Review Article

Surgery versus active surveillance in clinical complete response

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Contributions: (I) Conception and design: Both authors; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: None; (V) Data analysis and interpretation: None; (VI) Manuscript writing: Both authors; (VII) Final approval of manuscript: Both authors.

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Abstract: Esophageal adenocarcinoma is an aggressive disease that is often treated with trimodality therapy for locoregionally advanced cases. However, about a quarter of these patients are found to have pathologic complete response (pCR) on resection, which raises the question of whether we can avoid esophagectomy in favor of active surveillance in patients who appear to have a complete response on clinical evaluation after neoadjuvant chemoradiation (nCRT). Two prospective trials—the SANO trial and ESOSTRATE trial—are currently ongoing in an attempt to study this question. While awaiting the results of these trials, in order to consider active surveillance as a viable alternative to upfront surgery, we must understand the accuracy of clinical tools currently used to evaluate for pCR, establish safe, efficient and reliable surveillance protocols, and finally, understand the risk of selecting either strategy. Currently available clinical tools include FDG-PET/CT, CT with IV contrast of the chest and abdomen, MRI, endoscopy with biopsy and endoscopic ultrasound. None of these modalities has been found to be reliable to independently predict pCR, and although MRI may perform better than other studies, nearly all the available data is from small scale feasibility studies. Recognizing these limits, the SANO group developed a novel technique of bite-on-bite biopsy which appears to perform better than preexisting methods (74% sensitivity and 77% specificity for residual tumor detection). However, outside of the SANO group publications, there is virtually no data regarding this technique at this time. In the meanwhile, the risk balance of either approach continues to evolve. Esophagectomy and its perioperative management continue to evolve with improved short- and long-term outcomes and improved survivorship. The objective estimation of a specific patient's perioperative risk continues to be elusive and therefore heavily relies on subjective evaluations by clinicians. On the other hand, delayed (salvage) esophagectomy is often found to have increased morbidity, and there is no clear data establishing the safest and most effective active surveillance protocol. At this point, we find that our current ability to detect true pCR and predict outcomes after either surgery or surveillance is limited, which severely diminishes the safety of active surveillance for patients with clinical complete response. As we await the results from the aforementioned trials, any decision made in a patient with clinical complete response after nCRT must be individualized, keeping in mind the goals of care for any given patient but recognizing the limits of available data and high stakes.

Keywords: Esophageal cancer; esophageal adenocarcinoma (EAC); clinical complete response; pathologic complete response (pCR); active surveillance; esophagectomy

Received: 22 February 2021; Accepted: 14 April 2021; Published: 25 September 2021.
doi: 10.21037/aoe-2020-20
View this article at: http://dx.doi.org/10.21037/aoe-2020-20

Introduction

Esophageal adenocarcinoma (EAC) is an aggressive disease process that requires carefully individualized treatment decisions based on stage and patient characteristics. For those patients with locoregionally advanced stage II or III EAC, a strategy using trimodality therapy is most commonly recommended. This treatment paradigm is the result of evolution over previous decades, with the latest major randomized trial establishing its efficacy (1,2), While this strategy is well established for patients who are good operative candidates, as we move into an era of progressively individualized medicine, controversy is raised regarding whether a cookie-cutter approach is appropriate for all patients in this category. The aforementioned CROSS trial demonstrated that 29% of resected specimens (23% of adenocarcinomas, 49% of squamous cell carcinomas) had no residual viable tumor cells in the specimen (pathologic complete response; pCR), consistent with other studies' findings (3,4) with similar trends in histologic differences. This finding poses an attractive question: is it possible to avoid esophagectomy after neoadjuvant chemoradiotherapy (nCRT) and use a strategy of active surveillance instead? This organ-preserving strategy is currently being evaluated by the ESOSTRATE and SANO trials (5,6) but continues to be a matter of controversy.

Current NCCN guidelines recommend neoadjuvant therapy with intent to follow with esophagectomy for stage II or III EAC except for patients who refuse esophagectomy. The recommendations for response assessment are FDG-PET/CT, chest/abdominal CT scan with contrast, and endoscopy and biopsy (optional if surgery is planned) (7). When the patient is in good condition after nCRT with evidence of locoregional residual disease and without distant metastasis, the choice to proceed with esophagectomy is relatively straightforward. However, in patients who have no clinically detectable residual disease on response assessment (clinical complete response; cCR), in light of the possibility of a pCR, the choice of whether to undergo esophagectomy has become more controversial. Moreover, if the patient is deemed at higher risk for perioperative morbidity and mortality—even if not prohibitively high risk for esophagectomy—the decision becomes even more complex.

The rationale behind a strategy of active surveillance in patients with cCR is based on the hypothesis that esophagectomy would not affect oncological outcomes in patients without viable tumor cells within the specimen. It also takes into consideration the possibility of futile surgery, where either morbidity is so great that the patient's quality of life is unacceptable, the patient dies perioperatively, or the patient's long-term outcome is unchanged despite surgery. The patient population of interest in this discussion warrants careful definition. These are patients who are found to have locoregionally advanced EAC (stage II/III) and are felt to be candidates for trimodality therapy, continue to be surgical candidates after nCRT, and on subsequent response assessment are found to have a cCR. pCR is defined as having no viable tumor cells in the resected tissue on evaluation by a pathologist, including the esophagogastrectomy specimen as well as any lymph nodes resected. Ideally the patient who takes the route of active surveillance also is aware of the possibility of the need for esophagectomy should evidence of locoregional esophageal cancer be discovered in subsequent clinical evaluations and is willing to undergo surgery at that time (defined as salvage esophagectomy).

This dilemma can be examined from several angles. First, we must understand the accuracy of clinical tools used to determine cCR after nCRT. Second, we need to establish surveillance protocols that are safe, efficient and reliable. Third, we need to ensure that oncologic and perioperative outcomes are noninferior when comparing active surveillance *vs.* conventionally timed esophagectomy; namely: what is the risk of selecting either strategy?

Finally, we also note that this article is focused on adenocarcinomas, which have distinct behaviors when compared to squamous cell carcinomas. Importantly, when patients have recurrence after pCR, for squamous cell carcinoma the recurrence is more commonly noted in locoregional lymph nodes, as compared to adenocarcinomas where the recurrence is more likely to be a distant metastasis (8). This among other findings, including very different rates of pCR, suggest that adenocarcinomas and squamous cell carcinomas of the esophagus should be studied as individual entities in regard to this issue.

Clinical tools for assessment of response after nCRT

The ability to accurately predict pCR after nCRT is critical to the success of a strategy of active surveillance. The more a patient with cCR is likely to have pCR after resection, the easier it is to use cCR as a viable benchmark to make safe decisions. Theoretically, the more cCR rates approximate pCR rates, the more we would be able to use cCR to decrease the number of futile surgeries while increasing

the safety of active surveillance. However, the accuracy of various clinical tools to assess cCR has been found to be variable, and up to date we do not have a universal strategy that reliably detects pCR at acceptable accuracy.

The current NCCN guidelines recommend the use of FDG-PET/CT, CT scan of the chest and abdomen with contrast, and upper GI endoscopy and biopsy (optional if surgery is planned) for response assessment after nCRT (7). In addition to these modalities endoscopic ultrasound (EUS) and MRI have been evaluated as possible tools (9,10). More recently a study using a protocol of bite-on-bite biopsy technique has been developed and is currently being used in a trial that is underway (11). We shall review the data available for each method.

Prior to examining the data behind each clinical modality, it warrants mentioning that there are additional clinical tools such as a wide array of biomarkers and liquid biopsy that are altering the landscape of individualized medicine in the current age. While these exciting tools are promising as the true frontier of assessment of residual disease at a cellular and molecular level, the available data in regard to evaluation of pCR in EAC is scarce and therefore will not be included in the discussion within this manuscript. No doubt in the coming years we will witness new developments in this area.

FDG-PET/CT

FDG-PET/CT has the benefit of being able to generate a qualitative as well as a numerically quantifiable value in maximum SUV (SUVmax) in the lesion prior to and after neoadjuvant treatment that allows direct comparison, in addition to being able to assess for distant areas of uptake that are not otherwise detectable using local evaluation methods such as endoscopy. A recent meta-analysis investigating whether FDG-PET results correlate to tumor response after neoadjuvant treatment for either EAC or squamous cell carcinoma found moderately successful results (pooled sensitivities and specificities in 62% and 73% respectively) (12). More recently the SANO trial group published a prospective study evaluating use of FDG-PET/CT in response assessments after nCRT. They found that qualitative FDG-PET/CT was unable to detect 15% of patients with 11% or more viable residual tumor cells in the resected specimen. Sensitivity, specificity, and negative predictive value were 80%, 37% and 42% respectively. FDG-PET/CT detected a 10% rate of patients with new interval metastases. The authors concluded that FDG-PET/CT was unable to accurately detect residual disease and to discriminate substantial residual disease from benign inflammation-induced FDG uptake after nCRT. However, they felt that FDG-PET/CT is useful for the detection of interval metastases and therefore useful for an active surveillance strategy (13).

While most studies to date include both EAC and squamous cell carcinoma, a small number of studies focus on EAC alone. A retrospective analysis of EAC in a single institution demonstrated that a complete metabolic response (cMR) seen after nCRT yielded a sensitivity and specificity of 67% and 46% respectively when used as a surrogate marker for pCR. Eighty percent of those patients who had cMR had histologic evidence of residual tumor in the resected specimen. Interestingly they also found that a relative reduction in SUVmax was not significantly associated with improved disease-free survival or overall survival, suggesting that in adenocarcinoma FDG-PET/CT may have different trends in pre- and post-treatment findings. Neither cMR nor change in SUVmax was significantly associated with pCR (14). On the other hand, another retrospective analysis of a single institution experience found that a less than 45% decrease in SUVmax was predictive of residual disease with a positive predictive value of 91.7% but only a 38% positive predictive value for pCR. This suggests that although changes in SUVmax correlate to response to treatment, when used as a predictor for pCR, SUVmax performs poorly (15).

FDG-PET/CT alone appears to be insufficient to detect residual disease or differentiate between residual disease and treatment related inflammation, and its highest utility is to detect new distant metastatic disease that would avoid a futile surgery. Its role in a combined clinical assessment will be discussed in subsequent paragraphs.

CT scan of the chest and abdomen with contrast

There are fewer studies evaluating stand-alone CT scan as a tool for predicting pCR compared to FDG-PET/CT. All studies included in the most recent meta-analysis were from 2015 or earlier, and the criteria for cCR is also heterogenous, ranging from tumor wall thickness of less than 15 to 5 mm, volumetric assessment of the tumor, or CT perfusion blood flow values. None of these studies was focused on EAC, and only 47.8% out of the 471 total patients in the pooled patient population had EAC. Moreover, two of the included studies focused on ypT0 or ypN0 alone. The summarized diagnostic accuracy per imaging technique found sensitivity of 35% and specificity of 83% (12).

This demonstrates that the available data regarding the accuracy of CT scan for predicting pCR is not robust and must be interpreted cautiously. This likely has resulted in favoring PET/CT rather than contrasted CT scan alone as a part of the surveillance protocol in those patients undergoing active surveillance in the ongoing SANO trial (11). The exact protocol of the ESOSTRATE study is not published at this time (6).

Endoscopy and EUS

Endoscopy, EUS and biopsy are used to evaluate for locoregional response and are unable to assess for distant metastatic disease. The accuracy of endoscopic assessment is compromised by the difficulty of obtaining tissue samples in the irradiated luminal surface, as well as differentiating between treatment effect and residual tumor within the esophageal layers. In addition, residual disease after nCRT frequently involves the submucosa, and surface mucosa biopsy is an unreliable method for evaluation of pCR (16). A 2016 meta-analysis attempted to evaluate the accuracy of endoscopic biopsy alone, EUS alone and combining the two in detecting pCR patients. Unsurprisingly they found that endoscopic biopsy alone for detecting ypT0 had a sensitivity of 23.6% and specificity of 88.2% for EAC (compared to 49.3% and 90.6% respectively for ESCC), showing that it was an unreliable tool. EUS also did not perform significantly better, with pooled sensitivity of 10.9% for pCR in the primary tumor of all histologies and 56.7% for residual nodal metastases. They again found that sensitivity was significantly higher for ESCC compared to EAC when evaluating EUS for residual nodal metastases at 82.7% *vs.* 44.3% respectively. While this demonstrates the fact that EAC and ESCC behave independently, it also highlights the fact that when it comes to EAC, endoscopic tools are even less reliable (9). The previously mentioned meta-analysis evaluated EUS as well and found that it performed poorly in its summarized diagnostic accuracy, with sensitivity of 1% and specificity of 99% for detecting pCR (12). The conclusion from both these meta-analyses was that endoscopy with biopsy and EUS with or without FNA were not reliable methods to detect pCR.

Considering the poor performance of conventional endoscopic biopsy and EUS, the preSANO prospective diagnostic cohort study (11) published results of what they named bite-on-bite biopsies and FNA of any abnormal lymph nodes as defined as round, hypoechoic, or greater than 5 mm in diameter or any lymph nodes seen adjacent to the primary tumor. They defined bite-on-bite as a second, deep biopsy sample taken at the same location as a first location, in order to increase the chance of detecting residual disease—especially submucosal tumors. Of note, due to the unknown safety of the bite-on-bite biopsy technique, they included 84 patients with regular biopsies before introducing the bite-on-bite biopsy technique (in 123 patients) into their study cohort. No biopsy related or FNA related serious adverse events were encountered. The published results found that for endoscopy with regular biopsies and FNA there was a 31% false negative rate and sensitivity and specificity of 54% and 69% for residual tumor detection. When the bite-on-bite cohort was analyzed they found a 11% false negative rate and 74% and 77% for sensitivity and specificity, respectively. This study protocol included EUS with tumor thickness measurements and PET-CT; however both had poorer performance than that of the endoscopy with bite-on-bite biopsy and FNA of any suspicious lymph nodes. While within this study group we find that the novel method of bite-on-bite biopsies appears to have performed better than any conventional evaluation method, whether this level of accuracy is acceptable for application towards an active surveillance strategy after nCRT is a separate question, one that the SANO trial is attempting to answer. It is concerning, however, that in a study from the same group that compared active surveillance *vs.* immediate surgery using propensity matching and the same bite-on-bite technique in addition to conventional surface biopsy, in the resected specimens of the immediate surgery group, all of which were thought to have cCR based on inclusion criteria, only 24% had a pCR on final pathologic analysis of the resected specimen. Even when including all patients who had pCR in a non-matched group, the pCR rate in the immediate surgery group was only 33% (17,18). Moreover, given that the technique of bite-on-bite is relatively new, the safety and methodology of the technique itself warrants additional study and these results will need to be replicated across other investigations in order to be applicable in the broader management of esophageal cancer.

MRI

While the use of MRI has been validated in evaluating rectal cancer, its use in the context of esophageal cancer is limited and nearly all published studies are feasibility studies with limited numbers of patients. Moreover, as these studies are mostly pilot studies, the criteria used for detecting pCR *vs.*

detecting residual disease is variable. A recent study found that diffusion weighted MRI outperformed FDG-PET/CT (19) with sensitivity and specificity at 96% and 43%, *vs.* 69% and 43% respectively in detecting residual disease. This is borne out in a meta-analysis looking at MRI, with detection of pCR at sensitivity of 80% and specificity of 83%. Notably, only three studies were found that met the criteria to be included in the meta-analysis (12). While this is promising, there is a paucity of available data, and a larger prospective study will be needed before widespread applicability.

Composite assessments and nomograms

Recognizing the limitations of each individual clinical modality in accurately assessing pCR, there have been efforts to create a composite diagnostic protocol to combine the ability of multiple restaging modalities, and in fact, both ongoing trials of an active surveillance strategy *vs.* surgery include use of multiple diagnostic modalities. However, there has been wide variability of accuracy in studies that have evaluated various combinations of PET-CT, CT and endoscopy, likely reflecting the heterogeneity of studies being done as well as the overall unreliable quality of the individual studies themselves.

An attempt to develop a nomogram to predict the likelihood of pCR reported using sex, tumor grade, baseline tumor staging with post-treatment PET-CT findings, endoscopic biopsy results, and a corrected area under the curve of 70 (20). While this is fair quality for a nomogram, it has not been prospectively validated in clinical practice, nor is it robust enough to be reliably used as a decision making tool in patient care at this time.

The risk of esophagectomy

Understanding the question of whether esophagectomy can be avoided requires understanding the risk of undergoing esophagectomy. This risk includes perioperative morbidity and mortality, but also includes potential for lasting detrimental changes to the patient's quality of life.

The past decade has seen significant improvements in perioperative outcomes after esophagectomy. The active adoption of minimally invasive techniques in esophagectomy (21,22), improvement in perioperative care, including the implementation of Enhanced Recovery After Surgery (ERAS) protocols (23), and centralization towards high volume centers has allowed for decreased morbidity and mortality (24), without sacrificing oncologic outcomes (25). A detailed discussion about improvement in surgical outcomes is outside the scope of this manuscript, but a major retrospective study using the Society of Thoracic Surgery database found that operative mortality was 3.1%, and the major complication rate was 33.1% (26), which was improved compared to historical outcomes with mortality ranging from 5–10% and major morbidity between 15–50%.

The decision to submit a patient to trimodality treatment usually requires assessment by a multidisciplinary group of physicians which includes a surgeon. The workup involves subjective and objective assessments, i.e., a detailed history and physical, assessment of functional status, evaluation of any comorbidities and how well they are controlled, and evaluation of cardiopulmonary status. However, efforts to objectively quantify risk in an individual prospective esophagectomy patient are lacking.

Many areas of surgery have risk calculators that are designed to inform patients and physicians about the risk of postoperative complications (27,28). While these calculators are robust and have been regularly used for cardiac surgery or general surgery, no risk calculator exists that performs as well for esophagectomy. A recent study looking at using the American College of Surgeons (ACS) National Surgical Quality Improvement Program (NSQUIP) calculator applied in a series of patients undergoing Ivor Lewis esophagectomy found that while the risk calculator was useful for identifying risk of death or surgical site infection, it did poorly at discriminating the likelihood of other complications such as pneumonia, acute renal failure and cardiac complications (29). This study had only 100 patients and was a retrospective assessment, limiting its applicability. Another study looking at a frailty measurement index called the Risk Analysis Index within the NSQUIP database, which included 10,602 esophagectomy cases, found that it did not accurately detect mortality or morbidity in these patients (30). It seems that up to date there is no reliable way to quantify perioperative risk in patients being evaluated for esophagectomy, and the clinical judgement of the treating physicians continues to play an important role.

Health-related quality of life (HRQOL) is an important factor that has been a major motivator behind efforts to study organ preservation in EAC. Many studies have evaluated HRQOL after esophagectomy, and overall find that esophagectomy is associated with decreased scores on HRQOL questionnaires and patient reported outcomes that can last beyond the early postoperative period (31). It is important to note however, the HRQOL scores tend to improve until they are similar to the normal population

on long-term follow-up (32). The issues that impact HRQOL include emotional function, dysphagia, stenosis, pain, fatigue and dyspnea among many other things. Much of these issues arise from the surgery itself and loss of a normally functioning stomach. The NCCN guidelines list a number of gastrointestinal issues, many of which are related to postsurgical anatomic and functional changes. These are malnutrition/malabsorption, delayed gastric emptying, dumping syndrome, reflux symptoms, and dysphagia (7). As cancer survivorship is increasingly becoming an important area of study, recent studies find that a minimally invasive approach is associated with improved patient-reported QOL (33,34). We also know that perioperative complications are associated with worse HRQOL and can anticipate that as perioperative outcomes improve, we may also see improvement in metrics that measure HRQOL.

The risk of active surveillance

Understanding the risk of deferring surgery in a patient who is a surgical candidate requires assessing the risk of perioperative outcomes after delayed or salvage surgery as well as the long-term oncologic risk of potentially leaving undetected residual disease. The application of a successful strategy would include a surveillance strategy that would theoretically detect any recurrence in a timely fashion before distant metastases or locoregionally unresectable disease occurs. As reviewed above, the currently available strategies for clinical assessment of residual disease after nCRT do not perform reliably in detecting pCR. As the period of surveillance extends beyond the immediate response assessment, there is even less data that evaluates what would constitute a long-term active surveillance program that performs reliably.

The only data we have to address this issue largely comes from retrospective analyses that have looked at patients who refused surgery up front or patients who underwent definitive chemoradiotherapy but had recurrence and required salvage resection (35-37). The RTOG 0246 trial, a phase II single arm trial evaluating a strategy of selective surgery following definitive chemoradiation, was one of the first prospective trials describing an intense surveillance protocols for patients after chemoradiation (38). The surveillance strategy included a history and physical exam, serum chemistry profile, CT scan of the chest and abdomen, endoscopic biopsy, EUS and PET scan (optional but encouraged), performed every 3 months for 2 years, every 6 months for 2 years, then annually thereafter. The patient's clinical status was discussed in a multidisciplinary group of treating physicians, and decision to offer surgery was made collectively. This is certainly a more intense surveillance protocol compared to what most patients undergo after definitive chemoradiation. This study did not achieve its 1-year hypothesized survival rate (71% *vs.* the planned 77%) and did not proceed to a randomized trial. However, the SANO trial and ESOSTRATE trial are currently underway, prospectively evaluating the use of active surveillance, which will no doubt provide valuable insights into appropriate surveillance protocols.

The perioperative risk of delayed esophagectomy

Early literature describing delayed esophagectomy comes from experience performing salvage esophagectomy in patients who underwent definitive chemoradiation, with higher radiation doses up to 60 Gy, from a mostly ESCC population (37,39). These studies found that while there was a subset of long-term survivors, thereby justifying salvage esophagectomy in patients who had recurrence and otherwise had no other treatment options, perioperative outcomes including morbidity and mortality were inferior to patients who underwent early surgery as a part of planned trimodality therapy. This was thought to be related to obscured tissue planes from postradiation fibrosis, and generally recommendations were that salvage esophagectomy benefits from being done in a high-volume center. More recent data has emerged (40), showing that coupled with generally decreased doses of radiation and technical advances in surgery, outcomes are comparable to conventional esophagectomy. However, a very recent report from a group with high experience described frequent mortality (30-day 8.6%, 90-day 17.1%) and morbidity (71.4% compared to 36.6% in the planned surgery cohort) (41), demonstrating that delayed surgery is still a challenging endeavor.

The SANO group published a recent study describing their experience thus far with a nonrandomized propensity matched cohort of patients who were found to have cCR and either accepted or declined immediate surgery (29 patients in each cohort) (17). While the severity of postoperative complications was comparable in both groups (Clavien-Dindo grade 3 or higher: 43% active surveillance *vs.* 45% immediate surgery, mortality: 10% within 90 days in the immediate surgery group *vs.* none in the active surveillance), a closer look at the complications

reveals that a better powered study may demonstrate a difference. Out of the 29 patients who chose active surveillance, 14 underwent surgery eventually within the study period. When comparing the 14 *vs.* the 29 patients who underwent immediate surgery, pneumonia rates were 40% *vs.* 17%, pleural effusion was 21% *vs.* 7%, atrial dysrhythmia was 29% *vs.* 17%, and the leak rate was 21% *vs.* 14%. Conduit necrosis was higher in the immediate surgery group (type I 3%, type II 7%), but the only type III conduit necrosis occurred in the active surveillance group (3%). As mentioned, mortality was higher in the immediate surgery group. None of these findings achieved statistical significance but more likely related to an underpowered analysis. Therefore, the conclusions that perioperative outcomes are equivalent must be interpreted with caution, and we await the results from the larger trial.

Oncologic risks

Understanding the natural history of recurrences after cCR sets the stage for evaluating the oncologic risk of active surveillance. A study looking at trimodality-eligible patients who declined surgery after cCR (35) found that 5-year overall survival was 58.1%, with disease free survival of 35.3%. Fifty-four point one percent developed recurrences, and of these 39.4% had local recurrences, for which 92.3% underwent surgical resection, with median time to surgery after nCRT of 9.3 months (all were within 3 years). The remaining 60.6% had evidence of metastatic cancer. Within this 60.6% would be those patients for whom surgery would have been futile, due to undetected micrometastatic disease, but also patients who would have had undetected residual locoregional disease and could have benefited from surgery that may have decreased distant metastasis.

Thus far data assessing the strategy of active surveillance is retrospective. One study evaluated the outcomes of 59 patients treated with CRT and surveillance, using an intention-to-treat case-control study design (42). They found a 4.2% postoperative mortality rate in patients who underwent immediate surgery, with 34.6% of patients found to have residual tumor. They found that median survival was lower in the surveillance group—31 *vs.* 83 months—and these patients had more frequent, earlier disease recurrence (50.8% recurrence, locoregional in 46.7%) although only 2 salvage esophagectomies were performed in the entire surveillance group. This difference in overall survival compared to the previous study could be partly related to low salvage esophagectomy rates. Moreover, patients were not matched on specific comorbidities and were more likely to be from lower volume centers, which opens the study to significant selection bias that must be considered when interpreting these results.

A Cochrane review attempted to compare chemoradiotherapy *vs.* chemoradiotherapy plus surgery for esophageal cancer. Unsurprisingly they found that of eligible study data, 93% of included patients were of ESCC histology. They found that for this group the addition of esophagectomy had little or no difference on overall survival. Moderate evidence did suggest that surgery decreased locoregional relapse. This data should be interpreted in light of the higher likelihood of pCR in ESCC (43).

To date, to our knowledge, there is no data that directly focuses on EAC alone. The ongoing SANO and ESOSTRATE trials include both histologies, but we look forward to subanalyses devoted to EAC.

Conclusions

The question of whether esophagectomy can be avoided in locoregionally advanced EAC is an appealing question. Clearly there is a subset of patients who have both cCR and true pCR and undergo unnecessary surgery. It appears that there is also a subset of patients who can be surveilled and safely undergo delayed surgery with good long-term outcomes and who do not suffer deleterious effects of having foregone immediate surgery. However, as we have reviewed in this manuscript, currently our ability to detect true pCR and predict outcomes after surgery or surveillance is limited, severely diminishing the safety of active surveillance for all patients with cCR.

Any decision made in this aggressive disease with complex treatment must be made keeping in mind the patient's unique circumstances, and this is an area where truly individualized decision making is necessary. What constitutes an acceptable outcome to a given patient must be discussed using frank terms in language that a layman can understand. Within the spectrum of patient characteristics, what is an acceptable outcome for a younger, healthier patient may be very different to an older, frailer patient.

We are also witnessing the maturation of molecular tools that add depth to our understanding of cancer biology and specific outcomes. Reports of liquid biopsy that is able to detect pre-clinical disease recurrences in other malignancies add to the realm of possibilities that we can anticipate will

alter our ability to provide tailored care to these challenging patients. In the interim, we look forward to the results of the ongoing prospective trials.

Acknowledgments

Funding: Dr. Molena is supported, in part, by the National Institutes of Health/National Cancer Institute (P30 CA008748).

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editor (Riccardo Rosati) for the series "Current issues on GEJ adenocarcinoma" published in *Annals of Esophagus*. The article has undergone external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/aoe-2020-20). The series "Current issues on GEJ adenocarcinoma" was commissioned by the editorial office without any funding or sponsorship. DM serves as an unpaid editorial board member of *Annals of Esophagus* from Sept 2020 to Aug 2022. DM reports Consulting for Intuitive and Urogen about 1 and half years ago and currently do consulting for J&J and Boston Scientific and being in steering committee of AstraZeneca. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/aoe-2020-20
Cite this article as: Choe G, Molena D. Surgery versus active surveillance in clinical complete response. Ann Esophagus 2021;4:31.