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ORIGINAL ARTICLE

Retrospective evaluation of combined modality treatment and prognostic factors in patients with esophageal cancer

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Abstract

The influence of prognostic factors and combined modality treatment on survival was evaluated retrospectively for 156 patients with esophageal cancer receiving radiotherapy in different modalities between 1991 and 2001 at the University of Heidelberg and the Universitätsklinikum Mannheim. Forty-six patients (29.5%) were treated with radiotherapy alone, 74 patients (47.4%) had combined radiochemotherapy and 36 patients (23.1%) were operated on after receiving neoadjuvant radiochemotherapy. The median follow-up time was 10 months. Female patients showed a significantly better overall survival compared with male patients ($p = 0.031$), younger patients (age ≤ 60 years) a significantly better survival compared to older patients (age > 60 years) ($p = 0.02$). Patients with hemoglobin concentration > 13.4 g/dl before therapy (median hemoglobin concentration) had a significantly better overall survival than patients with lower hemoglobin concentration ($p = 0.044$). Patients who received combined radiochemotherapy (with or without operation) had a survival advantage compared with radiotherapy alone. Overall survival after neoadjuvant treatment followed by operation was significantly better than in the two other groups, median survival times were 20 vs. 9 (RCHT) vs. 8 months (RT) ($p = 0.003$). The data presented show for the first time that hemoglobin concentration in addition to gender and age was a prognostic factor for patients with esophageal cancer. A low hemoglobin value was a negative predictor.

Introduction

Today the prognosis for patients with esophageal carcinoma still remains quite poor. Before 1990, the standard treatment for patients with locoregional esophageal cancer was esophagogastrectomy [1]. Many patients, however, were not operated on, because of poor medical conditions, extensive disease, or localization not permitting adequate surgery, and were treated with radiotherapy [2,3]. Both treatment modalities had unsatisfactory results with 2-year survival rates being about 10% [4]. The introduction of chemotherapy in combination with either surgery or radiotherapy has shown some advantageous effects on survival [5,6]. In the randomized RTOG trial reported by Herskovic et al. radiotherapy (50.4 Gy) and concurrent chemotherapy (four courses of 5-FU/cisplatin) was compared with radiotherapy (64 Gy) alone [7]. Patients in the RT-CHT arm showed a significant improvement in the 2-year survival rate (36% vs. 10%). The trial was confirmed by longer follow-up (5-year survival rate 27% vs. 0%) and a non-randomized group [8].

Hypoxic areas are a characteristic property of solid tumors. Tumor hypoxia is a therapeutic problem, as it can make solid tumors resistant to ionizing radiation and chemotherapy [9]. Tumor hypoxia is intensified in anemic patients. Pre-irradiation hemoglobin concentration has been shown to be a prognostic factor for carcinomas of the head and neck [10,11] and uterine cervix [9,12]. Tumor hypoxia may be one of the mechanisms behind the high rates of locoregional recurrence after radiotherapy of esophageal cancer.

Here, the influence of prognostic factors and combined modality treatment on survival was

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evaluated retrospectively for patients with esophageal carcinoma receiving radiotherapy in different modalities at the University of Heidelberg and the Universitätsklinikum Mannheim.

Material and methods

Eligibility criteria for patients were as follows: histologically confirmed carcinoma of the esophagus and treatment with radiotherapy. Data were obtained retrospectively using the irradiation protocols and patient documents of the Department of Clinical Radiology, University of Heidelberg and of the Department of Surgery and Department of Radiation Oncology, Universitätsklinikum Mannheim.

A total of 156 patients with esophageal cancer who received radiotherapy between 1991 and 2001 were evaluated. Forty-six patients (29.5%) were treated with radiotherapy alone; 74 patients (47.4%) had combined radiochemotherapy without operation. Thirty-six patients (23.1%) were operated on after receiving neoadjuvant radiochemotherapy. Patient and tumor characteristics are given in Tables I and II. The mean age of patients was 61 years, range 39 to 87 years; 132 patients were male, 24 female. Staging procedures included esophagoscopy, contrast barium swallow, computed tomography of the neck, chest, and abdomen as well as a bone scan. If technically feasible endoscopic ultrasound was done. In all, 120 patients had biopsy-proven diagnosis of squamous cell carcinoma, 36 patients of adenocarcinoma; 42% of the patients had stage T3, 79% were N1. Twenty-five patients (16%) had distant metastases at the time of treatment. There was no preference in location of the esophageal carcinomas. Median pre-therapeutic hemoglobin concentration was 13.4 g/dl (range 5.5–18.0 g/dl). Patients receiving combined modality therapy were younger (age of patients $\geq$70 years: 8% vs. 41%) and had a better performance status (Karnofsky index 90–100: 48% vs. 26%) than patients receiving radiotherapy only. Between the RT-only patients and the RT-CHT patients, there was no significant difference in tumor stage.

External beam radiotherapy was administered using 23 MV photons. Dose per fraction was 2 Gy, during chemotherapy courses 1.8 Gy. Patients without operation received a mean total dose of 50 Gy. Patients in the neoadjuvant group were irradiated with a mean total dose of 43 Gy. Chemotherapy consisted of 5-fluorouracil (1000 mg/m^2, days 1-5) and Cisplatin (20 mg/m^2, days 1–5). The next

Table I. Pretreatment patient and tumor characteristics.

Characteristic	No.	%	Characteristic	No.	%
Age (years)			Node stage		
<60	75	48	N0	28	18
60–69	53	34	N1	124	79
≥70	28	18	Nx	4	3
Sex			Distant metastases		
Male	132	85	M0	106	68
Female	24	15	M1	25	16
			Not available	25	16
Histology			Location		
Squamous cell carcinoma	120	77	Upper	45	29
Adenocarcinoma	36	23	Middle	56	36
			Lower	55	35
Tumor stage			Karnofsky Index (%)		
T1	5	3	90–100	65	42
T2	24	16	70–80	46	29
T3	66	42	<70	13	8
T4	58	37	Not available	32	21
Not available	3	2			
			Hemoglobin (g/dl)		
			≤13.4 (median)	80	51
			>13.4	70	45
			Not available	6	4

Table II. Pretreatment patient and tumor characteristics of the three treatment groups (radiotherapy vs. radiochemotherapy without operation vs. radiochemotherapy with operation).

	RT		RCHT		RCHT+OP	
Characteristic	No.	%	No.	%	No.	%
Age (years)						
<60	14	31	39	53	22	61
60–69	13	28	29	39	11	31
≥70	19	41	6	8	3	8
Sex						
Male	41	89	58	78	33	92
Female	5	11	16	22	3	8
Histology						
Squamous cell carcinoma	37	80	62	84	21	58
Adenocarcinoma	9	20	12	16	15	42
Tumor stage						
T1	3	7	1	1	1	3
T2	14	30	7	9	3	8
T3	17	37	30	41	19	53
T4	11	24	34	46	13	36
Not available	1	2	2	3	0	0
Node stage						
N0	15	33	10	13	3	8
N1	30	65	62	84	32	89
Nx	1	2	2	3	1	3
Distant metastases						
M0	41	89	43	58	22	61
M1	5	11	18	24	2	6
Not available	0	0	13	18	12	33
Location						
Upper	15	33	22	30	8	22
Middle	12	26	33	44	11	31
Lower	19	41	19	26	17	47
Karnofsky Index (%)						
90–100	12	26	34	46	19	53
70–80	23	50	16	21	7	19
<70	6	13	5	7	2	6
Not available	5	11	19	26	8	22
Hemoglobin						
≤median concentration	24	52	38	51	19	53
>median concentration	21	46	31	42	17	47
Not available	1	2	5	7	0	0

course was started on day 29. Patients with N1 lymph node stage received an additional two courses of chemotherapy. In the case of secondary surgery two courses of neoadjuvant chemotherapy were applied. For the 36 patients with neoadjuvant radiochemotherapy resection of the esophagus was performed on average 1.6 months after radiotherapy.

Overall survival was calculated using the Kaplan–Meier method. Survival distributions were compared using the log-rank test (Statistica, StatSoft Inc.).

Results

The median follow-up time was 10 months. A total of 119 patients (76%) died. The median survival time for all 156 patients was 10 months.

Female patients showed significantly better overall survival compared with male patients. The median survival time for women was 16 months, for men 9 months ($p = 0.031$, Figure 1). Younger patients (age ≤ 60 years – median age) had a significantly better

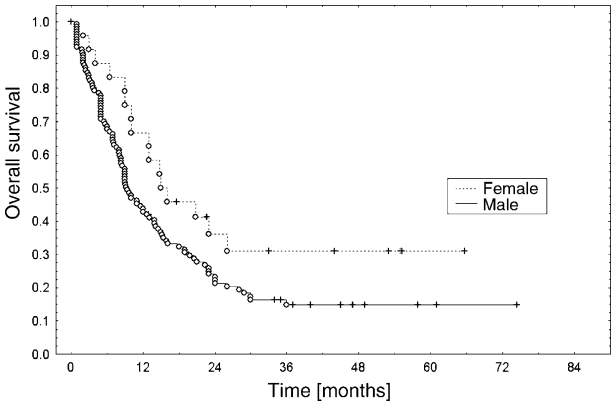

Figure 1. Overall survival regarding sex. Female patients showed a significantly better overall survival than male patients ($p = 0.031$).

overall survival than older patients (age >60 years); median survival times were 13 months vs. 9 months ($p = 0.02$, Figure 2). Tumor site or tumor stage had no significant influence on overall survival in this group.

Hemoglobin concentration before treatment was evaluable for 150 patients (96%). Patients with hemoglobin concentration >13.4 g/dl (median hemoglobin concentration) had a significantly better overall survival than patients with lower hemoglobin concentration; median survival times were 11 months vs. 9 months ($p = 0.044$, Figure 3).

Divided into the three treatment subgroups (radiotherapy, radiochemotherapy, radiochemotherapy+OP) the difference in survival according to hemoglobin concentration was only significant in the neoadjuvant group;, median survival times were 20 months vs. 12 months ($p = 0.006$). Patients who received a combination of chemotherapy and radiotherapy (with or without operation) had a survival advantage compared with radiotherapy alone. The median survival time for patients who received additional chemotherapy was 11 months, for patients with radiotherapy alone 8 months. The difference was borderline significant ($p = 0.052$, Figure 4). Overall survival of the 36 patients with neoadjuvant treatment was significantly better than the survival of the two other treatment groups; median survival times were 20 months vs. 9 months (RCHT) vs. 8 months (RT) ($p = 0.003$, Figure 5).

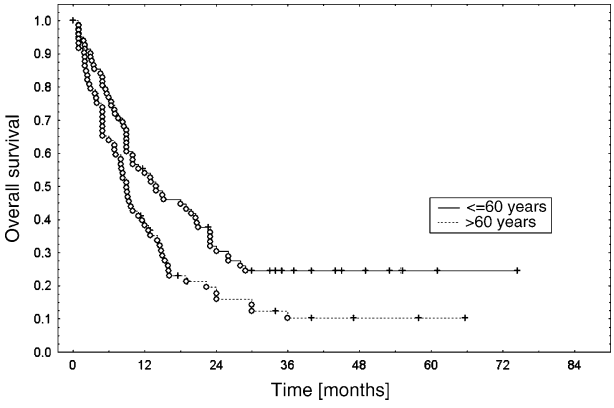

Figure 2. Overall survival regarding age. Younger patients (age $\leq$ 60 years) showed a significantly better overall survival than older patients (age >60 years) ($p = 0.02$).

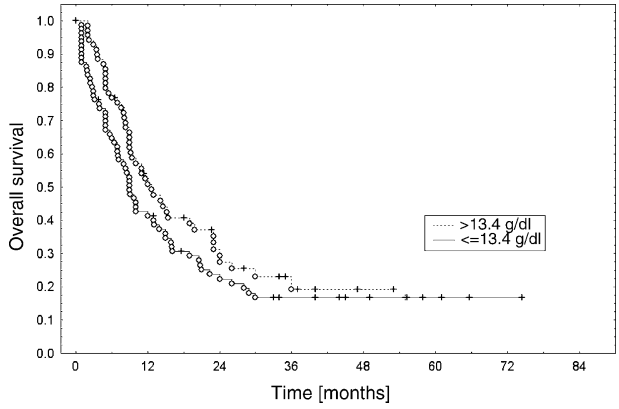

Figure 3. Overall survival regarding pre-therapeutic hemoglobin level (Hb >13.4 g/dl vs. Hb ≤ 13.4 g/dl). Patients with hemoglobin >13.4 g/dl had a significantly better overall survival than patients with lower hemoglobin ($p = 0.044$).

Discussion

Patient characteristics that influenced the outcome of patients with esophageal cancer in this study were sex, age, and hemoglobin concentration. Female patients had a better overall survival than male patients. It has already been shown in other studies that women with esophageal cancer tend to fare better than men [13,14]. It is known that older patients with esophageal cancer do worse than younger patients.

Patients with higher hemoglobin concentration (>13.4 g/dl) had significantly better overall survival

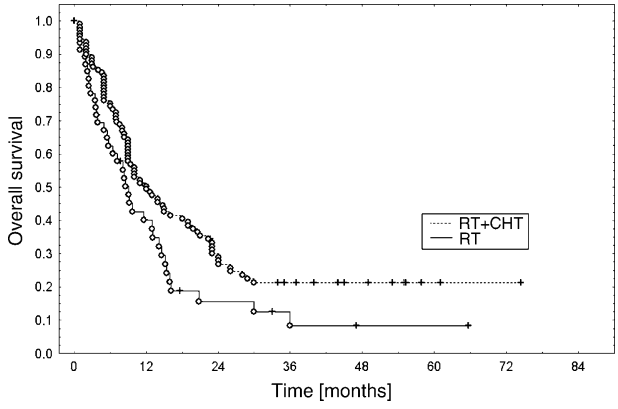

Figure 4. Overall survival of patients with radiotherapy alone vs. patients with radiochemotherapy (with or without operation). Radiochemotherapy resulted in a borderline significantly better overall survival ($p = 0.052$).

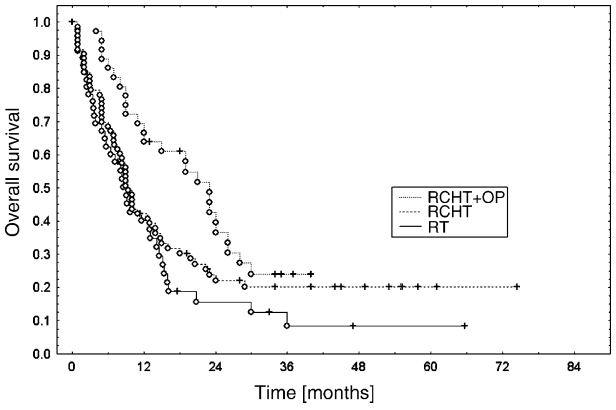

Figure 5. Overall survival of the three treatment groups (radiotherapy vs. radiochemotherapy without operation vs. radiochemotherapy with operation). Overall survival of the patients with neoadjuvant treatment was significantly better than the survival of the two other treatment groups ($p = 0.003$).

than patients with lower hemoglobin concentration. As for carcinomas of the head and neck [10,11] and uterine cervix [9,12], pre-irradiation hemoglobin concentration is a prognostic factor for esophageal cancer in this study. This is the first study that demonstrates an influence of hemoglobin concentration on survival of patients with esophageal cancer receiving radiotherapy. Our result, analyzing 150 patients, is contradictory to a retrospective study from Switzerland with 41 patients [15] and another retrospective analysis from Sweden with 126 patients [16], which had shown no influence of the hemoglobin concentration on survival. To the best of our knowledge, no other study regarding hemoglobin and radiotherapy of esophageal cancer has been published to date.

Tumor hypoxia is a therapeutic problem, as it can make solid tumors resistant to ionizing radiation and some types of chemotherapy, e.g. cisplatin. There are a variety of procedures, which include radiation sensitizers, blood transfusions, hemoglobin-oxygen affinity modifiers and erythropoietin (EPO), that try to counteract the negative influence of tumor hypoxia. In rats the correction of anemia by EPO increased tumor radiosensitivity of DS-sarcomas [17]. EPO may be of use in anemic tumor patients in whom the success of radiotherapy might be limited by tumor hypoxia. However, in a randomized trial for head and neck cancer patients undergoing radiotherapy reported by Henke et al. EPO did not improve cancer control or survival [18]. For head and neck and lung cancer patients further randomized trials that test the efficacy of EPO are ongoing. Our data implicate initializing similar studies for patients with esophageal cancer.

Our study demonstrates that patients with esophageal cancer who received a combination of systemic chemotherapy and radiotherapy have an almost significant survival advantage as compared with radiotherapy alone. Patients who had neoadjuvant radiochemotherapy and operation showed the best overall survival. While our study is retrospective, this result may be a selection phenomenon. Patients with good performance status could have been selected for radiochemotherapy and operation, patients with bad performance status for radiotherapy only. Indeed, analysis of the pretreatment characteristics showed that patients receiving combined modality therapy were younger and had a better performance status than patients receiving radiotherapy only. Herskovic et al. [7] showed in a randomized study a significant improvement in the 2-year survival rate by concurrent chemotherapy from 10% to 36%. Five-year survival rates were 27% (RT-CHT) vs. 0% (RT-only) as reported in the update from Al-Sarraf et al. in 1997 [8]. A German retrospective analysis in 2000 and a Cochrane review in 2001, analyzing 13 randomized trials, with one arm employing radiotherapy alone, and one arm employing combination radiotherapy with chemotherapy, showed that concomitant radiochemotherapy is superior to radiotherapy alone [19,20].

Conclusions

Combined modality therapy resulted in better overall survival compared with radiotherapy alone. Our data show for the first time that hemoglobin concentration in addition to gender and age was a prognostic factor for patients with esophageal cancer. A low hemoglobin value was a negative predictor. A prospective validation of hemoglobin as a prognostic factor is mandatory.

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