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ORIGINAL ARTICLE

Outcomes of patients with oesophageal cancer treated with preoperative chemoradiotherapy, followed by tumor resection: influence of nutritional factors

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Summary

Purpose: *To assess the impact of clinical and nutritional factors on overall survival (OS) and time to disease progression of oesophageal cancer patients treated with neoadjuvant chemoradiotherapy (CRT) and surgery.*

Methods: *We retrospectively studied and analysed several clinical and nutritional factors, such as performance status, weight changes before and during CRT, dysphagia, nutritional support, and serum albumin to see whether they exerted any impact on OS and time to disease progression.*

Results: *In 107 patients the average weight loss was 9.7% from the onset of signs of disease to the beginning of therapy and 3% during CRT. In univariate analysis, significant unfavorable impact on survival was proved for low performance status, severe dysphagia, need for nasogastric tube insertion, above-average weight loss before treatment, weight loss >5% during CRT, and serum albumin ≤ 35 g/l before or after CRT. Patients supported by oral nutritional supplements (ONS) had higher probability to attain full dosage of CRT and radical resection than did those obtaining dietary advice alone. In multivariate analysis, serum albumin level, nasogastric (NG) tube insertion and pretreatment body weight loss were independent prognostic factors for OS, while serum albumin level after CRT and NG tube insertion were prognosticators for time to progression.*

Conclusion: *Serum albumin level can serve as a useful prognostic factor for the outcome of patients with oesophageal cancer treated with neoadjuvant CRT and surgery. Appropriate nutritional support of these patients increased the probability of attaining full dosage of CRT and radical disease resection.*

Key words: neoadjuvant chemoradiotherapy, nutritional support, oesophageal cancer, serum albumin, weight loss

Introduction

Patients with oesophageal cancer have poor prognosis even if radical surgery is performed. A recent meta-analysis [1] proved a significant survival benefit of neoadjuvant CRT, with 13% absolute difference after 2 years, but higher risk of postoperative mortality and morbidity was reported [2]. These patients often have progressing dysphagia, resulting in a decrease of body weight. Weight loss > 10% during the 3-6 months before diagnosis of oesophageal cancer is considered an unfavorable prognostic factor [3]. These patients have worse performance status and more often will not be candidates for surgery [4].

Based on a 5-year follow-up of patients with oesophageal cancer treated with neoadjuvant CRT with or without radical surgery, we present an analysis of the relationships between several factors and OS or time to progression.

Methods

The study was approved by the institutional ethics committee. After signed informed consent the patients were subjected to a multimodal regimen comprising concurrent neoadjuvant CRT, followed by surgery. The clinical and nutritional factors we analysed included WHO performance status, weight changes before and during CRT, dysphagia, nutritional support and serum albumin levels.

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Our purpose was to see whether these factors exerted any impact on OS and time to disease progression.

Inclusion criteria

Patients had to fulfill the following inclusion criteria: histologically proved squamous or adenocarcinoma of the oesophagus, resectable tumor, fitness for surgery, age 18-75 years, and WHO performance status 0-1.

Exclusion criteria

Exclusion criteria were distant metastases, infiltration of the bronchi and large vessels, serious comorbidity (especially pulmonary or cardiovascular), and introduction of a metallic expandable oesophageal stent. The stage of disease was defined by the TNM system and the American Joint Committee on Cancer Classification (5th edition, Czech version, 2000) [5].

Body weight (kg) at the time of the first symptoms of the disease was established per patient report. Body weight from the start to completion of CRT was thoroughly recorded in 1-week intervals. Body mass index was calculated accordingly. Serum level of albumin was measured at the beginning and at the end of CRT.

The changes of body weight and body mass index (absolute and relative) were assessed in the reference periods as follows: Period A: From the onset of signs to beginning of CRT; Period B: From the beginning to the end of CRT.

Estimation of dysphagia

The degree of dysphagia was evaluated according to the following criteria: Mild dysphagia: the patient has problems, but is capable of full intake of food prepared in a usual way. Moderate dysphagia: the patient is able to maintain the necessary food intake with modifications of its preparation such as grinding, mixing and frequent washing down. Severe dysphagia: the patient is not able to maintain sufficient food intake even with modifications of its preparation.

Nutritional support

All patients were offered individual nutritional support. Its kind was indicated from the severity of malnutrition and dysphagia. Daily energy intake of 130-150 kJ/kg ideal body weight (i. b. wt.)/day was recommended. Patients with no or mild dysphagia were advised to increase protein and energy intake. In patients with moderate dysphagia, nutritional support by ONS was advised (200-500 ml) while in those characterized by severe dysphagia and insufficient tolerance of ONS enteral feeding by NG tube was ordered using isocaloric polymeric formula of enteral nutrition (2000 ml/day). In case of persisting weight loss (>1 kg/week) during the first week after the nutritionist's examination or at anytime during CRT despite dietary advice or ONS, enteral feeding was carried out using a NG tube. Rehabilitation of oral intake using modified diet and liquid ONS was performed simultaneously. The feeding tube was removed when >75% of the recommended oral intake corresponding to the energy of 130-150 kJ/kg i. b. wt/day was achieved. In case this was impossible to achieve the required energy or liquid intake by enteral feeding, parenteral nutrition was indicated.

Chemoradiotherapy

CRT consisted of two cycles of chemotherapy with carboplatin at AUC 6 or cisplatin at 80 mg/m^2 on days 1 and 22 from the start of treatment. Continuous infusional 5-fluorouracil was administered on days 1-42 at 200 mg/m^2/day. Paclitaxel 200 mg/m^2 by 3-h infusion on day 1 was a part of the combination in some patients. RT was delivered from day 1 concurrently, 1.8 Gy per fraction, 5 fractions per week, total dose 45 Gy in 25 fractions. RT dose was increased to 50.4-56.8 Gy if a contraindication to surgery occurred during the treatment course. Surgery followed 4-6 weeks after CRT unless it was contraindicated or refused by the patient. After surgery or definitive CRT, patients were followed up without further adjuvant therapy.

Statistical considerations

Time to progression and OS data were assessed as end points. Using univariate analysis (log-rank test), the impact of the following prognostic variables were assessed: gender, age, alcohol abuse, time from onset of symptoms to diagnosis, degree of dysphagia, body weight prior to treatment, TNM stage, histology, performance status, serum albumin level before and after CRT, NG tube insertion, ONS delivery, and change of body mass within the aforementioned periods. Kaplan-Meier survival curves were constructed and compared by log-rank test [6]. Multivariate analysis for the same endpoints and risk factors was performed using the Cox proportional hazard model [7]. For descriptive purposes, basic statistics (mean, median, standard deviation) were calculated for all continuous data. Changes in parameters over time were tested using paired t-test. The correlations of individual parameters were analysed by the Pearson correlation coefficient (R). All statistical tests were performed at significance level α=5%, and all of them were two-sided. All statistical analyses were performed in the program Statistica, version 7.0. (StatSoft, Inc., Tulsa, Oklahoma, USA, 2004, version 7, www.statsoft.com).

Results

One hundred and seven patients were treated according to the aforementioned protocol during January 2001 - August 2005. Basic patient and disease characteristics are presented in Table 1. After a median follow-up of 52 months (range 27-80), the median survival was 18 months while 2- and 5-year survival were 38% and 21%, respectively. The median progression-free survival was 15 months, while 2- and 5-year progression-free survivals were 39 and 31%, respectively.

Detailed analysis of the treatment results has been published elsewhere [8].

Body weight and its changes before and during CRT are summarized in Table 2. In patients with relative weight loss >5% during CRT (period B) there was a significantly lower probability to reach the full dose of chemotherapy (x^2, p=0.042) than in those with weight loss ≤2%. Relationships between weight loss and risk of grade 3-4 toxicity of neoadjuvant CRT and/or the complications of surgery were assessed separately for periods A and B. Weight loss >5% during CRT was significantly associated with severe (grade III or IV) radiation oesophagitis (p=0.02). On the other hand, no sig-

Table 1. Patient (n=107) and disease characteristics

Characteristics	*N*	*%*
Gender		
Male	93	87
Female	14	13
WHO performance status		
0	17	16
1	87	81
2	3	3
Risk factors		
Smoking	94	88
Alcohol daily	68	64
Histology		
Squamous	92	86
Adenocarcinoma	9	8
Other	6	6
Clinical stage		
II	44	41
III	57	53
IVa	6	6
TNM stage		
T2	11	10
T3	85	80
T4	11	10
N0 M0	49	46
N1 and/or M1a	58	54
Age, years, mean (range)	59 (44-75)	
Body weight, kg, mean (range)	72 (43-105)	
Body mass index, mean (range)	24 (14.5-34.7)	

nificant differences were found between adverse events occurring during the treatment (febrile neutropenia, thrombocytopenia, anaemia, neutropenia, leucopenia) in patients with weight loss ≤2% or >5% during any observed period (periods A, B).

Relationships between weight loss and OS and/or time to progression were assessed separately for the periods A and B. For the period A (from first signs of the disease until start of treatment), weight loss > 9.7% (average) was associated with significantly worse OS (log-rank, p=0.007, Figure 1). For the period B, there was no significant correlation between above- or below-average body weight loss and OS. Consequently, the relationship between no or only minor weight loss (i.e. <2%) or significant weight loss (i.e. >5%) in the periods A and B was assessed. It was found that patients with relative weight loss >5% during CRT had significantly shorter OS than did those with relative loss ≤2% (p=0.008), as well as shorter time to progression (p=0.034).

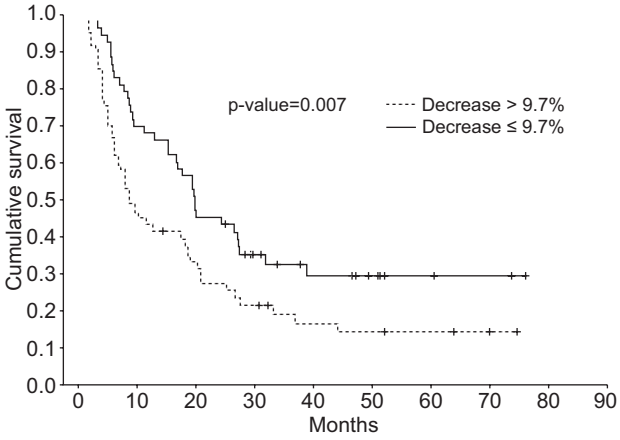

Figure 1. Influence of relative change of body weight in the pre-treatment period on survival (groups divided relative to 9.7% average weight loss).

Dysphagia was present in most patients before the start of treatment. In only 9 cases dysphagia was absent. Thirty-nine patients were characterized by mild, 37 patients by moderate, and the remaining 22 by severe dysphagia. All patients suffering from moderate or severe dysphagia were supported by ONS or total enteral nutrition using an NG tube before starting CRT. While for 27 of these patients use of an NG tube had been advised, it was actually used only in 20 patients. Three patients had refused NG tube insertion, while food intake of 4 others improved substantially after 1 week of ONS and so nutritional support by NG tube was not necessary. During CRT, 3 patients with severe dysphagia were hospitalized because of progressive malnutrition despite supportive NG tube nutrition. In these patients, parenteral nutrition was used. Only 8 of 22 patients with severe dysphagia could undergo radical resection and 4 of them died of surgical complications.

Table 2. Body weight, serum albumin and their changes before and during chemoradiotherapy

Variable	*BW or weight loss in kg Mean (SD)*	*Percent relative value of BW Mean (SD)*	*Serum albumin g/l Mean (SD)*	*BW loss ≤2% N (%)*	*BW loss >5% N (%)*
Before symptoms	79.9 (14.5)	100	NA	NA	NA
At treatment start	72.1 (14.7)	90.1 (18.3)	40.4 (6.1)	NA	NA
At treatment end	69.8 (14.4)	87.3 (18.0)	38.6 (4.9)	NA	NA
BW loss (Period A)	7.8 (6.1)	9.7 (7.1)	NA	22 (20)	75 (70)
BW loss (Period B)	2.3 (3.3)	3.1 (5.0)	NA	44 (41)	45 (42)

BW: body weight, Period A: from the onset of signs until the beginning of chemoradiotherapy, Period B: from the beginning to the end of chemoradiotherapy, NA: not applicable, SD: standard deviation, N: number of patients

In 40 patients with moderate to severe dysphagia, ONS alone without NG tube or without intravenous nutritional support was done. Patients supported by ONS alone (n=40) had longer median OS (20.2 vs. 13.0 months, p=0.16) and longer time to progression (17.6 vs. 11.5 months, p=0.22) than the patients with dietary advice alone (n=47), but differences were not statistically significant. Patients supported by ONS had non-significantly higher rate of radical resection than patients with dietary advice alone (70 vs. 57%, p=0.32). Patients with NG tube insertion (n=20) had shorter median OS (5.3 vs. 19.5 months, p=0.001) and shorter median time to progression (5.1 vs. 17.9 months, p=0.01) in comparison with the others (Table 3).

Serum albumin levels < 35 g/l were found in 12 (11%) patients before treatment and in 19 (18%) after CRT. The concentrations of serum albumin either at the start of CRT or after CRT influenced both median OS and time to progression. We found significantly longer median OS in patients with serum albumin concentration >35 g/l at the start of CRT than in those with lower albumin at that time (19.0 vs. 7.6 months, p=0.02). The median of time to progression was longer in patients with normal albumin at the start of CRT than in those with low albumin but the difference did not reach statistical significance (16.4 vs. 5.3 months, p=0.094). When evaluating the significance of serum albumin concentration at the end of CRT, we found that serum albumin > 35 g/l was associated with both significantly longer median OS and time to progression (19.9 vs. 7.9 months, p=0.004, and 17.9 vs. 3.3 months, p=0.0006, respectively) compared to low albumin (Figure 2). Serum albumin levels showed significant negative correlation with weight loss: patients with less weight loss in the period A had higher albumin level at the start of treatment (R =-0.189, p=0.029) and those with less weight loss in the period B had higher albumin at the end of treatment (R=-0.241, p=0.007).

Table 3. Prognostic variables: univariate analysis of overall survival and time to progression data

Variables	*N=107*	*Median OS (months)*	*p-value (log-rank test)*	*Median TTP (months)*	*p-value (log-rank test)*
Performance status					
0	17	35.8	0.004	NR	0.03
1+2	90	13.0		11.2	
T stage					
2	11	21.5	0.654	16.0	0.782
3	85	20.0		13.0	
4	11	11.1		7.3	
N stage					
0	49	13.8	0.132	8.0	0.137
1	58	20.0		15.9	
Dysphagia					
none to moderate	85	21.0	0.001	18.0	0.015
severe	22	8.0		7.0	
Weight loss in period A (%)					
≤9.7	54	21.0	0.007	17.4	0.11
>9.7	53	9.5		11.0	
Weight loss in period B (%)					
≤2	44	19.4	0.008	18.1	0.034
>5	45	8.6		7.2	
Serum albumin before CRT (g/l)					
>35	93	19.0	0.020	16.4	0.094
≤35	12	7.6		5.3	
Serum albumin after CRT (g/l)					
>35	83	19.9	0.004	17.9	0.0006
≤35	19	7.9		3.3	
NG tube					
Yes	20	5.3	0.001	5.1	0.01
No	87	19.5		17.9	
ONS					
Yes	40	20.2	0.160	17.6	0.221
No	47	13.0		11.5	

Period A: from onset of signs until beginning of chemoradiotherapy, period B: from beginning to end of chemoradiotherapy, TTP: time to progression, OS: overall survival, ONS: oral nutritional supplements, CRT: chemoradiotherapy, NG tube: nasogastric tube, NR: not reported

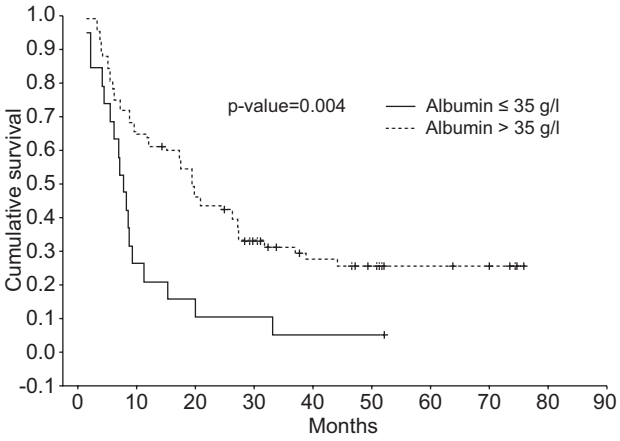

Figure 2. Survival according to serum albumin level after chemoradiotherapy (> 35 or ≤ 35 g/l).

The impact of prognostic variables on OS and time to progression was assessed using univariate analysis. The results are summarized in Table 3. Significant impact on OS was shown for the following variables: performance status (0 vs. 1+2), degree of dysphagia (none to moderate vs. severe), weight loss before treatment start below or above average, weight loss during CRT >5% or <2%, serum albumin ≤35 g/l or >35 g/l before or after CRT, and NG tube insertion (yes vs. no). Significant unfavorable impact on time to progression was proved for worse performance status, severe dysphagia, need for NG tube insertion, weight loss >5% during CRT, and serum albumin ≤35 g/l after CRT.

Multiple regression (Cox) analysis was performed to identify factors that were independently associated with both OS and time to progression. This analysis (Table 4) showed that serum albumin level after CRT (beta = -0.733, p=0.009), NG tube insertion (beta = 0.804, p=0.003) and body weight loss above average in the period A (beta = 0.471, p=0.047) were independent prognostic factors of OS. Similarly, we found that serum albumin level after CRT (beta = –0.973, p=0.001) and NG tube insertion (beta=0.956, p=0.001) independently influenced time to progression.

Discussion

Oesophageal cancer is characterized by early development of malnutrition, that negatively influences the patients' prognosis, but prognostic factors in oesophageal cancer remain unclear. In this study we retrospectively analysed the impact of several clinical factors and indices of the nutritional status on the outcome of patients with oesophageal cancer treated with preoperative CRT. Consistent nutritional support was carried out before surgery. In univariate analysis, overall survival was significantly influenced by baseline performance status, grade of dysphagia, serum albumin levels before and after CRT, NG tube insertion and either pretreatment weight loss or weight loss during CRT, while baseline performance status, grade of dysphagia, pretreatment weight loss, serum albumin levels after CRT and NG tube insertion were significantly associated with time to progression. Multivariate analysis revealed, that serum albumin level after CRT, pretreatment weight loss, and NG tube insertion were independent prognostic factors of OS, while as for time to progression, only serum albumin level after CRT and NG tube insertion were independent indices for prognosis.

Mean pretreatment body mass loss was 7.8 kg (9.7%). This is the value also referred to in the literature as being critical for worsened prognosis [3]. Another study of CRT in locally advanced oesophageal cancer had shown initial weight loss to be predictive of response to therapy [9]. Several studies have shown that even 5% weight loss is connected with shortened survival [10,11]. In the present work, weight loss during CRT significantly influenced both OS and time to progression. In univariate analysis, it was found that patients with weight loss > 5% during CRT in comparison with those having no or minor weight loss (≤2%) were characterized by significantly shorter OS and time to progression. It has been suggested that the worse prognosis of patients with weight loss relates to the fact that they receive significantly less chemotherapy and develop more toxicity rather than to any specific reduction in

Table 4. Multivariate analysis of overall survival and time to progression

Variable	*Value of variable*	*N*	*Median OS (months)*	*beta*	*p-value (Cox)*	*Median TTP (months)*	*beta*	*p-value (Cox)*
Weight loss (%)	≤ 9.7	54	21.0	0.471	0.047	17.4	NA	NS
Period A (%)	> 9.7	53	9.5			11.0		
Serum albumin after CRT (g/l)	> 35	83	19.9	–0.733	0.009	17.9	–0.973	0.001
	≤ 35	19	7.9			3.3		
NG tube	Yes	20	5.3	0.804	0.003	5.1	0.956	0.001
	No	87	19.5			17.9		

Period A: body mass change from onset of signs until beginning of CRT, OS: overall survival, TTP: time to progression, CRT: chemoradiotherapy, NG tube: nasogastric tube, N: number of patients, beta: parameter of Cox regression model, NA: not applicable, NS: nonsignificant

tumor responsiveness to treatment [4]. On the contrary, weight gain during chemotherapy can be associated with better overall response rate and 5-year survival [12]. This coincides with our finding that weight loss >5% during CRT was associated with a significantly lower probability of reaching the full dose of chemotherapy (x^2, p=0.042) than in those with weight loss ≤2%.

The side effects of CRT have been reported as more prominent in patients with initial weight loss [4], but in our series this observation was not confirmed. Severe radiation oesophagitis only was connected with weight loss >5% during CRT (p=0.02), but here weight loss was probably caused by the oesophagitis. No other significant influence of initial weight loss or weight loss during CRT was noticed on either occurrence of adverse events during treatment or risk of surgical complications or postoperative mortality. It could be explained by the favorable proportion between efficacy and toxicity of the chemotherapeutic regimen used in this study. 5-fluorouracil was given as long term continuous infusion of low daily dose, with lower risk of mucositis and haematological toxicity than higher daily doses in 4-5 days infusion or bolus infusion of the same drug [13].

In the present study, the concentrations of serum albumin after CRT predicted both OS and time to progression. Serum albumin is considered as one of the most significant indices of nutritional status for patients with cancer, being negatively influenced by malnutrition and inflammation [14]. In one retrospective review of patients who had undergone gastrectomy for gastric cancer, a serum albumin level, together with tumor location and lymphocyte count were the most important preoperative risk factors that determined the appearance of surgical complications [15]. In another study in patients with locally advanced oesophageal cancer treated with definitive CRT, serum albumin level >3.5 g/dL was found to be the only independent prognostic factor of complete response to CRT (p = 0.009), but not of OS [9].

In a recent meta-analysis of 59 studies, pretreatment serum albumin was reported to be a significant prognostic factor of OS [16]. Based on our results it can be supposed that consistent nutritional support during CRT helps maintain serum albumin concentrations appropriate for better prognosis of treatment. It was found that patients suffering from moderate dysphagia nourished using ONS did not differ in albumin levels from those with mild dysphagia and who were only advised with respect to diet. Nevertheless, we have not been able to prove statistically significant impact of ONS usage on both OS and time to progression. The reasons for this finding are not clear; perhaps the small number of patients and the high variability of both OS and time to progression may play a role. Moreover, neither markers of inflammation nor oxidative stress have been investigated, which are known to influence serum albumin levels [14]. We have found longer OS in patients without NG feeding tube than in those having NG tube inserted. It must be remembered, however, that the NG tube was ordered for the patients with severe dysphagia. Severe dysphagia was also associated with worse survival prognosis. Severe dysphagia can be a likely indicator of advanced disease, cachexia syndrome and cancer dissemination, so unfavorable prognosis can not be affected by nutritional support.

There were some limitations in our study. We have not analysed indices of inflammation or of oxidative stress, which could modify the nutritional status of the patients and the effectiveness of nutritional support. Moreover, in our group of patients we did not carry out staging using endosonography or PET/CT scanning. This could be the reason for non-significant prognostic value of T and N stage. Lack of precisely defined and followed nutritional support in the postoperative period was another weakness of the study.

In conclusion, in the presented study serum albumin after CRT was prognostic for both OS and time to progression in patients with oesophageal cancer treated with preoperative CRT and consecutive resection. OS could be prognosticated by pretreatment weight change, as well. Weight stabilization during CRT, achieved due to careful individualized nutritional support, increased the probability of attaining full chemotherapy dosage and radical resection. In addition, nutritional support with NG feeding tube failed to improve the outcome in patients with most severe degree of dysphagia. We suppose that further studies with larger number of patients investigating broader spectrum of nutritional status and inflammation indices are needed to better understand the role of nutritional support of oesophageal cancer patients treated with combined modality protocols.

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