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Radiochemotherapy in esophageal cancer

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Summary Esophageal cancer is one of the ten most frequent tumors worldwide. There are two major histologies: squamous cell carcinomas, which appear more frequently in the upper part of the esophagus, and adenocarcinomas, which are predominantly found in the distal part and at the gastroesophageal junction. Most patients suffer from locally advanced tumors, for which the prognosis is still poor with a 5-year survival rate of 15–25%. Treatment is based on histology, tumor stage, location of the tumor, performance status, age, and comorbidities and it consists of surgery, chemotherapy, or radiotherapy or a combination of these. Over the past decades, neoadjuvant radiochemotherapy followed by surgery became standard of care in patients with locally advanced squamous cell carcinomas suitable for surgery. The treatment of locally advanced adenocarcinomas and junctional tumors is still under debate and consists of either perioperative chemotherapy or neoadjuvant chemoradiotherapy followed by surgery. In patients not suitable for surgery, definitive radiochemotherapy is considered the treatment of choice. Modern radiotherapy in esophageal cancer is increasingly conformal and the dose at organs-at-risk could be reduced over the years to lower the rate of treatment-related side effects. Individualization of treatment and new combinations of systemic agents are under investigation to improve treatment outcome.

Keywords Gastroesophageal junction · Definitive treatment · Multimodal treatment · Neoadjuvant treatment · Locally advanced tumors

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Introduction

Esophageal cancer is one of the ten most frequent tumors worldwide. Despite advances in the treatment over the past decades, outcome especially in locally advanced tumors remains poor with a 5-year survival rate of about 15–25%. A distinction between squamous cell carcinoma, which can mostly be found in the proximal part of the esophagus, and adenocarcinoma, which is predominantly located in the distal part or at the gastroesophageal junction, must be made. In Western countries, the incidence of adenocarcinoma of the esophagus and the gastroesophageal junction showed a marked increase over the past decades. For patients with limited disease (i.e., cT1-2 cN0 M0), surgery without perioperative treatment is standard of care. Nonsurgical approaches are indicated only in patients unwilling or unable to undergo surgery. By contrast, in patients with locally advanced tumors (i.e., cT3-4 or cN+ M0), perioperative treatment should be performed. This may consist of radiotherapy in combination with chemotherapy or chemotherapy alone, depending on histology, tumor stage, location of the tumor, performance status, age, and comorbidities. In patients unwilling or unfit for surgery, or for inoperable tumors, definitive radiochemotherapy is indicated. Over the past years, modern radiochemotherapy concepts became standard of care in neoadjuvant and definitive treatment settings.

Neoadjuvant treatment

Patients with locally advanced tumors should be presented in a multidisciplinary tumor board for evaluation of a multimodal therapy approach with curative intention. The aim of neoadjuvant radiochemotherapy in the treatment of locally advanced esophageal

cancer is to raise R0 resection rates as well as local control rates resulting in an improved overall survival. In squamous cell carcinoma, neoadjuvant radiochemotherapy is standard of care. By contrast, in adenocarcinoma, treatment can consist of either perioperative chemotherapy or neoadjuvant radiochemotherapy. Several randomized phase III trials comparing neoadjuvant radiochemotherapy followed by surgery with surgery alone showed a clear benefit regarding local control and overall survival in favor of preoperative treatment. Meta-analyses indicate the superiority of preoperative (radio-)chemotherapy over surgery alone [1]. In the CROSS trial, patients with clinically resectable, locally advanced cancer of the esophagus or the gastroesophageal junction were randomly assigned to neoadjuvant radiochemotherapy (41.4 Gy with five concurrent cycles of carboplatin and paclitaxel) followed by surgery, or surgery alone. After neoadjuvant treatment, R0 resection was possible in 92% of patients and 29% showed a pathologically complete response, while R0 resection could only be performed in 69% of patients in the surgery-only group. After a median follow-up of 84.1 months, median overall survival was 48.6 months in the neoadjuvant radiochemotherapy group versus 24.0 months in the surgery-only group. The survival benefit was shown for squamous cell carcinoma (81.6 months vs. 21.1 months) as well as for adenocarcinoma (43.2 months vs. 27.1 months). Postoperative complications were similar in both groups with no significant difference in in-hospital mortality (4% vs. 4%). Therefore, the authors concluded that neoadjuvant chemoradiotherapy as described in the CROSS trial followed by surgery should be regarded as standard of care for patients with resectable, locally advanced esophageal or gastroesophageal junctional cancers [2, 3]. In international guidelines, neoadjuvant radiochemotherapy is seen as standard of care in the treatment of locally advanced squamous cell carcinoma of the esophagus. In locally advanced adenocarcinomas and junctional tumors, the question of whether perioperative chemotherapy [4] or neoadjuvant radiochemotherapy should be applied is still open and under debate [5]. An ongoing multicenter phase III trial (ESOPEC) focuses on that question and compares perioperative chemotherapy (FLOT) with neoadjuvant chemoradiation in patients with adenocarcinoma of the esophagus [6]. Whether there is a need for surgery after neoadjuvant radiochemotherapy, especially in those patients who show good response or even a complete remission to neoadjuvant therapy, is another unresolved question. Stahl et al. compared induction chemotherapy followed by radiochemotherapy with and without surgery in patients with locally advanced squamous cell carcinoma of the esophagus. The authors concluded that adding surgery to radiochemotherapy improves local tumor control but does not increase survival. They further assumed that tumor response to induction chemotherapy identifies a favorable prognostic group [7]. Similar results were found in the FFCD 9102 trial, which compared radiochemotherapy followed by surgery with radiochemotherapy alone. Median survival time as well as the 2-year local control rate did not differ significantly in both arms, but the mortality rate was significantly higher in the surgery arm. The authors suggested that there is no benefit for the addition of surgery after radiochemotherapy in patients with locally advanced esophageal cancer who respond to radiochemotherapy compared with the continuation of additional radiochemotherapy [8]. Omitting surgery after neoadjuvant radiochemotherapy is an attractive option especially for complete responders. However, this concept needs further evaluation in randomized trials and cannot yet be recommended outside of clinical trials.

Definitive radiochemotherapy

For unresectable esophageal cancer (e.g., located in the upper third of the esophagus) and patients not suitable or unwilling to undergo surgery, definitive radiochemotherapy is the treatment of choice. Early studies already showed that concurrent radiochemotherapy is superior to radiotherapy alone in patients with carcinoma of the esophagus in terms of local tumor control, distant metastasis, and survival at the cost of increased side effects [9]. Since then, several trials with different chemotherapy agents concurrent to radiotherapy have been conducted, mainly on patients with squamous cell carcinomas. The 2014 French PRODIGE5/ACCORD17 trial was a randomized phase II/III trial aimed at assessing the efficacy and safety of the FOLFOX (folinic acid, fluorouracil, oxaliplatin) treatment regimen versus fluorouracil and cisplatin as part of chemoradiotherapy in 259 patients with localized esophageal cancer unsuitable for surgery. After a median follow-up of 25.3 months, median progression-free survival was 9.7 months in the FOLFOX group and 9.4 months in the fluorouracil and cisplatin group ($p = 0.64$; [10]).

Whether higher radiation doses result in higher tumor control rates is still an unresolved question. The INT 0123 phase III trial compared local and regional control, survival, and toxicity of combined modality therapy using high-dose (64.8 Gy) versus standard-dose (50.4 Gy) radiotherapy with concurrent fluorouracil and cisplatin for the treatment of patients with esophageal cancer. There was no significant difference in median survival (13.0 vs. 18.1 months), 2-year survival (31% vs. 40%), or locoregional failure and locoregional persistence of disease (56% vs. 52%) between the high-dose and the standard-dose arm [11]. The PRODIGE26/CONCORDE trial is an ongoing randomized phase II/III trial to test concomitant chemoradiotherapy for patients with nonresectable esophageal cancer with and without dose escalation up to 66 Gy on the primary tumor as well as involved

nodes using a 3D conformal technique combined with 40 Gy elective nodal irradiation on regional lymph nodes that harbor a risk of microscopic involvement of ≥20% [12]. In the ART DECO phase III trial, patients are randomized between the standard dose of 50.4 Gy in fractions of 1.8 Gy and the experimental arm of 50.4 Gy combined with a concomitant boost of 11.2 Gy to the primary tumor, leading to a total tumor dose of 61.6 Gy in daily fractions of 2.2 Gy. In both arms, chemotherapy consisting of paclitaxel 50 mg/m^2 and carboplatin (AUC = 2) will be administered weekly as radiosensitizer [13].

Irradiation dose and technique

In the neoadjuvant setting, 41.4–45 Gy is considered an adequate radiation dose [3]. The dose for definitive radiochemotherapy is more controversial, ranging from 50.4 Gy to over 60 Gy [11]. Today, highly conformal treatment techniques, such as intensity-modulated radiotherapy (IMRT) or volumetric arc therapy (VMAT), are standard of care in the treatment of esophageal cancer and offer the possibility of applying higher treatment doses while providing maximum protection of organs at risk, thereby reducing treatment-related side effects [14].

Treatment-related complications

Acute side effects of radiotherapy include radiodermatitis, mucositis, odynophagia, dysphagia, fatigue, pneumonitis, or pericarditis. These are mostly temporary, and treatment is usually symptom-based. By contrast, late side effects are often chronic, and treatment is often difficult. These include fibrosis or hyperpigmentation of the skin, pulmonary fibrosis, esophageal stricture or perforation, and myelopathy. Chemotherapy-related adverse effects depend on the substances used and include fatigue, nausea, vomiting, myelosuppression, or peripheral neuropathy. Importantly, concurrent chemotherapy may amplify radiotherapy-related side effects and vice versa.

Conclusion

The benefit of combined radiochemotherapy in esophageal cancer, either neoadjuvant or definitive, has been proven by many prospective trials. Neoadjuvant radiochemotherapy followed by surgery is considered state of the art for patients with resectable locally advanced squamous cell carcinoma of the esophagus. In patients not suitable for surgery, definitive radiochemotherapy is considered the treatment of choice. The optimum treatment for locally advanced adenocarcinoma of the esophagus and the gastroesophageal junction is not yet defined, with perioperative chemotherapy and neoadjuvant radiochemotherapy being valid options. Dose escalation trials and new chemotherapeutic combinations, concurrent to radiation therapy, are currently under investigation to improve local control and survival in patients unsuitable for surgery. Despite the aforementioned studies, many questions in the management of esophageal cancer remain unanswered and many topics are under debate, such as indications for positron emission tomography–computed tomography (PET-CT), omission of surgery in the case of complete remission after neoadjuvant radiochemotherapy, optimal treatment of adenocarcinoma, evaluation and implementation of biomarkers, and the role of targeted therapeutics.

Take-home message

Radiochemotherapy is an essential part of the multimodal treatment of esophageal cancer. In patients with locally advanced disease suitable for surgery, neoadjuvant radiochemotherapy is standard of care in squamous cell carcinoma. In adenocarcinoma and junctional tumors, there is still debate about which patients benefit from adding radiotherapy to the neoadjuvant treatment. In patients not suitable for surgery, definitive radiochemotherapy is standard of care with good results.

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Conflict of interest E. Mayer, C.R. Arnold, U. Ganswindt, and R. Jäger declare that they have no competing interests.

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