidence of tumor persistence or recurrence (6-8). European trials in predominantly squamous cell cancers have demonstrated that a similar strategy could potentially be successfully employed for lower thoracic esophageal squamous cell cancers (9,10). Consequently, an interest in esophageal-preserving therapy has emerged and delayed operations, or surveillance strategies with selective salvage esophagectomies, have become more common (11) due to both patient and provider preferences.

In clinical management, this has created an area of ambiguity for patients with thoracic esophageal cancers who have an apparent complete response after induction therapy, as well as those with earlier stage disease considered high-risk operative candidates due to factors such as age or comorbid status. These areas of controversy are highlighted in Figure 1, organized by stage and contrasted with usual care. In this article, we aim to review the existing evidence that may contribute to nuanced decision-making for these less straight-forward patients, focusing on the central question: what is optimal care if a patient appears to have a complete response on restaging?

### Identifying this patient population

To set the stage for this discussion, it is first important to define the terms clinical complete response (cCR) and pathologic complete response (pCR), as well as to distinguish between the two. A cCR is the absence of demonstrable persistent cancer with the non-operative diagnostic tools available following induction chemoradiation. In the literature, there is some variability in this definition based on the modalities employed for restaging a patient. These include: repeat endoscopic biopsies that are negative for residual tumor, no apparent cancer in the esophageal wall or lymph nodes on endoscopic ultrasound (EUS) or CT, a percentage reduction in PET SUV above various empiric thresholds (most commonly

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**Figure 1** Typical treatment strategies and areas of controversy.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Typical treatment</th>
<th>Controversy</th>
</tr>
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<tbody>
<tr>
<td>T1a N0</td>
<td>Esophagectomy OR Endoscopic mucosal resection</td>
<td>For surgically high-risk patients: Induction therapy then surveillance with selective surgery</td>
</tr>
<tr>
<td>T1b N0</td>
<td>Esophagectomy</td>
<td>For fit patients with clinical complete response: Induction therapy then surveillance with selective surgery</td>
</tr>
<tr>
<td>T2 N0</td>
<td>Esophagectomy OR Induction therapy then surgery</td>
<td></td>
</tr>
<tr>
<td>T3+ or N1+</td>
<td>Induction therapy then surgery</td>
<td></td>
</tr>
<tr>
<td>T4b</td>
<td>Definitive chemoradiation</td>
<td></td>
</tr>
<tr>
<td>M1</td>
<td>Chemotherapy, palliative radiation</td>
<td></td>
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30–50%), a resolution of PET SUV uptake back to physiologic levels or in a pattern consistent with post-treatment esophagitis, or a composite clinical response in which there is no apparent residual cancer on multiple modalities (12-14).

A pCR is the absence of viable tumor cells in the esophagectomy specimen and all associated nodes as determined by a pathologist following surgical resection. Depending on the series, a pCR can be seen in 11–56%, though this favorable outcome is generally reported in the range of 20–30% of patients, and has consistently been associated with improved overall survival (15-17). A cCR is suggestive of a pCR, but there is not perfect correlation as no current staging modality can definitively exclude the presence of residual microscopic disease.

As there have been improvements in care of esophageal cancer patients and increasing use of neoadjuvant chemoradiation in locally advanced disease, thoracic oncologists of all specialties are seeing patients with cCRs more frequently. A provider’s choice regarding whether or not to recommend esophagectomy in this patient population can be based on three primary questions:

1. What is the accuracy of the clinical restaging?
2. What is the risk of an operation for this patient?
3. What is the risk of surveillance for this patient?

An outline of this clinical approach and related considerations is depicted in Figure 2, and provides the structure of the remainder of this review.

**The accuracy of clinical re-staging**

Our ability to accurately predict whether a patient has been effectively cured with induction chemoradiation alone is a center point in this discussion. Specifically, we would like to quantify the likelihood of a pCR in a patient with a cCR.

The recommended diagnostic modalities frequently used for restaging include endoscopy with surface biopsies, EUS with directed FNA to deeper areas of concern in the esophagus and adjacent nodes, CT alone, and PET/CT. CT scanning of the chest and abdomen is an option, though the ability to distinguish between residual tumor and post-treatment inflammation in this setting is less accurate with CT alone than with the addition of PET (18). The utility of repeat EUS at this phase is debatable since
the sensitivity and specificity for identifying residual cancer has been demonstrated to be low. Finally, there has been some interest in the use of MRI to identify residual tumor, although this data is very preliminary. Here, we will discuss the reliability of five modalities: endoscopy, EUS, PET, CT, and MRI, all considered independently and in various combinations, for predicting a pCR following neoadjuvant chemotherapy. A summary of selected studies can be found in Table 1.

### Endoscopy and EUS

Even prior to neoadjuvant treatment, endoscopy and EUS have some limitations in their ability to accurately stage tumors, most notably in detecting microscopic nodal metastases. Several studies have shown non-trivial rates of unanticipated nodal disease in initial staging of both early and locally advanced cancers that are treated surgically: 24% in cT1, 39–55% in cT2, and 78% in cT3 (19,20). Post-treatment effects, such as ongoing inflammation in the esophageal wall, enlarged reactive lymph nodes, and radiation-induced alterations in the echogenicity of lymph nodes seem to further limit reliable restaging with these techniques alone.

Single center studies have unsurprisingly shown poor correlation between restaging with endoscopic modalities (including endoscopic assessment, endoscopy with biopsies, and EUS) and actual pathologic stage after resection with negative predictive values (NPV) and accuracy assessments around 70% (17,21,22). Many additional studies examine the ability of these modalities to predict tumor and nodal responses separately, without directly assessing a combined pCR. A recently performed meta-analysis (15) of these studies found pooled estimates for tumor staging of sensitivity and specificity of endoscopic biopsy to be 34.5% (26.0–44.1%) and 91% (85.6–94.5%), and of EUS to be 96.4% (91.7–98.5%) and 10.9% (3.5–29.0%), respectively. When examining the pooled estimates for nodal disease, the sensitivity and specificity of EUS were similarly unimpressive at 62% (46.0–75.7%) and 56.7% (41.8–70.5%). They also specifically examined the NPV of these tests. Endoscopic biopsy for tumor staging had an overall NPV of 47% and EUS for nodal staging had an overall NPV of 47% and EUS for nodal staging had an overall NPV of 47% and EUS for nodal staging had an overall NPV of 47% and EUS for nodal staging had an overall NPV of 47% and EUS for nodal staging had an overall NPV of 47% and EUS for nodal staging had an overall NPV of 47% and EUS for nodal staging had an overall NPV of 47% and EUS for nodal staging had an overall NPV of 47% and EUS for nodal staging had an overall NPV of 47% and EUS for nodal staging had an overall NPV of 47% and EUS for nodal staging had an overall NPV of 47% and EUS for nodal staging had an overall NPV of 47% and EUS for nodal staging had an overall NPV of 47% and EUS for nodal staging had an overall NPV of 47% and EUS for nodal staging had an overall NPV of 47% and EUS for nodal staging had an overall NPV of 47% and EUS for nodal staging had an overall NPV of 47% and EUS for nodal staging had an overall NPV of 47% and EUS for nodal staging had an overall NPV of 47% and EUS for nodal staging had an overall NPV of 47% and EUS for nodal staging had an overall NPV of.
Endoscopic techniques, especially with biopsies, can provide very useful information if evidence of post-induction residual cancer is detected: those patients, as a group, have no non-surgical curative therapy available and they will have improved survival with an esophagectomy. In contrast, an inability to demonstrate residual cancer with endoscopic modalities alone does not yet offer justification to avoid an operation for a typical-risk patient.

**PET and PET/CT**

PET as a restaging modality has an advantage in that it reflects changes in tissue metabolism that may precede the observable structural changes that might be noted on CT or EUS when assessing response (14). A couple of systematic reviews and meta-analyses have been performed examining the question of PET accuracy in predicting a pathologic response. It is worth noting that these meta-analyses were done with the explicit goal of assessing whether a patient is responding vigorously or poorly to induction therapy and whether that patient should stop induction early and proceed to surgery if the response was poor. This is a far different aim from deciding whether to avoid or delay a potentially unnecessary operation in patients with a complete response. Consequently, these meta-analyses included studies of PET performed at any time point after initiation of chemoradiation—sometimes during the ongoing therapy. The studies also differed in the way they defined a histopathologic response, but most commonly they used <10% viable residual tumor cells, with few studies examining the ability to predict a pCR. Even in this setting, the pooled sensitivities and specificities of PET were only 67–70% and 68–70%, respectively (13,14). Although these publications include the largest numbers of patients, these results should be interpreted with caution in our discussion, because the presence of residual microscopic disease would suggest surgery rather than surveillance.

To get a better sense of PET accuracy in our specific population of interest, we turn instead to individual studies that explicitly focused on PET to evaluate for pCR. Two studies have prospectively compared PET or PET/CT to other restaging modalities in small cohorts of patients, of which 35–45% of patients had a pCR after esophagectomy. They found that PET or PET/CT predicted a complete response accurately in 71–88% of these patients and had a NPV of 64–94%, which is much higher than the accuracy and NPV of CT (58–73%, 44–71%) or EUS (70–71%, 67%) respectively (17,22). A subsequent small retrospective study (16) examining PET or PET/CT did not reveal the same encouraging predictiveness, with an accuracy of 56% and NPV of only 35%. This heterogeneity reflects the variability seen in the meta-analyses mentioned above, and may be due to the small sample size of the studies, the use of PET with or without CT information, or the variability in definition of what constitutes a positive or negative restaging scan.

**MRI**

Use of MRI in restaging of esophageal cancer is not standard, but the modality has been shown to be useful in some other gastrointestinal cancers, such as rectal cancer. Because our current tests are imperfect and there is interest in individualizing treatment based on clinical response, investigators have conducted a small pilot study of diffusion weighted MRI for predicting pCR. Scans from 20 patients undergoing induction chemoradiation followed by surgery, of which 4/20 (20%) had a pCR, were examined and the investigators were able to identify an imaging threshold at which there was high sensitivity and specificity of MRI in this small subset of patients (23). Obviously larger studies are needed to confirm the findings, and the combined value of MRI and other restaging modalities has not been explored.

**Composite clinical responses**

Perhaps the most useful studies are those that examine the combined ability of multiple restaging modalities to predict a pCR. This approach is more pragmatic and provides the closest approximation of a provider’s actual clinical approach to decision making. Several studies have examined various combinations of PET, CT, endoscopy, and esophagography in cohorts of 60–280 patients and have found a physician-assessed clinical response to have an accuracy between 46–79% and NPV between 31–74% (17,24,25). Again, this variability may reflect the combination of modalities used, the prevalence of pCRs in their source populations, or different definitions of what constitutes a positive vs. negative screening result.

**Risk prediction model**

The group at MD Anderson performed a retrospective study of 322 patients, of which 70 had a pCR, and developed a nomogram that incorporates the patient characteristics
of sex, tumor grade, and baseline tumor staging with post-
treatment data from PET scanning and endoscopic biopsy
results to predict the likelihood of a pCR. The corrected
AUC for this model was 0.70 (26), which is considered ‘fair’ accuracy. While this model has not been validated in
another patient cohort, the group has shown that
dichotomized nomogram scores also correlate with overall
and disease-free survival outcomes (27).

There certainly are consequences to choosing incorrectly
whether to operate on or observe a specific patient. There
are essentially competing risks of the two strategies:
the risks of surgery, including operative morbidity and
mortality, and the opposing risks of surveillance, including
missed residual disease that may progress to unresectability
or metastasize. The threshold needed to favor a surveillance
strategy depends on the balance of competing surgical risks
for a patient. Risk prediction models and probabilities based
on composite clinical metrics can inform the provider of the
likelihood of a pCR, and provide a background upon which
to consider the risks of an esophagectomy or surveillance
strategy.

Predicting the risk of an operation
A futile operation is one that results in perioperative death
or debilitating morbidity, or alternatively does not prolong
survival over what would be gained without surgery. When
a patient is diagnosed with locally advanced esophageal
cancer, they frequently undergo their staging workup and
a multidisciplinary clinical evaluation to determine if they
are a candidate for trimodality therapy or if they should
get definitive chemoradiation instead. This workup often
includes subjective and objective measures of health status
and is meant to risk-stratify patients for surgery, ideally
identifying those for whom an esophagectomy may be a
prohibitively high-risk venture. This workup includes a
history and physical, functional status assessment, as well
as any additional indicated cardiovascular and pulmonary
function testing. Despite preoperative evaluation,
esophagectomy is an operation that carries a morbidity rate
between 15–40% and a mortality rate usually less than 5%
but occasionally up to 10% (28). In a recent large series
using the STS database, the morbidity is 33% and the
mortality is 3% (29).

Several national databases and risk calculators have
been created in an attempt to predict risk of an operation
by entering baseline patient factors, and subsequently
tracking outcomes based on tumor, patient, and hospital
characteristics. These databases are voluntary and the
data entered is audited for accuracy to a varying degree.
One study that compared the STS database and the
National Surgery Quality Improvement Program (NSQIP)
database found that rates of complications differed
significantly within a single institution based on whether a
comprehensive (STS) or partial sampling (NSQIP) database
was used for assessment. For example, the observed rates of pneumonia and mortality in esophagectomy varied by 3-fold
depending on whether all cases were included or incomplete
subsets were utilized (30). Another study compared the STS
database to both the NSQIP and National Inpatient Sample
(NIS) databases and found that the national mortality
rates of esophagectomy varied by greater than 2-fold,
depending on the database used. There were also significant
and meaningful differences between the databases in
hospital length of stay (28). This variability in captured
morbidity and mortality obviously has implications for
reliably predicting outcomes using risk calculators that are
numerically based on these databases. To date, there is no
widely agreed upon method to predict the risk of mortality
or major morbidity for esophagectomy.

Predicting the risk of surveillance
To advocate for observation after chemoradiation in
selected patients, an effective surveillance strategy needs
to be in place, and the risks of a delayed operation need
to be reasonable. The goal is to reliably detect a local
recurrence prior to the cancer metastasizing or prior to it
becoming locally unresectable by invading adjacent
structures. Surveillance strategies differ nationally, with
the primary variations found in the frequency of use for
PET and endoscopy. To provide a basis for this discussion,
an outline of a possible surveillance strategy is provided in
Figure 3 that combines recommendations from the existing
literature (3,31).

Early risks
A small number of studies have examined the risks of
a short delay prior to esophagectomy. One study (32)
examined 325 patients who participated in the CROSS trial,
and demonstrated that a delay of up to twelve weeks was
associated with a very small increased risk of complications
(OR 1.2 for each week delay after 6.5 weeks), though these
patients also had an increased likelihood of a pCR (OR
1.35 per week). This led the authors to conclude that the
observed findings allow for safe testing of a ‘wait-and-see strategy’. Another single institution study (33) reviewed 266 patients who underwent esophagectomy sooner than or later than 8 weeks after completion of neoadjuvant treatment. They found there was no significant difference in morbidity and mortality rates, the difficulty of the operation based on surrogate measures, or the rate of pCR. They did note that there was a slight nonsignificant trend towards more anastomotic leaks (16% vs. 11%), more pulmonary complications (35% vs. 31%), higher mortality (3% vs. 2%), and shorter overall survival (39 vs. 53 months) for the delayed vs. early group, though this study explicitly excluded patients choosing initial surveillance and needing an eventual salvage esophagectomy, so membership in the delayed group may have signalled higher medical risk at baseline.

**Late risks**

Patients who undergo definitive chemoradiation or have a cCR after neoadjuvant treatment and choose not to have immediate surgery may develop a local or regional recurrence and thus become a candidate for a salvage esophagectomy. Older studies of salvage procedures showed high morbidity and mortality rates with anastomotic leaks occurring in 21–38% of patients and 30-day mortality ranging widely between 4–33%, but with 5-year survival rates that were similar to that of patients undergoing

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**Figure 3** Surveillance strategy—combination of approaches from NCCN and MD Anderson. NCCN, National Comprehensive Cancer Network; EGD, esophagogastroduodenoscopy.
planned surgeries (34). Subsequent studies, however, have actually started to show more comparable rates of major postoperative events, perioperative mortality, and median survival. One retrospective study of 65 patients undergoing a salvage operation compared to 521 patients undergoing planned trimodality therapy found leak rates were 18.5% vs. 11.3%, 30-day mortality was 3.1% vs. 2.9%, 3-year survival was 48% vs. 57%, and 5-year survival was 32% vs. 45% for the two groups respectively (35). Another small matched study actually showed a trend towards better survival in patients who declined initial surgery after neoadjuvant chemoradiation, and got a salvage esophagectomy if they recurred locally, versus the strategy of getting a planned operation: the median survival was 58 vs. 51 months (36). This shift may reflect improvements in operative technique and perioperative care, lower doses of neoadjuvant radiation usage, or better patient selection with multidisciplinary care (34). Regardless, the improved outcomes in patients undergoing salvage procedures after surveillance provides encouragement that this may be a viable strategy for a subset of patients.

Risk of locoregional vs. systemic recurrence

Understanding the risk of a patient developing a locoregional recurrence versus systemic disease is useful for considering two very different circumstances in which an operation may be futile: first, in the setting of a pCR where a patient may be at greater risk of death from competing comorbidities or the morbidity of the operation; and second, where the patient has undetected distant micrometastatic disease where local control with an esophagectomy will not improve survival. To quantify this risk, we examine patterns of recurrence after chemoradiation treatment.

One source of this information is the natural history of the cohort of patients undergoing planned definitive chemoradiation. A single institution study of 276 patients who underwent definitive chemoradiation found that 70% of patients had a cCR at the time of their first follow up. Of these complete clinical responders, 47% never developed a relapse. Among the 53% of the initial cohort that did recur: 43% had a local recurrence only, meaning they could be potential candidates for salvage esophagectomy, while 40% had distant metastases only and an operation would have been futile, and 17% had both a local recurrence and distant metastases detected simultaneously. In this last subpopulation, it is unclear whether upfront surgery would have prevented metastatic spread. Of the patients who were candidates for salvage esophagectomy, their corresponding survival was quite good: median, 58.6 months; 3-year, 61%; and 5-year, 45%. An impressive 98% of the relapses developed within 3 years, indicating this is the period where regular surveillance is most important if the patient is considered a candidate for additional treatment (31).

Another population to consider is the cohort of patients who refuse an operation when they have a cCR. One study evaluated a group of 61 such patients who declined an esophagectomy but were trimodality-eligible at their institution and found that 54% had recurrences, and the distribution was very similar to the cohort undergoing planned definitive chemoradiotherapy: approximately 40% were local (nearly all patients were able to undergo salvage esophagectomy) and 60% were metastatic. The overall 5-year survival rate was 58% (12).

Existing evidence

There is currently no randomized controlled trial that directly compares surveillance to surgery in patients who have had a cCR to neoadjuvant treatment. Perhaps the most well-known data comes from the RTOG 0246 trial, which was a non-randomized phase II study that aimed to study selective esophagectomy in patients who had residual disease after induction chemoradiation or who developed progressive or recurrent disease while undergoing surveillance. This study enrolled 41 eligible patients: all of whom underwent standard pretreatment staging (endoscopy, EUS, CT of the chest and abdomen with or without PET), were deemed to have resectable disease, and received two cycles of induction chemotherapy followed by induction chemoradiation. If the patients had evidence or suspicion of residual disease on restaging, they were considered for esophagectomy, otherwise they underwent a multimodality surveillance strategy. After neoadjuvant treatment, 18/41 underwent selective esophagectomy for persistent cancer and 23/41 did not have proof of persistence and were thus observed. During surveillance, an additional 3 patients were found to have suspicion of recurrent disease and ultimately had an operation. The 1-year survival rate for this entire enrolled cohort was 71%, and they did not observe an increased operative morbidity or mortality. The authors had suggested before the trial that a 1-year survival threshold of 77% or higher would be incentive to move this strategy forward to a randomized trial. The threshold survival rate
was not reached, but the early data was encouraging for the use of a selective surveillance strategy (37). A follow up report of these patients indicated that a cCR occurred in 15 patients with 5-year survival of 53% and 7-year survival of 47%. Esophagectomy was avoided in half of the patients in the trial, demonstrating a potential to selectively operate in these patients with good short and long-term outcomes (38).

Several additional retrospective reviews have examined the question of surveillance versus surgery, but these have significant limitations with regards to patient selection. One group performed an intention-to-treat case-control study looking retrospectively at a total of 222 patients with a cCR. In this study, 59 patients underwent initial post-induction surveillance and were matched 1:2 with controls undergoing an immediate operation. They found evidence of residual cancer in 34.6% of pathologic specimens, and noted shorter survival (31 vs. 83 months) and faster locoregional recurrence for the surveillance group. It is worth noting that while these groups were matched on important patient and tumor characteristics, they were not matched on specific comorbidities that may have influenced operative decisions. Patients were preferentially assigned to surveillance if they were treated at low volume centers, whereas surgery was proposed and patients made a decision regarding their treatment plan after a risk-benefit discussion at high volume, tertiary referral centers (39). Given the data supporting improved outcomes for patients treated at high-volume cancer centers in general (40), it is difficult to interpret how much of the observed difference in survival was due to the effects of upfront surgery and how much is attributable to other factors.

Perhaps the largest published retrospective study is a National Cancer Database study that used propensity score matching to compare 1,774 matched pairs of patients who underwent induction chemoradiation for stage II/III esophageal cancer with or without subsequent esophagectomy. In the overall cohort, esophagectomy substantially improved survival (32.5 vs. 14.2 months), but this study did not specifically examine patients based on clinical response. Also, importantly, it is likely that the authors would have excluded many of the older, frailer patients by way of creation of their propensity score: patients for whom a more nuanced discussion of risks and benefits is merited. This study is also at risk of substantial confounding by indication (41).

One interesting study did specifically focus on the older individuals that are so often excluded from trials—the authors examined esophagectomy versus surveillance in patients over 70 in a study of 56 patients after chemoradiation, of which 25 had a cCR. Six of those patients underwent an operation and four truly had a pCR. Survival was similar for those undergoing an operation vs. surveillance: the whole cohort with cCRs had a median survival of 47 months (61 months for those undergoing an upfront surgery and 29 months for those who had a salvage operation) versus 46 months for the subset that did not undergo resection. Despite this being a very small retrospective study subject to treatment selection bias, there is a suggestion that overall there may not be a survival advantage to a non-selective progression to surgery in this particular population (42).

Quality of life considerations

Numerous studies have looked at health-related quality of life (HRQOL) after esophagectomy, using metrics that explore individual symptoms, a variety of functional scales, or global assessments. Essentially all have shown that patients experience a decrease in multiple aspects of quality of life in the short-term following an esophagectomy, though HRQOL may recover to baseline values over time. The decreases can be more substantial in patients who experience major complications and, in fact, poor HRQOL after the immediate post-operative dip is associated with worse overall survival. The most significant areas where surgical patients suffer are predictably related to loss of their stomach’s normal function: eating problems, reflux symptoms, loss of appetite, and diarrhea. However, these patients also had worse scores with general health measures like fatigue and dyspnea, and experienced lower overall physical function, vitality scores, and health perception than controls long-term (43). Notably, organ preservation in esophageal cancer patients has been shown to be predictive of global measures of HRQOL (44).

Summary

In the context of all of this data, the question remains for the thoracic surgeon: what is the best course of treatment for the individual patient who presents to clinic with an apparent cCR after induction therapy for a distal esophageal adenocarcinoma?

The answer to this question of surveillance versus surgery is unfortunately unlikely to be found by way of a prospective
randomized controlled trial. Patients and providers often have preferences regarding their personal treatment strategy based on perceived risks or quality of life considerations that may limit enrollment of a sufficient number of patients to a classic randomized trial. Additionally, these trials are often not pragmatic, and inclusion and exclusion criteria may not appropriately represent the range of patients seen in the typical thoracic practice. Therefore, even if an adequate number of patients could be accrued for randomization, a formal trial may still leave providers uncertain as to how to apply the results to an individual based on the patient's health or age, the center's surgical outcomes, the imaging modalities used for staging, or the pretreatment tumor characteristics.

Furthermore, there is likely not a single best answer for the entire group of patients. In critically evaluating all of this available evidence, it is apparent that our ability to predict the likelihood of true pCR, the risk of an operation, and the risks associated with a surveillance strategy are less than ideal. Consequently, we try to weigh the balance of estimated risks for an individual—both from the surgeon and patient perspectives. For a fit patient who is less likely than others to have major operative complications, a risk of persistent cancer in the range of 30–40% may be too high, even with an aggressive surveillance strategy and plan for salvage operation if recurrence is detected. Avoiding surgery and surgical complications may not be worth the risk of progression to unresectability or metastasis, or the burden of anxiety about cancer recurrence that can occur with organ preservation strategies. Conversely, in the older or sicker patient who has more competing morbidities, a 60–70% chance that the cCR patient truly has a pCR may be good enough: when one considers the fact that if there is residual cancer, it is likely to become metastatic half the time and therefore not be treatable by an esophagectomy, which would come at increased risk of complications with numerous quality of life sacrifices. For patients that fall in the middle of this spectrum, the clinical decision is more complicated. No studies currently capture all of these patient-important factors, so clinical judgment and experience remain at the center of these decisions which results in wide variability of care. Accumulation of additional rich observational patient data from multiple sites with the goal of improving risk prediction or enhancing the foundation for a shared decision-making process may be the best alternative strategy for refining the treatment pathways for these patients, especially if subgroups can be identified for whom one treatment strategy or the other is likely to be preferable.

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Footnote

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

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