# Long-Term Outcome of Mitomycin C- and 5-FU-Based Primary Radiochemotherapy for Esophageal Cancer*

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**Background and Purpose:** For definitive radiochemotherapy, 5-fluorouracil/cisplatin protocols have been considered the standard of care for esophageal carcinoma over the last 2 decades. By contrast, most patients treated at the University Hospital, LMU Munich, Germany, received 5-fluorouracil/mitomycin C. The objective of this retrospective analysis was to determine the value of 5-fluorouracil/mitomycin-C-based therapy.
**Patients and Methods:** Tumor stage, treatment received, and outcome data of patients treated for esophageal cancer between 1982 and 2007 were collected; endpoint of the analysis was overall survival.
**Results:** 298 patients with inoperable cancer of the esophagus were identified (16.8% adenocarcinoma, 77.5% squamous cell carcinoma). At diagnosis, 61.7% (184/298) had UICC stage III–IV, 54.4% (162/298) positive lymph nodes, and 26.5% (79/298) metastatic disease. 74.5% of all patients (222/298) received radiation doses between 55 and 65 Gy, 65.8% (196/298) were subjected to concomitant chemotherapy. The median follow-up period (patients alive) was 4.1 years. A significant increase of overall survival ($p < 0.0001$) in the radiochemotherapy versus the radiotherapy-alone group was observed. 52% (102/196) in the 5-fluorouracil/mitomycin C group had tumor stages comparable to the RTOG 85-01 study cohort (T1–3 N0–1 M0). The median survival in this subgroup was 18.2 months, 3- and 5-year survival rates were 22.7% (21/102) and 15.0% (13/102), respectively.
**Conclusion:** Despite being nominally inferior to platinum-based radiochemotherapy, the overall survival rates are in a similar range. Thus, the mitomycin-C-based radiochemotherapy approach may considered to be as effective as the standard therapy. However, there is no randomized trial available in order to prove the equality.

**Key Words:** Esophageal cancer · Radiochemotherapy · 5-fluorouracil and mitomycin C

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**Langzeitergebnisse nach primärer Radiochemotherapie mit Mitomycin C und 5-Fluorouracil bei Ösophaguskarzinom**

**Hintergrund und Ziel:** Radiochemotherapie mit 5-Fluorouracil und Cisplatin gilt seit 2 Jahrzehnten als Standard für die primäre Behandlung des Ösophaguskarzinoms. Im Gegensatz dazu erhielten die meisten Patienten, die im Klinikum der LMU München behandelt wurden, eine definitive Radiochemotherapie mit 5-Fluorouracil und Mitomycin C. Retrospektiv wurde geprüft, zu welchen Ergebnissen das angewandte Regime im Vergleich zur Standardtherapie führte.
**Patienten und Methodik:** Retrospektiv wurden Tumorstadium, Therapieform und das Outcome der Patienten mit Ösophaguskarzinom, die zwischen 1982 und 2007 behandelt wurden, erhoben (Tabelle 1). Primärer Endpunkt war das Gesamtüberleben (Abbildungen 1a bis 1c).
**Ergebnisse:** 298 Patienten (16,8% Adenokarzinome [50/298], 77,5% Plattenepithelkarzinome [231/298]) wurden primär behandelt. Bei Diagnosestellung wiesen 61,7% (184/298) UICC-Stadien III–IV, 54,4% (162/298) einen positiven Lymphknotenstatus sowie 26,5% (79/298) Fernmetastasen auf. 74,5% aller Patienten (222/298) erhielten eine Bestrahlungsdosis zwischen 55 und 65 Gy. 65,8% (196/298) bekamen parallel dazu eine Chemotherapie. Der mediane Nachbeobachtungszeitraum betrug 4,1 Jahre. Es zeigte sich ein signifikant längeres Überleben in der Radiochemotherapiegruppe im Vergleich zur Radiotherapiegruppe ($p < 0,0001$). 102/196 Patienten (52%) in der Radiochemotherapiegruppe hatten Tumorstadium T1–3 N0–1 M0, entsprechend

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der RTOG-85-01-Kohorte. In dieser Subgruppe zeigten sich ein medianes Überleben von 18,2 Monaten und Überlebensraten von 22,7% (21/102) bzw. 15,0% (13/102) nach 3 respektive 5 Jahren (Tabellen 2 und 4).

**Schlussfolgerung:** Obwohl in diesem unselektionierten Kollektiv der Standardtherapie mit Cisplatin/5-Fluorouracil nominell unterlegen, sind die Überlebensraten in einem vergleichbaren Bereich (Tabelle 3). Eine Radiochemotherapie mit 5-Fluorouracil und Mitomycin C scheint ähnlich effektiv wie die Standardtherapie zu sein. Allerdings gibt es keine randomisierte Studie, um dies zu beweisen.

**Schlüsselwörter:** Ösophaguskarzinom · Radiochemotherapie · 5-Fluorouracil und Mitomycin C

## Introduction

Based on the results of the RTOG 85-01 trial, the use of radiochemotherapy with cisplatin and 5-fluorouracil (5-FU) is a well-accepted standard for the definitive treatment of esophageal cancer [21]. The trial revealed increased local control rates and improved overall survival by addition of both agents [1]. Furthermore, the results have been reproduced and confirmed in patients treated outside of the original trial [1, 14]. More recently, other drugs including taxanes and irinotecan [22, 23, 29] have been introduced as active radiochemotherapy agents. However, none of these agents have been tested prospectively against cisplatin/5-FU. Notably, in the initial radiochemotherapy trials that proved the superiority of radiochemotherapy over radiotherapy alone, mitomycin C (MMC) was used [13]. Although being a well-established radiosensitizer for the treatment of head and neck cancer [9, 20], cancer of the anal canal [17], pancreatic carcinoma [7, 37], vulvar and cervical cancer [5, 27, 38, 39] the drug has not only lost acceptance in the treatment of esophageal cancer, but its effectiveness has been seriously called into question [19].

## Patients and Methods

Radiochemotherapy with 5-FU/MMC has been the standard of care for cancer of the esophagus at the Department of Radiation Oncology, University Hospital, Ludwig Maximilian University (LMU) Munich, Germany, for the last 2 decades, based on the clinical experience made by using the Coia protocol [13].

In a retrospective approach, the following data were systematically retrieved from the patient files as well as from the Munich Tumor Registry: tumor stage, treatment, and outcome of all patients with either squamous cell carcinoma (SCC) or adenocarcinoma (AC) of the thoracic esophagus, excluding AC with cardia and gastric involvement, treated between 1982 and 2007 at the Department of Radiation Oncology, University Hospital of the LMU Munich. For this analysis, only patients who received either definitive radiochemotherapy or radiotherapy were eligible. Patients who received adjuvant or neoadjuvant radio(chemo)therapy or brachytherapy were excluded, as well as those in whom treatment was aborted prematurely or whose data were incomplete. All patients were classified to TNM according to UICC criteria.

Survival was calculated from diagnosis to death by Kaplan-Meier survival analysis using the software package SSPS® 17.0. Patient characteristics were compared using the $\chi^2$-test. The log-rank test was used to compare overall survival rates between the treatment groups. Prognostic factors related to survival were identified by means of the Cox proportional hazards regression model ($p < 0.05$).

## Results

Between February 1982 and August 2007, 504 patients with cancer of the esophagus were admitted. 298 patients were considered to be inoperable because of poor Karnofsky Performance Score (KPS), comorbidities, locally unresectable or metastatic disease. 72 patients received neoadjuvant or adjuvant radio(chemo)therapy, in 65, treatment was stopped prematurely, 20 patients with other aforementioned exclusion criteria and 49 patients with missing data were excluded. Of the 298 remaining patients, 77.5% (231/298) had SCC, 16.8% (50/298) AC, and 5.7% (17/298) unknown histology. The median age at diagnosis was 61 years (range 36–91 years). At diagnosis, 34.9% (104/298) of the patients were categorized as stage II, 35.2% (105/298) as stage III, and 26.5% (79/298) as stage IV, according to the UICC staging system. 57.7% (172/298) were T3 and 21.8% (65/298) T4 tumors. Nodal involvement was documented in 54.4% of the patients (162/298), and 26.5% (79/298) already presented with metastatic disease. The predominant tumor sites were the middle third of the esophagus with 29.9% (89/298) and the lower third with 34.2% (102/298). 15.1% (45/298) had second malignancies, independent of esophageal cancer.

The radiation dose was at least 54 Gy in 80.5% of the cases, 49.7% of the patients (148/298) received doses between 60 and 65 Gy. Until 1998, dose prescription was 2-D based and the reference isodose was 95%. From 1998 onward, a computed tomography-(CT-)based 3-D planning approach was used for 121 patients (40.6% of the total cohort).

65.8% of all patients (196/298) were treated by concomitant radiochemotherapy, 68.9% (135/196) of these (45.3%) of all patients, 135/298) received 5-FU plus MMC, only a minority of 8.6% (17/196) of the patients were treated with 5-FU and cisplatin (for patient characteristics and details on treatment in the group receiving radiotherapy and the group undergoing radiochemotherapy with 5-FU and MMC see Table 1).

The median follow-up period (patients alive) was 4.1 years (range 22–283 months).

Median survival was 12 months for patients with combined-modality therapy versus 9.3 months for radiotherapy

**Table 1.** Pretreatment patient characteristics. AC: adenocarcinoma; F: female; 5-FU: 5-fluorouracil; M: male; MMC: mitomycin C; RCT: radiochemotherapy; RT: radiotherapy; SCC: squamous cell carcinoma.

**Tabelle 1.** Patientencharakteristika vor Behandlung. AC: Adenokarzinom; F: weiblich; 5-FU: 5-Fluorouracil; M: männlich; MMC: Mitomycin C; RCT: Radiochemotherapie; RT: Radiotherapie; SCC: Plattenepithelkarzinom.

| | | RT | | RCT with 5-FU + MMC | | |
|---|---|---|---|---|---|---|
| | | 102 patients | | 135 patients | | |
| | | n | (%) | n | (%) | p-value |
| Gender | M | 75 | (73.5) | 112 | (83.0) | |
| | W | 27 | (26.5) | 23 | (17.0) | 0.78 |
| Age at | < 60 | 33 | (32.4) | 68 | (50.4) | |
| diagnosis | 60–69 | 18 | (17.6) | 53 | (39.3) | |
| (years) | ≥ 70 | 51 | (50.0) | 14 | (10.4) | **< 0.0001** |
| | Median | 69.5 | | 59.2 | | |
| | Range | 38–91 | | 36–83 | | |
| Histology | AC | 20 | (19.6) | 14 | (10.4) | |
| | SCC | 73 | (71.6) | 115 | (85.2) | **0.037** |
| | Unknown | 9 | (8.8) | 6 | (4.4) | |
| Grading | G1 | 6 | (5.9) | 5 | (3.7) | |
| | G2 | 38 | (37.3) | 55 | (40.7) | |
| | G3 | 42 | (41.2) | 65 | (48.1) | |
| | G4 | 4 | (3.9) | 2 | (1.5) | |
| | Unknown | 12 | (11.8) | 8 | (5.9) | 0.28 |
| T | T1–T2 | 19 | (18.6) | 29 | (21.5) | |
| | T3 | 55 | (53.9) | 85 | (63.0) | |
| | T4 | 25 | (24.5) | 20 | (14.8) | |
| | Tx | 3 | (2.9) | 1 | (0.7) | 0.13 |
| N | N0 | 50 | (49.0) | 64 | (47.4) | |
| | N1 | 49 | (48.0) | 71 | (52.6) | |
| | Nx | 3 | (2.9) | 0 | (0) | 0.12 |
| M | M0 | 70 | (68.6) | 111 | (82.2) | |
| | M1 | 29 | (28.4) | 24 | (17.8) | |
| | Mx | 3 | (2.9) | 0 | (0) | **0.016** |
| UICC | I–IIB | 38 | (37.3) | 58 | (43.0) | |
| | III–IV | 61 | (59.8) | 77 | (57.0) | |
| | Unknown | 3 | (2.9) | 0 | (0) | 0.48 |
| Localization | Cervical | 6 | (5.9) | 7 | (5.2) | |
| | Proximal | 16 | (15.7) | 32 | (23.7) | |
| | Proximal/medial | 6 | (5.9) | 7 | (5.2) | |
| | Medial | 36 | (35.3) | 35 | (25.9) | |
| | Medial/distal | 4 | (3.9) | 9 | (6.7) | |
| | Distal | 34 | (33.3) | 45 | (33.3) | 0.49 |
| RT dose | ≤ 54 | 22 | (21.5) | 20 | (14.8) | |
| (Gy) | > 54 < 60 | 15 | (14.7) | 40 | (29.6) | |
| | ≥ 60 | 65 | (63.8) | 75 | (55.6) | 0.049 |
| Planning | 2-D | 85 | (83.3) | 73 | (54.1) | |
| | 3-D | 17 | (16.7) | 62 | (45.9) | **< 0.0001** |

alone. After 2 years, 10.8% (11/102) of the radiotherapy-only group were alive, compared to 29.1% (57/196) of the radiochemotherapy group. 3-year survival was 3.9% (4/102) in the radiotherapy-alone arm, in contrast to 16.8% (33/196) in the combined-modality group. 5-year survival in this group was 10.2% (20/196; Table 2). The log-rank comparison of the survival rates revealed a statistically significant difference with a p-value < 0.0001 (hazard ratio [HR] 0.77; 95% confidence interval [CI] 0.68–0.87; Figure 1b). Within the radiochemotherapy group (196/298), no statistically significant difference

**Table 2.** Overview of overall survival (OS). 5-FU: 5-fluorouracil; MMC: mitomycin C; RCT: radiochemotherapy; RT: radiotherapy.

**Tabelle 2.** Übersicht zum Gesamtüberleben (OS). 5-FU: 5-Fluorouracil; MMC: Mitomycin C; OS: Gesamtüberleben; RCT: Radiochemotherapie; RT: Radiotherapie.

| | | RT (102/298) | | RCT (196/298) All RCT | | RTC with 5-FU + MMC (135/196) | | T1–3 N0–1 M0 (102/135) | |
|---|---|---|---|---|---|---|---|---|---|
| | | n | (%) | n | (%) | n | (%) | n | (%) |
| Years | 0 | 102 | 34.2 | 196 | 65.8 | 135 | 68.9 | 102 | 52.0 |
| | 1 | | 34.0 | | 51.0 | | 58.5 | 61 | 60.4 |
| | 2 | | 10.8 | | 29.1 | | 34.8 | 36 | 37.5 |
| | 3 | | 3.9 | | 16.8 | | 20.7 | 21 | 22.7 |
| | 4 | | 0 | | 13.0 | | 14.9 | 17 | 18.4 |
| | 5 | | 0 | | 10.2 | | 11.4 | 13 | 15.0 |
| Median OS | (months) | 9.3 | | 12 | | 15.6 | | 18.2 | |

in regard to survival could be detected between patients with different histologies (p = 0.059; HR 0.68; 95% CI 0.46–1.02). However, for all patients (298), AC was found to be a negative prognostic factor (p = 0.029; HR 1.42; 95% CI 1.04–1.94; univariate analysis).

Survival improved when higher dose levels were used. The difference was significant > 54 Gy (p = 0.002; HR 0.62; 95% CI 0.46–0.82; Figure 2) and less significant ≥ 60 Gy (p = 0.036; HR 0.78; 95% CI 0.61.–0.98) for the whole cohort. In the radiotherapy-only group, a dose ≥ 60 Gy was significantly better (p = 0.025), while there was no significance seen in the radiochemotherapy group at this dose level (≥ 60 Gy), but at a radiation dose of > 54 Gy (p = 0.009; HR 0.61; 95% CI 0.42–0.88).

Grading, T-stage, N-stage, concomitant chemotherapy with MMC and 5-FU, radiation dose > 54 Gy were significant prognostic criteria in the univariate Cox regression analysis. No significance was seen using 3-D versus 2-D planning, for age at diagnosis and tumor site (see Table 4).

Including histology, grading, T- and N-stage, dose level > 54 Gy and concomitant chemotherapy in the multivariate Cox regression analysis, only histology and N-stage did not remain significant.

A subgroup of 102/298 patients (34%) with T1–3 N0–1 M0 who received radiochemotherapy with 5-FU and MMC showed 2-year, 3-year, and 5-year overall survival rates of 37.5% (36/102), 22.7% (21/102), and 15% (13/102), respectively. At 10 years, eight patients were alive, the median survival rate was 18.2 months.

## Discussion

Our cohort represents one of the largest nonselected patient cohorts followed over an extremely long period. Remarkably, several findings already indicated comparable patient characteristics and overall survival rates also observed in this retrospective analysis [2, 3, 14, 16, 18, 24, 31, 34, 41] (Table 3, Figure 1a). The predominant regimen with 5-FU and MMC used in a definitive approach during the last 2 decades at the University Hospital of the LMU Munich does not yield results similar to standard therapy in so far as an overall survival rate of 15% at 5 years is nominally inferior to an overall survival rate of 27% at 5 years reported by using cisplatin and 5-FU [21]. Our results confirm the importance of radiochemotherapy in improving survival of patients with unresectable esophageal cancer [1, 8, 13, 14, 21, 25, 40] (Figures 1b and 1c). However, due to the retrospective setting, the patient distribution is balanced in favor of the radiochemotherapy group with statistically significant differences concerning age at diagnosis (p < 0.0001), histology (p = 0.037), M-stage (p = 0.016), and irradiation technique (p < 0.0001).

Benefits from adding chemotherapy had been already reported in the early 1980s by using 5-FU and MMC. The latter can be administered with little toxicity in a range of solid tumors, but it seems to be less efficient than cisplatin [13, 19, 21].

There may be two reasons for the less favorable outcome in this study as compared with the literature: worse patient selection and lower efficiency of MMC. Our cohort is characterized by a higher proportion of patients with advanced tumor stage (57.7% T3, 21.8% T4, 54.4% N1, 26.5% M1, 61.7% UICC III–IV) than in other studies [11, 28, 33, 35]. Additionally, a high rate of discontinuation of treatment, therapy-related mortality, and the fact that more than one third (102/298) of the patients did not receive concomitant chemotherapy because of comorbidities show a negatively biased selection of patients with poor prognosis. For example, the ratio of T2/T3 was 82%/8% and that of N0/N1 82%/13% in the RTOG 85-01 trial, compared to a T1–2/T3 ratio of 25.5%/74.5% and N0/N1 of 52.9%/47.1% in our subgroup (T1–3 N0–1 M0) selected according to the RTOG 85-01 trial.

A very high rate of SCC represents an association with tobacco and alcohol abuse, hence a low socioeconomic status with manifest comorbidities as described in epidemiologic studies [6, 15]. Under these circumstances, the administration of MMC seemed to be a more adequate option to improve survival [12]. Patients with AC were mainly detected in an ad-

vanced stage, which also contributed to worse outcome than described in the literature [15, 25].

Another reason could be the lower efficiency of MMC compared to cisplatin, which in fact has never been evaluated head to head in a randomized clinical trial, yet radiobiological estimations may help out here. In a systematic overview of preoperative radiochemotherapy trials including 1,012 patients with 311 pathologic complete remissions, the influence of MMC was not found to be significant [19].

Overall survival in the radiotherapy-alone group was poor and did not exceed 5% (4/102) at 3 years, which is comparable to other studies [32, 36, 40] even when taking into account that the randomized trials did not include metastatic patients. However, a selection bias may be seen here, as the radiotherapy-only arm may be a surrogate marker for poor general condition of the patient with a poor KPS at diagnosis, which implies less treatment tolerance.

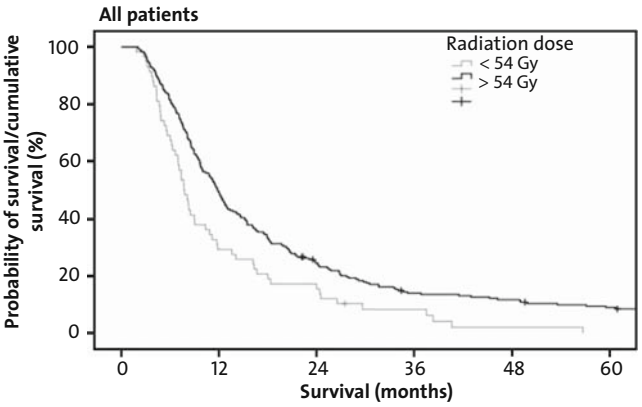
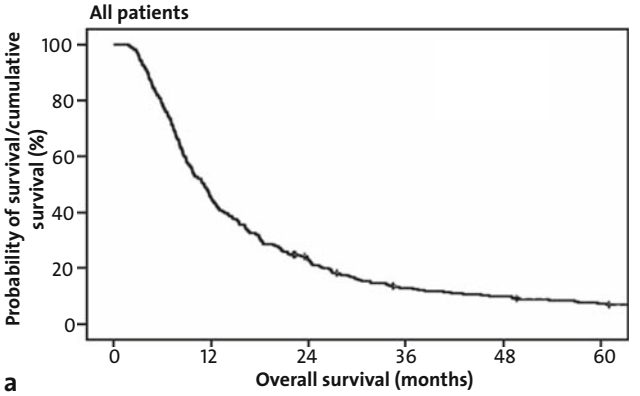
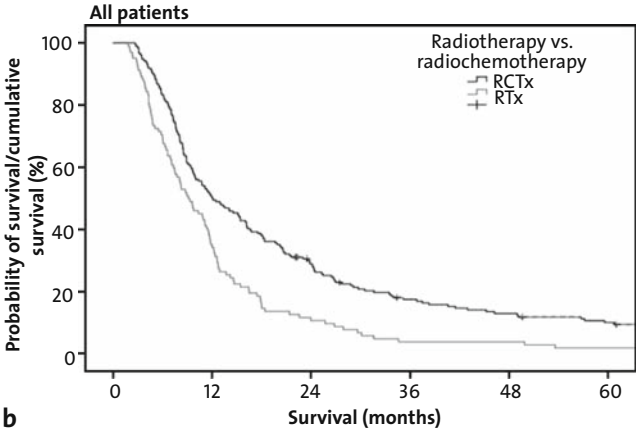
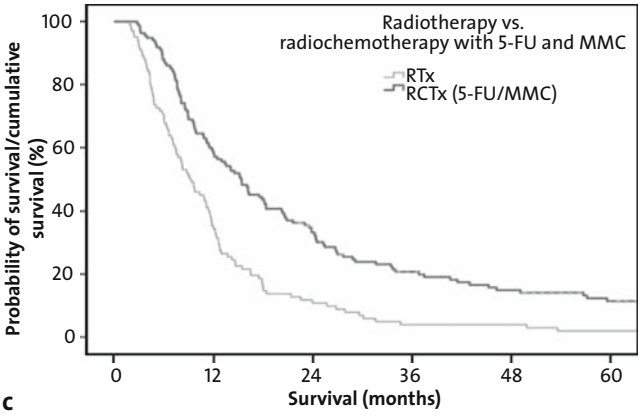



**Figure 2.** OS for radiation doses ≤ and > 54 Gy: significantly better OS at a dose level > 54 Gy (p = 0.002; HR 0.62; 95% CI 0.46–0.82).

**Abbildung 2.** OS bei Strahlendosen ≤ 54 Gy und > 54 Gy: signifikant besseres OS bei einer Strahlendosis > 54 Gy (p = 0,002; HR 0,62; 95%-CI 0,46–0,82).




Patients in this group who were treated with doses ≥ 60 Gy had a significantly better outcome than those who received a lower dose (37 vs. 65 patients; p = 0,026; 95% CI 0.42–0.95).

Although no survival advantage could be found by 3-D CT-based planning in the whole patient cohort, an adequately applied radiation dose > 54 Gy seems to play a role (Table 4), even if the patient is not suitable for concomitant chemotherapy. Therefore, our data do not confirm the results of the INT 0123 trial, which showed no benefit from dose escalation [4, 29], but suggests an impact of radiation dose on outcome

**Figures 1a to 1c.** a) Kaplan-Meier overall survival (OS) curve of the whole cohort (298 patients), median OS 11.3 months. b) OS after radiotherapy (102/298) versus radiochemotherapy (196/298): significantly better OS (p < 0.0001, HR 0.77; 95% CI 0.68–0.87) in the concomitant radiochemotherapy arm. c) OS after RT (102/298) versus RCT (135/298) with 5-FU and MMC: significantly better OS (p < 0.0001, HR 0.994; 95% CI 0.991–0.996) by applying RCT with 5-FU and MMC. 61 patients received other chemotherapy schemata (40 patients only 5-FU, 17 patients 5-FU and cisplatin, four patients others).

**Abbildungen 1a bis 1c.** a) Kaplan-Meier-Kurve des Gesamtüberlebens (OS)der behandelten Patienten (n = 298), medianes OS 11,3 Monate. b) OS nach Radiotherapie (102/298) versus Radiochemotherapie (196/298): signifikant besseres Gesamtüberleben (p < 0,0001; HR 0,77; 95%-CI 0,68–0,87) im Radiochemotherapiearm. c) Gesamtüberleben nach RT (102/298) versus RCT (135/298) mit 5-FU und MMC: signifikant besseres OS (p < 0,0001; HR 0,994; 95%-CI 0,991–0,996) nach RCT mit 5-FU und MMC. 61 Patienten erhielten andere Chemotherapieschemata (40 Patienten nur 5-FU, 17 Patienten 5-FU und Cisplatin, vier Patienten andere).

**Table 3.** Comparison of overall survival (OS) estimates (Kaplan-Meier) of randomized clinical trials for primary radiotherapy (RT) versus radiochemotherapy (RCT).

**Tabelle 3.** Vergleich des Gesamtüberlebens (OS) in randomisierten klinischen Studien für Radiotherapie (RT) versus Radiochemotherapie (RCT).

| Time (years) | 0 | 1 | 2 | 3 | 4 | 5 | 6 | Median (months) |
|---|---|---|---|---|---|---|---|---|
| | n (%) randomized for RT/RCT | n (%) alive following RT/RCT | n (%) alive following RT/RCT | n (%) alive following RT/RCT | n (%) alive following RT/RCT | n (%) alive following RT/RCT | n (%) alive following RT/RCT | RT/RCT |
| Andersen 1984 | 42/40 (100) | | 5 (11.9)/5 (12) | | | | | 6.8/6.3 |
| Araujo 1991 | 31/28 (100) | x (55)/x (64) | x (22)/x (38) | | | x (6)/x (16) | | – |
| Cooper 1999 | | | | | | | | |
| • Randomized | 62/61 (100) | 21 (34)/32 (52) | 6 (10)/22 (36) | 0/18 (30) | 0/17 (30) | 0/14 (26) | 0/12 (22) | 9.3/14.1 |
| • Nonrandomized | 62/69 (100) | 21 (34)/43 (62) | 6 (10)/24 (35) | 0/18 (26) | 0/13 (19) | 0/10 (14) | 0/6 (10) | 9.3/16.7 |
| Gao 2002 | 41/40 (100) | | | (43.2)/(40) | | | | 25.4/32.6 |
| Earle 1980 | 44/47 (100) | | | | | | | 6.4/6.2 |
| Kaneta 1997 | 12/12 (100) | 3 (23.8)/5 (40) | | | | | | 7/9 |
| Slabber 1998 | 36/34 (100) | | | | | | | 4.8/5.6 |
| Zhu 1999 | 33/33 (100) | 17 (51.5)/18 (54.4) | 9 (27.3)/15 (45.5) | 5 (15.2)/13 (39.4) | 4 (12.1)/10 (30.3) | | | 12/16 |

**Table 4.** Prognostic factors. Uni- and multivariate Cox regression analysis. AC: adenocarcinoma; F: female; 5-FU: 5-fluorouracil; HR: hazard ratio calculated with 95% confidence intervals (CI) by Cox proportional hazards model; M: male; MMC: mitomycin C; RCT: radiochemotherapy; RT: radiotherapy; SCC: squamous cell carcinoma.

**Tabelle 4.** Prognostische Faktoren. Uni- und multivariate Cox-Regressionsanalyse. AC: Adenokarzinom; F: weiblich; 5-FU: 5-Fluorouracil; HR: Hazard-Ratio mit 95-Konfidenzintervall (CI); M: männlich; MMC: Mitomycin C; RCT: Radiochemotherapie; RT: Radiotherapie; SCC: Plattenepithelkarzinom.

| Comparison | Univariate p, HR (95% CI) | Multivariate p, HR (95% CI) |
|---|---|---|
| M vs. F | 0.57, 0.96 (0.83–1.11) | |
| Age at diagnosis ≤ 70 vs. > 70 years | 0.095, 0.78 (0.61–1.04) | |
| AC vs. SCC | **0.029, 1.42 (1.04–1.94)** | 0.639, 0.91 (0.63–1.33) |
| G1 + G2 vs. G3 | **0.03, 0.77 (0.6–0.99)** | **0.011, 0.69 (0.52–0.92)** |
| T1 + T2 vs. T3 | **0.001, 0.58 (0.42–0.79)** | **0.019, 0.66 (0.47–0.94)** |
| T4 vs. T1 + T2 | **< 0.0001, 2.87 (1.94–4.24)** | |
| T3 vs. T4 | **0.005, 1.51 (1.13–2.03)** | |
| N0 vs. N1 | **0.006, 0.72 (0.57–0.91)** | 0.108, 0.78 (0.58–1.05) |
| III–IV vs. 0—IIb | **< 0.0001, 1.7 (1.3–2.2)** | |
| Cervical-proximal/medial vs. distal | 0.211, 1.19 (0.91–1.56) | |
| ≤ 54 Gy vs. > 54 Gy | **0.001, 1.615 (1.2–2.17)** | **0.008, 1.66 (1.14–2.4)** |
| ≥ 60 Gy vs. < 60 Gy | **0.036, 0.78 (0.61–0.98)** | |
| 2-D vs. 3-D | 0.094, 1.23 (0.97–1.56) | |
| RT vs. RCT | **< 0.0001, 0.59 (0.46–0.76)** | **0.001, 0.77 (0.65–0.9)** |
| RCT with 5-FU + MMC vs. RCT with 5-FU | **0.001, 0.54 (0.37–0.78)** | |

like several other reports do [10, 26, 32, 36].

As stated by Coia et al., concurrent radiochemotherapy by addition of 5-FU and MMC to radiotherapy improves overall survival and even achieves long-term cure also in unfavorable tumor stages as shown here [13]. The RTOG 85-01 trial achieved even better results by using combined fluorouracil and cisplatin [21]. The addition of chemotherapy increased the survival rate from 10% to 38% at 2 years; the median survival was 8.9 months as compared with 12.5 months in the radiochemotherapy group.

A subgroup of patients (102/298) in our study cohort had T1–3 N0–1 M0, which is similar to the patient selection in the RTOG 85-01 trial. These patients revealed an increase in survival rate from 10.8% in the radiotherapy group to 37.5% in the combined group at 2 years, the corresponding median survival was 9.3 and 18.2 months, respectively (see Table 2). Despite the limitations of a retrospective analysis, these results are in the range of the prospectively designed RTOG 85-01 trial. However, the 5-year survival of 15% in our subcohort

is clearly inferior to the 27% reported by Cooper et al. [14], although the number of long-term survivors may be too small to draw conclusions.

## Conclusion

Overall survival observed in this unselected collective is comparable with data of published trials. An overall survival rate of 15% at 5 years in the patient group receiving 5-FU and MMC is nominally inferior to reported results by using cisplatin and 5-FU. The limitations of a retrospective analysis do not permit a more profound evaluation. Cisplatin/5-FU-based concomitant radiotherapy is the accepted standard for unresectable esophageal cancer or inoperable patients. Hence, as long as there is no randomized trial available in order to prove the equality, radiochemotherapy with 5-FU and MMC instead of cisplatin may only be applied in case of contraindications to cisplatin.

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