Neoadjuvant and definitive radiochemotherapeutic approaches in esophageal cancer: a retrospective evaluation of 122 cases in daily clinical routine

Patrick Mayr, Benedikt Martin, Verena Fries, Rainer Claus, Matthias Anthuber, Helmut Messmann, Gerhard Schenkirsch, Vera Blodow, Klaus Henning Kahl, Georg Stüben

Angaben zur Veröffentlichung / Publication details:

Mayr, Patrick, Benedikt Martin, Verena Fries, Rainer Claus, Matthias Anthuber, Helmut Messmann, Gerhard Schenkirsch, Vera Blodow, Klaus Henning Kahl, and Georg Stüben. 2020. "Neoadjuvant and definitive radiochemotherapeutic approaches in esophageal cancer: a retrospective evaluation of 122 cases in daily clinical routine." *Oncology Research and Treatment* 43 (7-8): 372–79. https://doi.org/10.1159/000507737.

Neoadjuvant and Definitive Radiochemotherapeutic Approaches in Esophageal Cancer: A Retrospective Evaluation of 122 Cases in Daily Clinical Routine

Patrick Mayr[a, b] Benedikt Martin[c] Verena Fries[a] Rainer Claus[b] Matthias Anthuber[d] Helmut Messmann[e] Gerhard Schenkirsch[f] Vera Blodow[g] Klaus Henning Kahl[a] Georg Stüben[a]

[a]Department of Radio-Oncology, University Hospital of Augsburg, Augsburg, Germany; [b]Department of Hematology and Oncology, University Hospital of Augsburg, Augsburg, Germany; [c]Department of Pathology, University Hospital of Augsburg, Augsburg, Germany; [d]Department of Surgery, University Hospital of Augsburg, Augsburg, Germany; [e]Department of Gastroenterology, University Hospital of Augsburg, Augsburg, Germany; [f]Department of Tumor Data Management, University Hospital of Augsburg, Augsburg, Germany; [g]Department of Nuclear Medicine, University Hospital of Augsburg, Augsburg, Germany

Keywords
Esophageal cancer · Radiochemotherapy · Neoadjuvant treatment · Definitive approach

Abstract
Introduction: Esophageal cancer (EC) is a common malignant tumor entity with increasing occurrence. The incidence of esophageal adenocarcinoma (AC), particularly, is constantly rising in the Western world. The mainstays of therapy with curative intent for EC in advanced stages are neoadjuvant radiochemotherapy (neoRCT) with surgery and definitive radiochemotherapy (defRCT). ***Methods:*** We examined our internal files to identify patients suffering from EC. Palliative cases were excluded. Statistical testing was performed by χ^2 test, Student's *t* test, Kaplan-Meier analyses, and the Mann-Whitney U test. ***Results:*** One hundred and twenty-two cases were included. Histology revealed squamous cell carcinoma in 92 cases and AC in 23 cases. Ninety-five patients underwent defRCT, 27 underwent neoRCT, and 114 (in both therapy regimes) received simultaneous chemotherapy. There was no difference in the overall survival (OS) (p = 0.654; HR 1.145; 95% CI 0.629–2.086) or and progression-free survival (PFS) (p = 0.912) of patients who underwent neoRCT or defRCT. Median OS was 13.5 (2–197) months for defRCT patients and 19.5 (2–134) months for neoRCT patients (p = 0.751). Karnofsky index (KI) with a cut-off of 70% was strongest, but not a significant parameter for OS (p = 0.608) or PFS (p = 0.137). ***Conclusion:*** defRCT is a valid and an equal alternative to neoRCT for patients suffering from EC. Selection of patients for therapy is of crucial relevance. Further studies and improvements in follow-up are needed when neoRCT has been completed before surgery, in order to spare the patient undergoing operative treatment if there is complete remission. The identification of valid markers urgently needed to limit treatment side effects.

Introduction

Esophageal cancer (EC) is the eighth most common cancer entity in the world, and the sixth most common cause of cancer-associated deaths worldwide [1, 2]. The

Dr. med. Patrick Mayr
Department of Hematology and Oncology
University Hospital of Augsburg
Stenglinstrasse 2, DE–86156 Augsburg (Germany)
Patrick.Mayr@uk-augsburg.de

incidence of EC has been rapidly increasing in the industrialized world within the last years. In Germany, the incidence is 2.2/100,000 for women and 9.3/100,000 for men. Esophageal adenocarcinoma (AC) accounts for 11.6 % of cases and squamous cell cancer (SCC) for the remaining 88.4% worldwide [3]. In the last years, a trend towards AC has been observed in industrialized countries [4, 5]. Gastroesophageal reflux disease, and its association with obesity and immobility, is thought to be one of the most important underlying causes in the Western world.

The rate of 5-year-survival is 37.8 % at localized stages (up to stage II) according to the Union for International Cancer Control (UICC), and around 19.8–47 % in patients with node-positive disease who undergo adjuvant radiochemotherapy (neoRCT); survival rates in patients with metastasized stages often do not exceed 1 year [1, 2, 5].

To date, there has been much discussion about superior therapy schemes [6]. The constitution of patients, the evaluation of perioperative risks, and examination of histology are major factors that influence therapeutic decisions. However, there is a considerable lack of evidence available from daily clinical routine.

Early-stage disease is commonly treated by endoscopic mucosal/submucosal resection [6]. Therapeutic approaches for more advanced disease and curative intent include esophagectomy. Definitive radiochemotherapy (defRCT) is increasingly being seen as a potential alternative in resectable disease, especially in patients unfit for surgery. Advanced-stage tumors need multimodal treatment in order to reduce recurrence rates and achieve higher rates of local control and survival [7, 8]. Another aim is preoperative downstaging of the tumor to minimize the extent of the surgery performed as well as targeting potential micrometastases to reduce the risk of distant recurrence [6, 8]. To date, discussions are ongoing regarding the dose of radiotherapy (RT), the scheme of concomitant chemotherapy (CTx), indications, and time of operative intervention. Determining patient selection criteria for therapeutic approaches, i.e., surgery, RT, and RCT is also important.

The aim of our study was to evaluate radiotherapeutic and surgical treatment modalities in terms of therapy-associated morbidity, overall survival (OS), disease recurrence, patient selection criteria with regard to patients' constitution (measured by means of the Karnofsky index [KI]), age, and tumor stage. In terms of RT, we analyzed the applied dosage, the CTx, and the occurrence of stenosis following RT. We evaluated a single-center collective of cases taken from daily clinical routine, without the preselection bias that is frequently observed in clinical trials. Furthermore, this study was performed for internal quality assurance and standard of care aspects.

Methods

We screened the radiotherapeutic information system (MOSAIQ, Elekta, Stockholm, Sweden) for cases of EC treated with curative intent (i.e., a neoadjuvant or definitive approach) at our Radiation Oncology Department in the period 2000–2018. These cases were matched and completed with reference to the Tumor Data Management (TDM) database, in order to obtain additional follow-up and survival data. Finally, we screened our clinic information system to gather missing information about clinical course and follow-up data. In total, 122 cases were collected.

Statistics

Statistical analysis was performed by IBM's SPSS v24 software suite. p values ≤ 0.05 were estimated as significant. Mean values were compared by Student's t test. Cross-table comparison analysis was performed with the χ^2 test and Fisher's exact test for small numbers. Additionally, Kaplan-Meier and log rank analyses were performed for survival analyses. The Mann-Whitney U test was used in cases of ordinal data and unequally distributed data. Follow-up times were measured according to the method of Schemper and Smith [9].

Results

Therapeutic Decisions and Radiotherapeutic Planning

All treatment decisions at our institute are consensus-based and made by the inhouse interdisciplinary tumor board. The tumor board comprises experts from surgery, radiology, oncology, nuclear medicine, pathology, gastroenterology, and radiation oncology. If RCT is the therapy of choice, staging by PET-CT, endoscopic sonography, and clip marking of the tumor are routinely performed pretherapeutically. If PET-CT is not performed because of high therapeutic pressure, CT of the thorax and abdomen is performed. Afterwards, planning CT is merged with data from the PET-CT or diagnostic CT. Safety margins are 5 cm oral and aboral to the primary tumor. The radiation technique is based on intensity-modulated RT (IMRT) with consideration of the constraints posed by the surrounding anatomical structures, i.e., with maximum protection of the spinal cord, heart, and lungs.

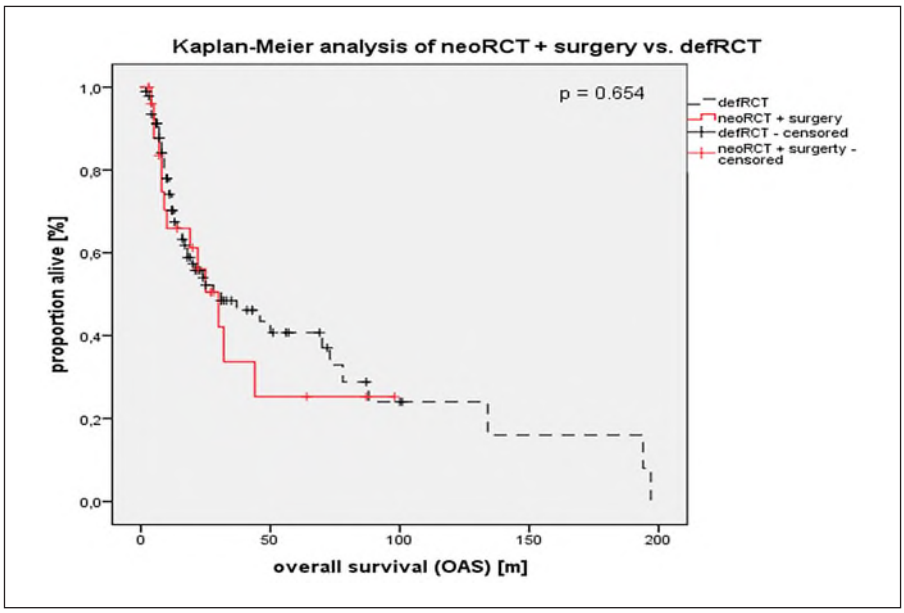
Clinical Data

An overview of the cases and clinical data from this study is given in Table 1. Patients undergoing defRCT were significantly older than those who received neoRCT and surgery ($p = 0.033$). There was no difference in the distribution of sex ($p = 0.412$). Histology was significantly differently distributed: SCC was significantly more common in the defRCT group (75 cases) than in the neoRCT group (17 cases), while ACs were about equal in number (13 with defRCT and 10 with neoRCT) ($p = 0.015$). UICC stage was marginally not significantly different in the 2 treatment groups, according to the Mann-

Table 1. Overview of clinical data on 122 study subjects

	All patients	neoRCT + surgery group	defRCT group	*p* value
Age, years	64 (21–82)	61 (37–77)	55 (21–82)	0.033
Follow-up, months	14.5 (2–197)	19.5 (3–134)	13.5 (2–197)	0.751
Therapy intended, *n*		29	93	
Therapy performed, *n*		27	95	
PEG tube implantation				0.004
No	39 (32.5)	15 (55.6)	24 (25.8)	
Yes	81 (67.0)	12 (44.4)	69 (74.2)	
Karnofsky index available, %		90 (50–100)	90 (40–100)	0.997
A Karnofsky index of at least 70%				0.578
No	6 (5.1)	1 (3.7)	5 (5.6)	
Yes	111 (94.9)	26 (96.3)	85 (94.4)	
Sex	122			0.412
Female	27 (22.1)	5 (18.5)	22 (23.2)	
Male	95 (77.9)	22 (81.5)	73 (76.8)	
UICC stage				
I	10 (8.2)	0 (0)	10 (11.1)	0.083
II	20 (17.2)	2 (7.7)	18 (20.0)	
III	77 (66.4)	23 (88.5)	54 (60.0)	
IV	9 (7.8)	1 (3.8)	8 (8.9)	
Not available, *n*	6	1	5	
Location in esophagus				<0.001
Upper third	47 (38.5)	0 (0.0)	47 (49.5)	
Middle third	36 (31.1)	10 (37.0)	26 (27.4)	
Lower third	38 (29.5)	17 (63.0)	21 (22.1)	
Multiple locations	1 (8.0)	0 (0.0	1 (1.1)	
Histology				0.015
Squamous cell carcinoma	92 (80.0)	17 (63.0)	75 (85.2)	
Adenocarcinoma	23 (20.0)	10 (37.0)	13 (14.8)	
Not available	7	0	7	
Chemotherapy				0.436
No	8 (6.6)	1 (3.7)	7 (7.4)	
Yes	114 (93.4)	26 (92.3)	88 (92.6)	
Chemotherapy completed				0.453
No	12 (10.5)	2 (7.7)	10 (12.8)	
Yes	102 (89.0)	24 (92.3)	78 (87.2)	
Progress in the course of disease				0.366
No	53 (43.4)	13 (48.1)	40 (42.1)	
Yes	69 (56.6)	14 (51.9)	55 (57.9)	
Distant metastasis in course of disease				0.229
No	86 (70.5)	17 (63.0)	69 (72.6)	
Yes	36 (29.5)	10 (37.0)	26 (27.4)	
Death				0.577
No	59 (48.4)	13 (48.1)	46 (48.4)	
Yes	63 (51.6)	14 (51.9)	49 (51.6)	
Death within 30 days after completion of therapy				0.280
No	117 (95.6)	27 (100.0	90 (94.7)	
Yes	5 (4.3)	0 (0.0)	5 (5.3)	
Death within 90 days after completion of therapy				0.434
No	107 (87.7)	23 (85.2)	84 (88.4)	
Yes	15 (12.3)	4 (14.8)	11 (11.6)	
Overall survival, months	14.5 (2–197)	19.5 (3–134)	13.5 (2–197)	0.751
Local recurrence after therapy				
No	41 (73.2)	4 (66.7)	37 (74.0)	0.515
Yes	15 (26.8)	2 (33.3)	13 (26.0)	

Values are expressed as median (range) or *n* (%), unless otherwise indicated. neoRCT, neoadjuvant radiochemotherapy; defRCT, definite radiochemotherapy; PEG, percutaneous endoscopic gastrostomy; UICC, Union for International Cancer Control.



Color version available online

Fig. 1. Kaplan-Meier analysis of overall survival with neoRCT and surgery versus defRCT.

Whitney U analysis ($p = 0.083$), as was the case for the KI ($p = 0.997$; the median KI was 90% in both groups). Percutaneous endoscopic gastrostomy (PEG) tube implantation was more often performed with defRCT than with neoRCT ($p = 0.004$).

Patients' Condition

In the defRCT group, 85/95 patients had a KI of at least 70% and 10 had a KI of <70%. KI was not retrievable in the archive data in 5 cases and was therefore excluded in the further analysis. The neoRCT group showed a KI of ≥70% in 26/27 cases, and just 1 patient had a KI of <70%. KI 70% was not significantly different in the neoRCT and defRCT groups ($p = 0.578$).

Histology and Tumor Characteristics

The local distribution of tumors was about equal in all parts of the esophagus (Table 1). In 1 patient, the tumor was found at multiple locations. Esophagectomy was performed in 17 cases of distal EC and in 10 cases of middle-localized tumors, while almost half of all the cases that underwent defRCT (47/95 cases) were in the upper esophagus. Location was significant for the choice of therapy in the χ^2 analysis ($p < 0.001$). Upper EC was solely treated by defRCT in this case series.

SCC was found in 92/122 cases and AC in 23. In 4 cases, no histologic diagnosis was available and 3 cases were defined as "carcinoma of no profound histology." Significantly more patients suffering from SCC (i.e., 75 cases) received defRCT than those suffering from AC (13 cases) ($p = 0.015$).

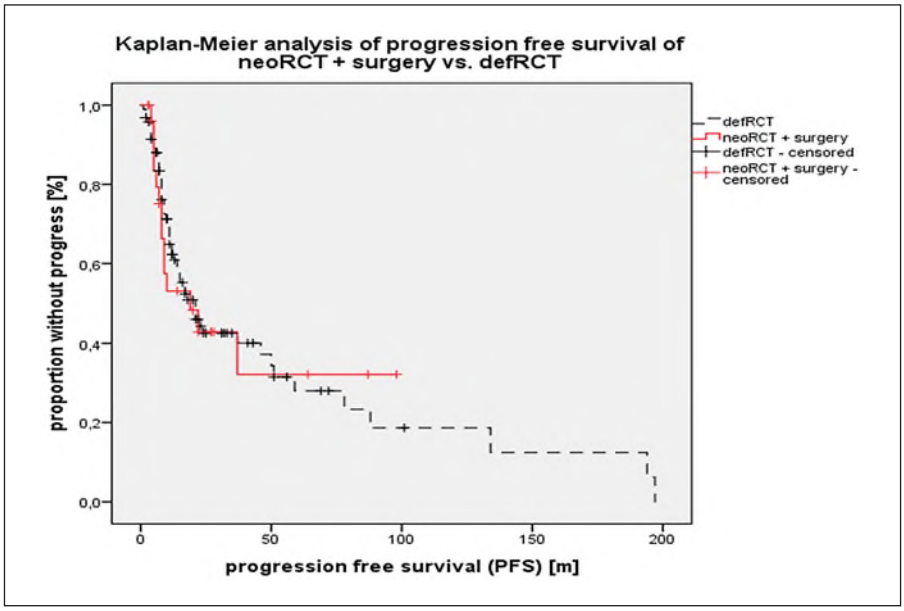
M-stage ($p = 0.514$) was not significantly different in cases of neoRCT and defRCT. Patients in the M-stage were at an oligometastasized stage and treated with curative intent. The T-stage ($p = 0.033$) was significantly higher in defRCT than in neoRCT cases, and the N-stage ($p = 0.063$) trended towards a higher stage in the defRCT patients.

Choice of Therapy

In 101 cases (82.8% of all cases), treatment planning was performed on the basis of PET. There was no PET available in 21 cases (17.2%). There was no significant difference in PET availability in cases of neoRCT or defRCT, but a very slight trend towards the surgical approach (PET was available in 26/28 neoRCT cases and 75/94 defRCT cases; $p = 0.103$).

Ninety-five patients (initially intended: $n = 93$) were treated by defRCT and 27 received neoRCT (initially intended: $n = 29$). One patient was switched to defRCT due to inoperability, while 3 patients were not operated on after neoRCT because of their reduced overall condition ($n = 2$) or a switch to palliative care ($n = 1$). On the other hand, 1 patient received salvage surgery after defRCT, and another had surgery for 1 tumor and the other treated by defRCT. Percutaneous RT was applied in 108 cases, intraluminal brachytherapy in 1, and percutaneous RCT and consequent intraluminal brachytherapy in 13.

CTx (scheme: 5-fluorouracil [1,000 mg/m^2 with a maximum of 1,800 mg/day]) and cisplatin (20 mg/m^2) were applied on days 1–4 of weeks 1 and 5 of the RT course in 114 patients. CTx was applied in 102 cases with no difference between the 2 therapy approaches ($p = 0.453$). Incomplete CTx was associated with a trend towards a higher risk of disease progression in 9/11 cases ($p = 0.062$).



Color version available online

Fig. 2. Kaplan-Meier analysis of progression-free survival with neoRCT and surgery versus defRCT.

Data on local recurrence were available in 56 cases. There was no difference between defRCT and neoRCT ($p = 0.515$) or for dose escalation ($p = 0.139$). Dose escalation in the defRCT setting (>60 Gy vs. 50.4 Gy + brachytherapeutic boost) was not more significant for stenosis than lower doses (i.e., ≤60 Gy) ($p = 0.316$).

Of 27 patients undergoing surgery, 14 showed downstaging in their operation specimen compared to preoperatively performed staging as described above, while 7 did not. There was a discrepant course in 2 cases. In 5 cases, data were insufficient. Patients with downstaging tended to have a better OS than patients with no downstaging ($p = 0.079$) or with a discrepant course ($p = 0.065$).

Progression Free Survival/Overall Survival

Median survival time was 14.5 months (2–197 months) and overall follow-up was 32 months (95% CI 19–45 months) from the day of diagnosis to the day of death from any cause. Deaths occurring within 30 days (D30) and 90 days (D90) after treatment completion were not significantly different between therapy approaches. D30 and D90 occurred in 0 and 14.8% (4/27 cases) of patients treated with neoRCT and in 5.2% (5/95 cases) and 11.6% (11/95) of defRCT cases (D30: $p = 0.280$; D90: $p = 0.434$), respectively.

Median follow-up was 28 months in the neoRCT group and 32 months in the defRCT group. OS was not significantly different between neoRCT and defRCT ($p = 0.751$) in the Kaplan-Meier analysis (Fig. 1). Proportional HR also showed no significant difference between neoRCT and defRCT (1,145; 95% CI 0.629–2.086). Median OS was 13.5 (2–197) months in defRCT and 19.5 (2–134) months in the neoRCT group ($p = 0.751$). Tumor location and applied radiation dose ($p = 0.649$ [in defRCT setting: $p = 0.468$]) did not influence OS ($p = 0.758$) and PFS (location: $p = 0.854$ and radiation dose: $p = 0.480$). There was no significant difference in the PFS of neoRCT and surgery patients and those who underwent the defRCT approach ($p = 0.912$) (Fig. 2). Histology (SCC vs. AC) also showed no significant difference (OS: $p = 0.927$ and PFS: $p = 0.908$). KI cut-off of 70% had a strong trend to significance ($p = 0.052$) for overall survival, but not for PFS ($p = 0.137$).

PFS did not differ according to the application of CTx ($p = 0.608$) but was trending for the completion of CTx ($p = 0.071$) as it was for PEG tube implantation ($p = 0.106$). PET-based planning was not significant for OS ($p = 0.923$) or PFS ($p = 0.970$).

Discussion

The choice of therapy for EC depends mainly on disease stage and the performance status of the patient [10, 11]. Another important aspect is the tumor location; while the surgical approach is routinely performed in the middle or lower esophagus, tumors in the upper third are primarily treated by RT or RCT. According to Sohda et al. [10], surgery only is the preferred therapy option, while advanced disease is preoperatively treated by neoRCT/RT [8, 12]. defRCT is routinely applied in cases of UICC stage III/IV disease or primary tumor extension beyond the esophageal wall (T4). Another indication for defRCT is elevated operative risk, e.g., due to a reduction in the general condition of the patient. In our case series, there was a majority (77/122) of UICC stage III cases of

EC, while cancer stage itself tended to be significantly associated with therapy approach ($p = 0.083$). We also found that patients treated only with RT/RCT were significantly older than the neoRCT group.

To date, the choice of an ideal therapy is under permanent consideration in recent literature. Recent reports reveal a fundamental controversy about the further treatment strategy for patients with tumor remission/regression after neoRCT. Some authors claim that remission/regression might be a strong indicator for performing surgery whereas others report it as an indicator for dose escalation and the continuation of RCT without surgery [13–18].

In terms of OS, there was no significant difference between patients who underwent defRCT and those undergoing surgery after neoRCT ($p = 0.751$). In the published literature, 3-year OS varied within a range of 20–58% for the neoRCT and surgery approach, depending on the surgical technique [19–21]. In our study, 3-year OS was reported in 14.8% of neoRCT cases (4/27) and 22.1% of defRCT cases (21/95). DefRCT may be the only curative option for those patients with an impaired general condition, as measured by KI in our study. Thus, comparable end results in OS are very satisfying [6, 22]. Valid predictive criteria for therapeutic decisions are urgently needed as well as diagnostic modalities for determining residual disease after neoRCT has been performed [23]; patients can be spared the strain of possibly unnecessary surgery. A topic of particular interest in cases of operatively high-risk situations, e.g., comorbidities, advanced age, etc., is the watch-and-wait approach after RT/RCT due to surgery-associated risks [24, 25]. With regard to comparable D30 and D90 in defRCT and neoRCT, this approach may be a valid option. Stahl and Ruhstaller [26] proclaimed salvage surgery after defRCT to be an option in elevated operative risk situations; they suggested that if defRCT fails, surgery can still be performed. A study published by Castoro et al. [27] supports this suggestion and shows no disadvantage when pursuing the operative approach in cases of failure of neoRCT. Nevertheless, the authors recommend improved restaging protocols. Another important aspect is missing markers. Liquid biopsy may be an applicable method. Further studies are urgently needed.

In our department, a dose escalation up to 66 Gy is routinely applied to stage T4 EC and nodal involvement without distant metastases, while the published literature shows 50.4 Gy to be the widely accepted/performed standard dose [28, 29]. Dose escalation beyond 50.4 Gy showed no survival benefit in a large contemporary analysis performed by Brower et al. [30] in 2016. De et al. [31] found no advantage in OS in an evaluation of cervical EC. This is in agreement with our results. On the other hand, a study published in 2017 showed a higher rate of local control with no increase in therapy-related toxicity [32]. The literature published so far proclaims the need of further studies especially with regard to improved radiation techniques, tumor histology, tumor localization, therapeutic alternatives, and salvage options in cases of local failure, e.g. surgery.

The application of CTx is of crucial relevance for the impact of RT and enhances its effect [8, 33, 34]. In daily clinical routine, comorbidities may be more common in patients undergoing defRCT rather than neoRCT and therefore limit CTx application [35]. Reduction of overall condition may also cause inoperability in neoRCT cases, e.g., due to CTx-induced thrombopenia. To sum up, negative selection might be one reason for the poorer outcome of EC patients treated by defRCT reported in the literature [22].

The proclaimed thesis of CTx-mediated effects applied to metastases not yet diagnosed in the course of initial staging by simultaneous CTx [36] was not observed in our study. Abscopal effects are increasingly observed and incipiently understood. In the future, a combination of immunotherapy and RT may allow control of microscopic seeds, which is of crucial relevance in AC as it tends to relapse distantly. Within this study about half of all cases of AC (11/23) showed metastases in the further course of disease versus only a quarter (23/92) of SCC ($p = 0.032$).

Patients with EC often suffer from relevant disease due to impaired oral food uptake by tumor-associated dysphagia [37]. Besides the impact on quality of life, this accelerates tumor cachexia and further reduces the condition of patients [38]. In the course of RT, dysphagia may be aggravated by therapy-associated side effects. Nutrition is of crucial relevance and supports patients during therapy and beyond as well as having a positive impact on survival and quality of life [39, 40]. Assurance of nutrition is done by PEG tube implantation at our department. Nevertheless, valid markers may be of help for the success of therapy while under RCT. In other words, therapy-associated side effects might be reduced by stopping therapy and the outcome improved if markers decline.

In conclusion, there was no significant difference in OS between neoRCT with surgery and defRCT in this study. Dose escalation had no significant impact on survival or further favorable aspects in the further course of the disease. More studies are needed to evaluate dose escalation protocols, especially with regard to histology and tumor location. The retrospective study design limited data quality and completeness. The total study size ($n = 122$) hampered subgroup analyses. Special effort must be spent on patients' selection criteria for the therapeutic concepts of surgery and/or neoRCT/defRCT (+ salvage surgery). Another pertinent issue is the identification of markers for therapy success and control to reduce therapeutic side effects and improve outcomes.

The data evaluated within this study consisted of unselected patients routinely treated at our hospital daily. The study is one of the most comprehensive studies to evaluate treatments of EC performed in Germany.

Acknowledgment

We thank Head of Department of Pathology at the University Hospital of Augsburg, Prof. Dr. Bruno Märkl, for his continuous and helpful input in daily routine and realization of studies.

Statement of Ethics

The idea and concepts of this study were reviewed and accepted by the internal ethics and review board of the University Augsburg Medical Center (approved April 23rd, 2019). Individual patient informed consent was not necessary as these anonymized retrospective analyses were covered by the German Hospital Law. We, the authors, declare that all research was performed according to the code of conduct of the World Medical Association and the Declaration of Helsinki.

Disclosure Statement

All authors declare there were no conflict of interests. The study was designed and performed only at the University Hospital of Augsburg and there was no influence on the study design, aim, or data analysis by external partners/financiers.

Funding Sources

This study was not funded externally. All work was done within daily routine.

Author Contributions

P.M.: study design, acquisition and analysis of data, and drafting of the manuscript. B.M.: data acquisition and analysis. R.C. and V.F.: drafting of the manuscript and data analysis. M.A. and H.M.: data acquisition. G. Schenkirsch: data acquisition and analysis. J.S. and K.H.K.: data acquisition. G. Stüben: study design.

References

1 Zhang Y. Epidemiology of esophageal cancer. World J Gastroenterol. 2013 Sep;19(34):5598–606.
2 Smyth EC, Lagergren J, Fitzgerald RC, Lordick F, Shah MA, Lagergren P, et al. Oesophageal cancer. Nat Rev Dis Primers. 2017 Jul;3(1):17048.
3 Arnold M, Soerjomataram I, Ferlay J, Forman D. Global incidence of oesophageal cancer by histological subtype in 2012. Gut. 2015 Mar;64(3):381–7.
4 Pennathur A, Gibson MK, Jobe BA, Luketich JD. Oesophageal carcinoma. Lancet. 2013 Feb;381(9864):400–12.
5 Kayani B, Zacharakis E, Ahmed K, Hanna GB. Lymph node metastases and prognosis in oesophageal carcinoma—a systematic review. Eur J Surg Oncol. 2011 Sep;37(9):747–53.
6 Kato H, Nakajima M. Treatments for esophageal cancer: a review. Gen Thorac Cardiovasc Surg. 2013 Jun;61(6):330–5.
7 Tepper J, Krasna MJ, Niedzwiecki D, Hollis D, Reed CE, Goldberg R, et al. Phase III trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for esophageal cancer: CALGB 9781. J Clin Oncol. 2008 Mar;26(7):1086–92.
8 van Hagen P, Hulshof MC, van Lanschot JJ, Steyerberg EW, van Berge Henegouwen MI, Wijnhoven BP, et al.; CROSS Group. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med. 2012 May;366(22):2074–84.
9 Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. Control Clin Trials. 1996 Aug;17(4):343–6.
10 Sohda M, Kuwano H. Current Status and Future Prospects for Esophageal Cancer Treatment. Ann Thorac Cardiovasc Surg. 2017 Feb;23(1):1–11.
11 Kullmann T, Gauthier H, Serrate C, Pouessel D, le Maignan C, Misset JL, et al. To Treat or Not to Treat Metastatic Cancer Patients with Poor Performance Status: a Prospective Experience. Pathol Oncol Res. 2017 Jan;23(1):139–44.
12 Huang FL, Yu SJ. Esophageal cancer: risk factors, genetic association, and treatment. Asian J Surg. 2018 May;41(3):210–5.
13 Putora PM, Bedenne L, Budach W, Eisterer W, Van Der Gaast A, Jäger R, et al. Oesophageal cancer: exploring controversies overview of experts' opinions of Austria, Germany, France, Netherlands and Switzerland. Radiat Oncol. 2015 May;10(1):116.
14 Stahl M, Budach W. Definitive chemoradiotherapy. J Thorac Dis. 2017 Jul;9(S8 Suppl 8):S792–8.
15 Wolf MC, Stahl M, Krause BJ, Bonavina L, Bruns C, Belka C, et al. Curative treatment of oesophageal carcinoma: current options and future developments. Radiat Oncol. 2011 May;6(1):55.
16 Stahl M, Stuschke M, Lehmann N, Meyer HJ, Walz MK, Seeber S, et al. Chemoradiation with and without surgery in patients with locally advanced squamous cell carcinoma of the esophagus. J Clin Oncol. 2005 Apr;23(10):2310–7.
17 Stahl M. Is there any role for surgery in the multidisciplinary treatment of esophageal cancer? Ann Oncol. 2010 Oct;21 Suppl 7:283–5.
18 Hegemann NS, Koepple R, Walter F, Boeckle D, Fendler WP, Angele MK, et al. Neoadjuvant chemoradiation for esophageal cancer: surgery improves locoregional control while response based on FDG-PET/CT predicts survival. Strahlenther Onkol. 2018 May;194(5):435–43.
19 Skinner HD, Lee JH, Bhutani MS, Weston B, Hofstetter W, Komaki R, et al. A validated miRNA profile predicts response to therapy in esophageal adenocarcinoma. Cancer. 2014 Dec;120(23):3635–41.
20 Straatman J, van der Wielen N, Cuesta MA, Daams F, Roig Garcia J, Bonavina L, et al. Minimally Invasive Versus Open Esophageal Resection: Three-year Follow-up of the Previously Reported Randomized Controlled Trial: the TIME Trial. Ann Surg. 2017 Aug;266(2):232–6.
21 Buderi SI, Shackcloth M, Page RD. Does neoadjuvant chemoradiotherapy increase survival in patients with resectable oesophageal cancer? Interact Cardiovasc Thorac Surg. 2017 Jan;24(1):115–20.
22 Faiz Z, van Putten M, Verhoeven RH, van Sandick JW, Nieuwenhuijzen GA, van der Sangen MJ, et al. Impact of Age and Comorbidity on Choice and Outcome of Two Different Treatment Options for Patients with Potentially Curable Esophageal Cancer. Ann Surg Oncol. 2019 Apr;26(4):986–95.
23 Walter F, Böckle D, Schmidt-Hegemann NS, Köpple R, Gerum S, Boeck S, et al. Clinical outcome of elderly patients (≥ 70 years) with esophageal cancer undergoing definitive or neoadjuvant radio(chemo)therapy: a retrospective single center analysis. Radiat Oncol. 2018 May;13(1):93.
24 Piessen G, Messager M, Mirabel X, Briez N, Robb WB, Adenis A, et al. Is there a role for surgery for patients with a complete clinical response after chemoradiation for esophageal cancer? An intention-to-treat case-control study. Ann Surg. 2013 Nov;258(5):793–9.

25 Wang J, Qin J, Jing S, Liu Q, Cheng Y, Wang Y, et al. Clinical complete response after chemoradiotherapy for carcinoma of thoracic esophagus: is esophagectomy always necessary? A systematic review and meta-analysis. Thorac Cancer. 2018 Dec;9(12):1638–47.
26 Stahl M, Ruhstaller T. Combined modality treatment of oesophageal cancer. Internist (Berl). 2014 Jan;55(1):7–8.
27 Castoro C, Scarpa M, Cagol M, Alfieri R, Ruol A, Cavallin F, et al. Complete clinical response after neoadjuvant chemoradiotherapy for squamous cell cancer of the thoracic oesophagus: is surgery always necessary? J Gastrointest Surg. 2013 Aug;17(8):1375–81.
28 Chun SG, Skinner HD, Minsky BD. Radiation Therapy for Locally Advanced Esophageal Cancer. Surg Oncol Clin N Am. 2017 Apr;26(2):257–76.
29 Blais E, Vendrely V, Sargos P, Créhange G, Huguet F, Maingon P, et al. [Chemoradiation for oesophageal cancer: A critical review of the literature]. Cancer Radiother. 2019 Feb;23(1):62–72.
30 Brower JV, Chen S, Bassetti MF, Yu M, Harari PM, Ritter MA, et al. Radiation Dose Escalation in Esophageal Cancer Revisited: A Contemporary Analysis of the National Cancer Data Base, 2004 to 2012. Int J Radiat Oncol Biol Phys. 2016 Dec;96(5):985–93.
31 De B, Rhome R, Doucette J, Buckstein M. Dose escalation of definitive radiation is not associated with improved survival for cervical esophageal cancer: a National Cancer Data Base (NCDB) analysis. Dis Esophagus. 2017 Apr;30(4):1–10.
32 Venkat PS, Shridhar R, Naghavi AO, Hoffe SE, Almhanna K, Pimiento JM, et al. Dose escalated neoadjuvant chemoradiotherapy with dose-painting intensity-modulated radiation therapy and improved pathologic complete response in locally advanced esophageal cancer. Dis Esophagus. 2017 Jul;30(7):1–9.
33 Tomasello G, Ghidini M, Barni S, Passalacqua R, Petrelli F. Overview of different available chemotherapy regimens combined with radiotherapy for the neoadjuvant and definitive treatment of esophageal cancer. Expert Rev Clin Pharmacol. 2017 Jun;10(6):649–60.
34 Wang T, Yu J, Liu M, Chen Y, Zhu C, Lu L, et al. The benefit of taxane-based therapies over fluoropyrimidine plus platinum (FP) in the treatment of esophageal cancer: a meta-analysis of clinical studies. Drug Des Devel Ther. 2019 Feb;13:539–53.
35 Jahic A, Iljazovic E, Hasic S, Arnautovic AC, Sabitovic D, Mesanovic S, et al. Prognostic Parameters of Acute Myeloid Leukaemia at Presentation. Med Arh. 2017 Feb;71(1):20–4.
36 He X, Xu K, Guo J, Zhu Y, Liang X, Liu L. A meta-analysis of neoadjuvant chemotherapy plus radiation in the treatment of locally advanced nasopharyngeal carcinoma. J Cancer Res Ther. 2015 Oct;11(6 Suppl 2):C205–8.
37 Zerbib F, Omari T. Oesophageal dysphagia: manifestations and diagnosis. Nat Rev Gastroenterol Hepatol. 2015 Jun;12(6):322–31.
38 Na BG, Han SS, Cho YA, Wie GA, Kim JY, Lee JM, et al. Nutritional Status of Patients with Cancer: A Prospective Cohort Study of 1,588 Hospitalized Patients. Nutr Cancer. 2018;70(8):1228–36.
39 Włodarczyk JR, Kużdżał J. Safety and efficacy of oesophageal stenting with simultaneous percutaneous endoscopic gastrostomy as a supplementary feeding route in unresectable proximal oesophageal cancer. Wideochir Inne Tech Malo Inwazyjne. 2018 Jun;13(2):176–83.
40 Grilo A, Santos CA, Fonseca J. Percutaneous endoscopic gastrostomy for nutritional palliation of upper esophageal cancer unsuitable for esophageal stenting. Arq Gastroenterol. 2012 Jul-Sep;49(3):227–31.