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Towards an Organ-Sparing Approach for Locally Advanced Esophageal Cancer

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Abstract
Background: Active surveillance after neoadjuvant therapies has emerged among several malignancies. During active surveillance, frequent assessments are performed to detect residual disease and surgery is only reserved for those patients in whom residual disease is proven or highly suspected without distant metastases. After neoadjuvant chemoradiotherapy (nCRT), nearly one-third of esophageal cancer patients achieve a pathologically complete response (pCR). Both patients that achieve a pCR and patients that harbor subclinical disseminated disease after nCRT could benefit from an active surveillance strategy. ***Summary:*** Esophagectomy is still the cornerstone of treatment in patients with esophageal cancer. Non-surgical treatment via definitive chemoradiotherapy (dCRT) is currently reserved only for patients not eligible for esophagectomy. Since salvage esophagectomy after dCRT (50–60 Gy) results in increased complications, morbidity and mortality compared to surgery after nCRT (41.4 Gy), the latter seems preferable in the setting of active surveillance. Clinical response evaluations can detect substantial (i.e., tumor regression grade [TRG] 3–4) tumors after nCRT with a sensitivity of 90%, minimizing the risk of development of non-resectable recurrences. Current scarce and retrospective literature suggests that active surveillance following nCRT might not jeopardize overall survival and postponed surgery could be performed safely. ***Key Message:*** Before an active surveillance approach could be considered standard treatment, results of phase III randomized trials should be awaited.

Introduction

Organ-sparing treatment has been emerging for several malignancies and it avoids loss-of-function of the organ due to surgical resection. Over 2 decades ago, this treatment strategy was introduced for head and neck cancers, more specifically for laryngeal cancer [1, 2]. Salvage surgery after initial organ-preservation was reported with acceptable rates of postoperative complications [3]. After

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promising results in laryngeal cancer, similar strategies were reported for prostate- and rectal cancer [4–9]. During the surveillance period, mostly after neoadjuvant therapy consisting of chemo- and radiotherapy, frequent checks are performed to detect residual- or progression of disease. Surgical resection is then reserved only for those patients in whom residual disease is proven or highly suspected in the absence of distant metastases. In laryngeal-, prostate- and rectal cancer, active surveillance has been reported a safe strategy without compromising overall survival (OS).

In esophageal cancer, 29% of patients show a pathologically complete response (pCR) after neoadjuvant chemoradiotherapy (nCRT) according to the CROSS-regimen [10]. Literature concerning organ-sparing treatment in esophageal cancer patients with a clinically complete response (cCR) after neoadjuvant therapy is scarce. Some studies show an OS comparable to standard esophagectomy [11–13]. The retrospective nature and small number of included patients in these studies urge the need for further research on this topic. Several challenges currently restrict widespread use of organ-sparing strategies in esophageal cancer. This review aims at providing an overview of the current treatment options and possible opportunities towards an organ-sparing treatment in esophageal cancer.

Surgery and (Neo)Adjuvant Therapy

Esophagectomy is still considered a crucial step in the curative treatment of locally advanced esophageal cancer. One of the first review articles reporting on the outcome of esophageal cancer surgery between 1953 and 1978 reported a mean 5-year survival rate of 12% and a hospital mortality rate of 29% [14, 15]. This 5-year survival rate increased to 20% between 1980 and 1988 with a hospital mortality of 13% [16]. Both transthoracic- and transhiatal esophagectomy showed similar OS of 20% as reported in a meta-analysis [17]. However, a Dutch trial (HIVEX-study) randomized 220 patients with adenocarcinoma of the mid-to-distal esophagus or the gastric cardia involving the distal esophagus and showed a 5-year OS of 27% for the transhiatal approach and 39% for the transthoracic approach with extended *en bloc* lymphadenectomy [18]. Although better patient selection and improvement of perioperative care resulted in higher survival rates over the last decades, the percentage of patients with tumor-free resection margins remained an issue. For both approaches, the HIVEX-trial reported 30% microscopically non-radical resections.

In order to reduce the number of non-radical resections, neoadjuvant therapies consisting of chemo- and/or radiotherapy-regimens have been thoroughly studied. The first completed, sufficiently powered, randomized controlled trial comparing trimodality treatment to surgery alone was published in 1996 [19]. This study included 113 patients with esophageal adenocarcinoma and reported a 3-year survival improvement from 6 to 32% after nCRT was added to surgery. Another trial comparing trimodality-therapy to surgery alone was the CROSS-trial [10, 20]. This Dutch multicenter randomized controlled trial included 366 patients with esophageal or junctional cancer. After nCRT, 92% of the patients underwent a radical resection of the esophagus versus 69% in the surgery alone group. A pCR was achieved in 29% of the patients (23% in adenocarcinoma and 49% in squamous cell carcinoma). Importantly, 5-year OS improved from 33 to 47% after adding nCRT to surgery. No increased postoperative complications were found in the patients undergoing nCRT. Since the publication of the CROSS-trial, nCRT followed by surgery has been adopted as a standard treatment for locally-advanced esophageal cancer in large parts of the western world.

Also, (neo)adjuvant chemotherapy has been shown to be effective in the treatment of esophageal cancer.

The OEO2-trial was the largest trial that investigated the efficacy of neoadjuvant chemotherapy for esophageal cancer [21]. Between 1992 and 1998, 802 patients with locally advanced squamous cell or adenocarcinoma of the esophagus from 42 European centers were randomized between preoperative chemotherapy (cisplatin and fluorouracil) followed by surgery versus surgery alone. In the preoperative chemotherapy group, both disease-free survival (DFS) (hazard ratio [HR] 0.75; $p = 0.0014$) and 2-year OS (HR 0.79; $p = 0.004$) were higher. Long-term results confirmed the improvement in DFS and OS [22]. The MAGIC- and the ACCORD-07-trials confirmed the efficacy of perioperative chemotherapy in patients with esophageal and gastric cancer [23, 24]. Surprisingly, the RTOG-8911 trial, randomizing 440 patients with locally advanced squamous cell or adenocarcinoma of the esophagus in the period 1990–1995 between preoperative chemotherapy followed by surgery and surgery alone, failed to show an improvement in 5- and 9-year OS after addition of preoperative chemotherapy, using cisplatin and fluorouracil [25, 26].

Both chemotherapy and chemoradiotherapy show a statistically significant improvement in OS compared to surgery alone. The improvement in OS that was observed in the CROSS-trial by adding nCRT to surgery (14%) was

comparable to the improvement in the MAGIC- and the ACCORD-07-trials (13 and 15% respectively). Chemoradiotherapy probably shows less morbidity and only moderately decreases quality of life [27–30]. To date, no randomized clinical trials powered on OS comparing chemotherapy to nCRT according to the CROSS-regimen have been published. Currently, 2 studies are addressing this question; the Neo-AEGIS trial and the ESOPEC trial [31, 32].

Twenty-nine percent of patients undergoing nCRT according to the CROSS-regimen showed pCR compared to 3 and 0% in the MAGIC- and ACCORD-07-trials respectively. Distant progression was seen after neoadjuvant therapy and surgery in 39% of the patients in the CROSS-trial after a median follow-up of 84.1 months and in 30% after a median follow-up of 68.4 months in the ACCORD-07 trial. This suggests that micrometastases are already present in many patients at time of diagnosis. Both the high pCR rate after CROSS and frequent development of distant metastases after (neo)adjuvant therapy followed by surgery imposes the dilemma whether all patients would eventually benefit from esophagectomy, or whether surgery should be reserved only for those patients in whom residual disease after nCRT has been proven or is highly suspected, in the absence of distant metastases. In this way, esophagectomy could be postponed or even avoided, not only in patients who happen to attain biologically complete response after nCRT, but also in patients developing distant metastases during active surveillance, since distant metastases will heavily determine survival in these patients.

Definitive Chemoradiotherapy

For patients unveiling unfit for surgery due to frailty or serious comorbidities or with an unfavorable location (e.g., the cervical esophagus) or stage of the tumor (cT4b), definitive chemoradiotherapy is the preferred curative standard treatment [33]. Definitive nonsurgical therapy mostly consists of concurrent chemoradiotherapy, since the RTOG 85-01 study reported superiority of chemoradiotherapy over radiotherapy alone [34–36].

Several trials have been performed to compare surgical and nonsurgical therapies in operable patients. Between 1994 and 2002, Stahl et al. [37] randomized 172 patients with locally advanced squamous cell carcinoma between nCRT followed by esophagectomy and dCRT. Three-year OS was similar in both groups. Although the local progression-free survival was better in the group undergoing esophagectomy (64.3 vs. 40.7%; HR 2.1, $p = 0.003$), treatment-related mortality was higher (12.8 vs. 3.5%; $p = 0.03$). Bedenne et al. [38] randomized 259 patients between 1993 and 2000 with locally advanced esophageal cancer between nCRT followed by esophagectomy and dCRT. Although the local recurrence rate after 2 years was higher in the patients undergoing dCRT (HR 1.63, $p = 0.03$), mortality in the first 3 months postoperatively was higher in the esophagectomy group (HR 1.63, $p = 0.002$). These results should be interpreted with caution, since 2-year OS after nCRT and surgery was only 33.6% in contrast to, for example, 67% in the CROSS-trial. Furthermore, the Bedenne et al. [38] trial excluded 43% of the patients not responding to nCRT. Subsequent analysis showed similar survival between responders and nonresponders undergoing esophagectomy, which seems hard to explain [39].

Although patients undergo dCRT mostly because they are not eligible for esophagectomy, a subgroup of patients become eligible after dCRT and undergo esophagectomy for residual or recurrent disease (so called salvage surgery). Several studies reported higher mortality and morbidity rates for surgery after dCRT compared to surgery after nCRT or compared to surgery alone [40–42]. Since 5-year OS was reported 25% in these patients undergoing salvage esophagectomy, the higher rates of complications, morbidity, and mortality were considered acceptable. However, the indication for salvage esophagectomy should be considered with caution and only for a selected group of patients. Furthermore, the term "salvage esophagectomy" is sometimes used for postponed esophagectomy after nCRT and thus, the definition seems unclear. However, salvage surgery after dCRT (50–60 Gy) and postponed surgery after nCRT (41.4 Gy) should be considered 2 different entities. Because postponed surgery after nCRT in the context of active surveillance is expected to be necessary in a considerable number of patients and dCRT substantially increases adverse postoperative outcomes, nCRT according to the CROSS-regimen (41.4 Gy) seems preferable in the setting of active surveillance [43, 44].

Clinical Response Evaluation

Before an active surveillance strategy can be implemented, one should address several challenges. Most importantly, OS should not be jeopardized. In order to prevent the development of non-resectable recurrences, residual disease should be detected at an early stage. Such

clinical response evaluations (CREs), mostly comprising endoscopy with biopsies, endoscopic ultrasonography (EUS), positron emission tomography with ^{18}F-fluorodeoxyglucose (PET), CT, and/or MRI should determine whether or not a patient is considered a clinically complete responder. Accurate CREs should have the ability to detect residual cancer while it is still resectable with a high chance of a complete tumor removal (radical resection). To justify an active surveillance strategy and to safely postpone surgery, the value and accuracy of CREs after nCRT should be thoroughly studied.

Since there are no standard protocols for CREs, studies concerning these evaluations come with large heterogeneity. For endoscopic biopsies, sensitivity of 30–40% and specificity of 100% were reported in 3 prospective studies [45–47]. Three prospective studies reported sensitivity and specificity for EUS ranging from 95 to 100% and 0 to 47% respectively [46, 48, 49]. Although PET-CT after nCRT is mainly used for the detection of distant interval metastases, the value in CREs has also been assessed. Two prospective studies reported a sensitivity of 51–60% and a specificity of 60–67% [45, 50]. One prospective study including 64 patients assessed a combination of any of these diagnostic modalities (endoscopic biopsies, PET and CT) and reported a sensitivity of 76% and specificity 82% [45]. The most recent and largest trial assessing a combination of diagnostic modalities is the preSANO-trial [51]. This prospective multicenter trial evaluated the accuracy of CREs and aimed to determine the optimal set of diagnostic modalities to accurately unveil residual esophageal cancer after nCRT. Some 207 patients with squamous cell or adenocarcinoma of the esophagus or esophagogastric junction were included between 2013 and 2016. The aim of this study was to assess the correlation between the CRE-results and the tumor regression grades (TRGs) in the resection specimen. The primary endpoint of the study was the proportion of TRG3–4 tumors (>10% residual tumor cells) as detected during CREs. It is assumed that TRG2 tumors (1–10% residual tumor cells) can initially be missed based on the assumption that these tumors will develop into detectable TRG3–4 residual disease during active surveillance and can be resected safely and at the right time. Consequently, falsely negative results were reflected by the number of patients showing TRG3–4 residual disease not detected with endoscopic biopsies, EUS with fine-needle aspiration (FNA) of suspected lymph nodes and/or PET-CT.

Six weeks after the completion of nCRT, patients underwent a first CRE (CRE-1) with only endoscopic biopsies according to the CROSS-regimen. If CRE-1 turned out to be negative, a second CRE (CRE-2) was performed 12 weeks after the completion of nCRT, consisting of PET-CT followed by endoscopic biopsies and EUS with FNA of all suspected lymph nodes. Afterwards, all patients underwent surgery. If no vital tumor cells were proven during both response evaluations, patients were considered cCR and these results were compared to the surgical specimen of the patients. Thirty-one percent of patients with TRG3–4 tumors were considered cCR using endoscopic biopsies and EUS with FNA of all suspected lymph nodes. This drastically improved to 10% after the introduction of bite-on-bite biopsies. It is thought that with bite-on-bite biopsies, deeper layers of the esophageal wall can be reached and thus, these biopsies are theoretically capable of unveiling buried tumors [52]. Furthermore, 10% of patients showed interval metastases, as detected with PET-CT during CRE-1 and CRE-2. These results were considered sufficient to proceed with the SANO-trial (Surgery as Needed for Oesophageal cancer); a phase-3 multicenter randomized controlled trial comparing active surveillance with immediate surgery [53].

Active Surveillance in Esophageal Cancer

Although literature on the outcomes of nCRT plus active surveillance compared to nCRT followed by immediate surgery in patients with esophageal cancer is scarce, some studies have been published. In 2012, Taketa et al. [11] retrospectively reviewed 622 patients after chemoradiotherapy and surgery. A cCR was defined as no vital tumor cells in biopsies and having a physiologic range of uptake by PET-CT. Sixty-one patients with a cCR refused surgery after nCRT and preoperative staging with endoscopic biopsies and PET-CT. These patients showed a 5-year overall- and recurrence-free survival of 58.1 and 35.3% respectively. One year later, outcomes between patients declining immediate surgery and patients who underwent standard trimodality-therapy were compared using propensity-score matching and no difference in 3-year OS was reported (62 vs. 56% respectively; $p = 0.28$) [12]. Thirty-one percent of patients who declined immediate surgery eventually underwent a postponed resection because of residual disease without distant metastases and all resections were radical. Castoro et al. [13] retrospectively included 77 patients with cCR after neoadjuvant therapy of whom 38 had declined surgery and 39 had undergone immediate surgery. After propensity-score matching, no differences were reported in 5-year OS and DFS.

Currently, the Dutch SANO- and the French ESOSTRATE-trials are comparing active surveillance with immediate surgery in patients with squamous cell- or adenocarcinoma of the esophagus showing cCR after nCRT according to the CROSS-regimen [53]. In the SANO-trial, cCR is defined as endoscopy with multiple bite-on-bite biopsies, EUS with FNA of all suspected lymph nodes and PET-CT, all showing no signs of residual disease or distant metastases twelve weeks after the completion of nCRT. After having reached cCR, patients are randomized to either active surveillance or immediate resection according to a stepped-wedge design, that is, based on randomization on institutional level and not on individual level, since randomization between conservative and surgical treatment on individual level often fail due to disappointing inclusion rates [54, 55].

Future Perspectives

Safe and careful implementation of an organ-sparing approach in esophageal cancer depends on several cornerstones. First of all, CREs need to be further improved in order to avoid the risk of developing irresectable residual disease during active surveillance. For this purpose, it should be analyzed why endoscopic bite-on-bite biopsies still show false-negative results. Probably, there are 2 main reasons; either the location of the residual tumor was superficial but biopsies were not accurately targeted or the residual tumor was too deep for endoscopic biopsies to reach the tumor as already suggested in earlier studies [56, 57]. Sampling of large areas of the esophagus during CREs could overcome the issue of sampling errors, for instance, the Endosponge® (Medtronic, Minneapolis, MN, USA) and the wide-area transepithelial sampling procedure [58, 59]. The latter technique uses a minimally invasive brush biopsy technique, which samples layers as deep as the muscularis mucosae. New biopsy instruments reaching deeper parts of the esophageal wall, like fine-needle biopsies (FNB), could overcome the issue of residual tumor buried under a tumor-free (sub)mucosal layer [57, 60, 61]. FNB is considered safe and is widely used in the gastrointestinal tract. Dynamic contrast-enhanced MRI has shown potential benefit in detection of residual disease after nCRT [62]. Although PET-CT does not seem accurate enough to determine whether or not a patient should undergo surgery early after nCRT due to high false-positive rates (mostly because of radiation esophagitis), the value of semi-quantitative assessment of residual disease with PET-CT could be of value during surveillance and is currently part of the surveillance strategy in the SANO-trial [51]. Furthermore, new biomarkers could possibly unveil residual tumors in the peripheral blood [63]. An example of such biomarkers is circulating tumor DNA (ctDNA) that is shed from necrotizing tumor cells freely into the peripheral blood. With the help of next-generation sequencing and whole exome sequencing, very small amounts of DNA containing esophageal cancer-specific mutations can be detected and thus, can possibly detect residual tumors in early phases and as such act as "liquid biopsies" [64, 65]. Even though CREs are considered accurate enough in unveiling residual disease, delayed detection of recurrences could theoretically result in increased distant dissemination rate due to prolonged in situ time of the primary tumor. Although previous studies showed no differences in distant dissemination rate between patients undergoing nCRT with and without surgery, this must be monitored with caution during active surveillance [12, 13]. Secondly, implementation of an active surveillance strategy should come with some side notes. Although an active surveillance strategy would have clear clinical advantages, concerns exist about whether the active surveillance strategy is warranted for all patients with cCR. Such a strategy comes with more frequent hospital visits and additional invasive diagnostic tests that could result in a psychological burden. Furthermore, patients could experience anxiety due to the fact that, potentially, the tumor has not been treated optimally and postponed surgery could still be necessary. These factors could outweigh the advantage of preventing surgery [66]. Earlier studies reported a discrepancy in decision-making between the patients and their doctors which underlines the necessity of shared-decision making [67]. A recent study suggested that, in the preoperative stage, esophageal cancer patients were willing to trade-off an average of 15% 5-year survival to decrease the need for esophagectomy from 100 to 35% [68]. Future studies should confirm these results in the postoperative setting. Furthermore, patient factors should be identified that are clearly correlated with a preference for either immediate surgery or active surveillance to better inform and advice patients in decision-making [69].

Conclusion

After nCRT up to one-third of patient shows pCR in the resection specimen. This evokes a discussion if active surveillance might be appropriate in patients with cCR.

Currently, the main challenge is to improve the clinical identification of tumor residue.

The scarce retrospective literature suggests that an organ-sparing approach with active surveillance after nCRT might not jeopardize OS and postponed surgery could be performed safely. Before an active surveillance approach can be considered part of standard treatment in patients with esophageal cancer, the results of randomized trials such as the ESOSTRATE- and the SANO-trial, should be awaited.

Disclosure Statement

The authors declare that they have no conflicts of interest to disclose.

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