Chapter 5

Nutrition during trimodality treatment in stage III non-small-cell lung cancer: Not only important for underweight patients

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Journal of Thoracic Oncology 2011; Vol 6, No 9, pp. 1563-1568

Abstract

Introduction: Trimodality treatment for stage III non-small-cell lung cancer (NSCLC), consisting of chemoradiotherapy followed by surgery, is associated with treatment-related toxicity, malnutrition, and postoperative complications. The aim of this retrospective study was to investigate the predictive value of nutritional parameters on postoperative morbidity, mortality, and survival.

Methods: Patients with stage III NSCLC undergoing concurrent chemoradiotherapy followed by surgery in one center between 2003 and 2009 were included. Age, sex, forced expiratory volume in 1 second, body mass index, weight change, and surgical and pathological factors were recorded and related to the occurrence of postoperative complications/mortality, overall survival (OS), and progression-free survival.

Results: Of 51 study patients, 17 (33%) had overweight (body mass index ≥25) at start of treatment and 20 patients (39%) were malnourished at hospital admission for surgery. Postoperative complications occurred in 25 patients (49%), 6 had major complications, and 2 died within 90 days after surgery, but no significant predictive factors were found. Overall, weight loss ≥5% during induction period was associated with shorter OS ($p = 0.03$), but especially overweight patients experiencing weight loss ≥5% during induction period ($n = 7$) had shorter OS (hazard ratio 4.63, $p = 0.005$; log-rank $p = 0.04$) and progression-free survival (hazard ratio 6.03, $p = 0.007$).

Conclusions: This study indicates that malnutrition especially in overweight patients negatively influences survival outcomes of trimodality treatment for stage III NSCLC.

Introduction

The debate for optimal treatment of stage III non-small-cell lung cancer (NSCLC) is mainly focused on the use of different modalities, i.e., chemotherapy with surgery and/or radiotherapy. However, survival still remains poor despite the use of several chemotherapy regimens, implementation of concurrent radiotherapy, and extensive restaging before surgery. In stage III NSCLC, the application of surgery after induction treatment is controversial because no survival benefit has been demonstrated in randomized clinical trials compared with chemoradiotherapy (CRT) alone.[1,2] In our practice, stage III NSCLC patients without mediastinal lymph node involvement and those with N2/N3 disease and proven mediastinal downstaging after concurrent CRT are selected for surgery. In this situation, consideration is given to the risk of local recurrence and technical resectability of the primary tumor.

A minority of patients treated with upfront surgery for NSCLC have a poor nutritional status, which has been shown to be an independent risk factor for postoperative death and reventilation after lung resection.[3] In addition, malnutrition in lung carcinoma is associated with advanced stage of disease and is a reason for careful and extensive staging.[4] Perioperative nutritional support in malnourished surgical patients has been shown to reduce the risk of postoperative complications and death and is advocated by international guidelines.[5] Apart from a negative effect on surgical morbidity and mortality, weight loss and catabolic state are associated with a negative impact on long-term oncological outcomes in patients with cancer, such as a reduced progression-free survival (PFS).[6–9] The mechanisms for this phenomenon are poorly understood, but immunologic processes may play an important role.[10–13] However, it is unknown whether nutritional support can ameliorate this phenomenon. Because cisplatin-based CRT is associated with nausea, vomiting, diarrhea, anorexia, and esophagitis, patients undergoing trimodality treatment may become malnourished before surgery. Surgery after CRT is associated with a higher morbidity and mortality, and weight loss and malnutrition which may occur during induction treatment may be one of the causes.[3,14] The importance of nutritional factors as an independent risk factor for outcome and long-term prognosis in patients operated after CRT is however poorly studied.

The objective of this retrospective study was to investigate nutritional status and weight change during induction CRT and to evaluate the influence of nutritional status variables on surgical morbidity/mortality and survival outcomes in stage III NSCLC patients receiving trimodality treatment.

Patients and Methods

Patient Selection

All consecutive patients with NSCLC who underwent induction treatment with cisplatin-based chemotherapy and concurrent thoracic radiotherapy followed by surgical resection from January 1, 2003, until December 31, 2009, in the VU University Medical Center (VUmc) Amsterdam were included in this study. NSCLC patients were selected for trimodality treatment on basis of one or more of the following criteria:

1. Pathologically proven mediastinal lymph node involvement (N2 or N3 disease), either by transbronchial fine needle aspiration and/or esophageal ultrasonography (endoscopic ultrasound-guided fine needle aspiration) or mediastinoscopy.
2. Superior sulcus tumor (SST).
3. Consensus in the VUmc multidisciplinary thoracic oncology meeting that the tumor should be staged as cT4 on basis of a combination of clinical signs (e.g., neurologic signs) and/or imaging studies such as computed tomography scan or magnetic resonance imaging (e.g., involvement of vertebra).
4. Eastern Cooperative Oncology Group performance status 0 and 1.
5. Ability to tolerate cisplatin-based chemotherapy.

Trimodality Treatment

Two different induction schemes were used: (1) one course of cisplatin and gemcitabine or pemetrexed followed by two courses of cisplatin-etoposide (course cycle of 3 weeks) combined with radiotherapy (daily fractions of 2 Gy to a total dose of 46–66 Gy); (2) six courses of weekly cisplatin-docetaxel combined with radiotherapy (daily fractions of 1.8 Gy to a total dose of 45 Gy). The latter scheme was used in patients participating in a phase II study (NVALT-6).[15] After CRT, restaging was performed using imaging studies and one or more of the abovementioned invasive staging techniques. When no residual mediastinal

lymph node involvement was encountered and the primary tumor was deemed resectable, patients underwent a thoracotomy approximately 5 weeks after the end of induction treatment. If possible, a macroscopically complete resection of the tumor was performed, preferably by lobectomy, combined with an ipsilateral mediastinal lymphadenectomy. In right-sided tumors, lymph node stations 2, 4, 7, 8, and 9 were removed and in left-sided tumors stations 5, 6, 7, 8, and 9, together with hilar and intralobar lymph nodes. The bronchial stump was reinforced with a pedicled intercostal muscle flap in all patients. SST were typically approached by a high posterolateral incision (Shaw-Paulson), and all other resections were performed through a standard posterolateral thoracotomy.

Morbidity and Mortality

Anesthetic risk was determined for all patients using the American Society of Anesthesiologists (ASA) score (http://www.asahq.org/clinical/physicalstatus.htm). Post-operative complications occurring within 90 days after surgery were recorded and classified for type and severity. The type of postoperative complications was subdivided into pulmonary, cardiac, infectious, or miscellaneous. Severity was classified as (1) minor (non–life-threatening, no need for reintubation, or admission to intensive care unit) or (2) major (potentially life-threatening, need for reintubation, and/or admission to intensive care unit).[16] Patients having both minor and major postoperative complications were classified as having major complications, although the nature of the minor complications was also recorded. A separate analysis was made of infectious complications, because previous studies have shown that these are especially related to nutritional status in abdominal and thoracic surgical patients.[14,17] Information on type of resection, length of postoperative hospital stay, and 90-day postoperative mortality was recorded. Follow-up data included last visit, first recurrence, and date/cause of death. Overall survival (OS) and PFS were calculated from date of surgery to October 5, 2010, or date of last radiological follow-up, respectively.

Nutritional Status

Nutritional status was assessed at start of first chemotherapy course (“baseline”) by recall of recent involuntary weight loss and by measuring body mass index (BMI). BMI was calculated as the ratio of body weight (kg)/height (m^2). Malnutrition was defined as ≥5% involuntary weight loss in the previous month[18] and/or underweight (BMI ≤18.5). Overweight was classified as BMI ≥25, according to the NIH classification of obesity (http://www.nhlbi.nih.gov/health/public/heart/obesity/lose_wt/bmi_dis.htm).

During induction period, development of nutritional status was investigated by follow-up of body weight at start of week 6 after baseline (during CRT) and at hospital admission for surgery (surgery). Body weight, without shoes and wearing light clothing, was measured on a compact digital flat scale (SECA 708) to the nearest 0.1 kg at hospital admissions for chemotherapy and surgery. The percentages of weight change between preillness and baseline, baseline and during CRT, and baseline and surgery were calculated. Throughout treatment, nutritional status was monitored by the medical staff, and the dietician was consulted whenever necessary. Energy requirements were estimated using the Harris Benedict 1984 equation including sex, age, body weight, and height.[19] To estimate total energy requirements, 130% of predicted resting energy expenditure was applied (according to guidelines of the Dutch Malnutrition Steering Group).[20] Patients received enteral nutrition in case of malnutrition and/or intake failure. Tube feeding was indicated in case of (expected) oral intake <75% of energy requirements for more than 3 days, combined with the inability to increase energy intake by oral food or sip feeds. Enteral nutrition was supplied by oral nutritional supplements or tube feeding, the latter via a nasogastric tube or a percutaneous endoscopic gastrostomy (PEG) tube. Patients participating in the NVALT-6 phase II study received a PEG tube before the start of CRT.

Statistics

Independent variables (age, sex, stage of disease [N2/N3 versus T4 or SST], ASA score, CRT schedule, forced expiratory volume in 1 second (FEV_1), extent of lung resection, postoperative pathological tumor node metastasis (TNM) stage, BMI, and percentage of weight change) were related to the occurrence of postoperative complications, 90-day postoperative mortality, OS, and PFS. Associations between independent variables and postoperative complications were investigated by logistic regression analyses. To identify factors associated with OS and PFS, Cox regression and Kaplan-Meier analyses were carried out. Outcomes were adjusted for the following confounding factors in the regression model (based on a >10% change of OR after adding a single factor): age, sex, stage of disease, chemotherapy scheme, pathological complete remission, and/or extent of lung resection. *p* values less than 0.05 were considered statistically significant.

Results

Patient and treatment characteristics

Fifty-one patients were included (26 males), 26 patients with involvement of N2/N3 lymph nodes and 41 patients with a SST or T4 tumor. Median age at start of treatment was 57 years (range, 39–74 years). ASA score was I in 4 patients, II in 30 patients, and III in 17 patients. Patient characteristics are summarized in **Table 1**. Of 44 patients, results of pulmonary function tests at diagnosis were available. Average FEV_1% of these patients was 87.5% (range, 33–126%). Forty-two patients (82%) generally received one course of cisplatin combined with gemcitabine or pemetrexed followed by two courses of cisplatin-etoposide. Nine patients (18%) received six weekly courses of cisplatin and docetaxel. Resections consisted of pneumonectomy (n = 4, 8%), bilobectomy (n = 3, 6%), lobectomy (n = 39, 77%), and 5 patients (10%) had a sublobar resection, because a more extended resection was impossible for functional reasons. Macroscopically complete resection was achieved in all patients. In three patients (6%), the resection margins were microscopically involved (R1 resection). These three cases were patients with a SST in whom the lateral chest wall was microscopically involved at the plane between the muscle fascia and the scapula. Finally, pathological complete remission was achieved in 15 patients (29%).

Table 1. Patient characteristics

Characteristic	Result	Range	%
Sex (n)			
Male	26		51
Female	25		49
Age at surgery (yr)			
Median	57	39-74	
<65 (n)	35		69
≥65 (n)	16		31
Baseline[a] nutritional parameters			
Mean body weight (kg)	70.3	46.8 – 98.1	
Mean BMI (kg/m^2)	24.0	18.0 – 40.3	
BMI (n)			
<18.5 (underweight)	2		4
18 – 25 (normal weight)	32		63
≥25 (overweight)	17		33
Mean weight change (%)			
Normal weight – baseline[a]	-1.03	-10 – 16.8	
Baseline[a] – during CRT	-2.7	-15.4 – 8.5	
Baseline[a] – admission for surgery	-3.1	-13.8 – 14.2	
Malnourished patients (n)			
At baseline[a]	12		24
During CRT	19		37
At surgery	20		39
ASA score (n)			
I	4		8
II	30		59
III	17		33
Patients with complications			
Minor	19		37
Major	6		12
Number of complications			
Pulmonary	14		
Cardiac	5		
Infectious	12		
Miscellaneous	6		

[a]Baseline is at start of first chemotherapy course. BMI, body mass index; CRT, chemoradiotherapy; ASA, American Society of Anaesthesiologists.

Nutritional status

At baseline and during CRT, 12 and 19 patients were malnourished, respectively. Most patients (69%) maintained weight between CRT and time of surgery, but on average, a weight loss of 3.1% (range, -13.8 to 14.2) was observed for the period between baseline and surgery. In addition, at time of surgery, 20 patients were malnourished. Specifications on nutritional status and weight change are shown in **Table 1**. Forty-two patients (83%) received one or more dietetic consultations. In 11 (22%) patients, a pretreatment PEG was inserted. During induction period, 9 patients received nasogastric tube feeding and 42 (83%) patients used oral nutritional supplements to increase their daily energy and nutrient intake.

Postoperative complications, survival, and cause of death

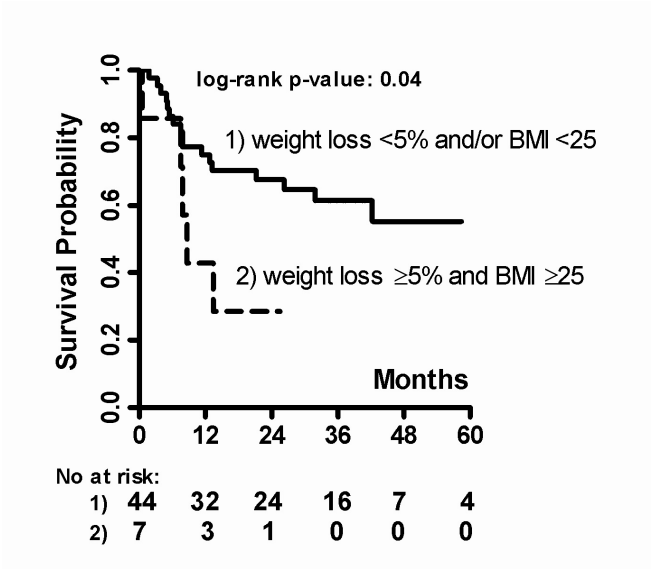
One or more postoperative complications occurred in 25 (49%) patients. Six patients had major complications and two patients died within 90 days after surgery. The cause of death in these two patients was acute respiratory distress syndrome (ARDS) after pneumonectomy in one and sepsis in the other. Age, FEV_1, sex, type of resection, and percentage of weight change during induction period were not significantly associated with postoperative complications or infectious complications in univariate analysis (data not shown). The mean length of postoperative hospital stay was 11.4 days (range, 6–31 days). After a median follow-up of 36.9 months, median OS had not been reached. The mean OS was 46.7 months and mean PFS 37.1 months. None of the preoperative variables were significantly associated with OS or PFS in univariate analysis (**Table 2**). However, pneumonectomy was associated with shorter PFS (HR 4.91, $p = 0.02$) and complete pathological remission with a longer PFS (HR 0.26, $p = 0.03$). Weight loss ≥5% from baseline until surgery was associated with shorter OS (HR 2.80, $p = 0.03$). Especially overweight patients who experienced a weight loss of ≥5% (n = 7) tended to have a shorter OS (adjusted HR 4.63, $p = 0.005$) and PFS (adjusted HR 6.03, $p = 0.007$). In addition, **Figure 1** shows the Kaplan-Meier OS curve for last-mentioned group compared with the other study patients (log-rank $p = 0.04$). At the date of survival analysis, in total 22 patients (43%) have died of which 10 were noncancer-related death. Respiratory failure was the cause of death in seven of latter patients. Finally, the overweight patients who experienced a weight loss of ≥5% died of cancer (n = 2) or respiratory failure (n = 3), but only one of them died within 90 days after surgery (ARDS).

Table 2. Associations between independent variables and overall/progression-free survival

	Overall survival			Progression-free survival		
	HR	95% CI	*p*	HR	95% CI	*p*
Sex (male vs. female)	1.91	0.73 - 4.97	0.19	1.81	0.75 - 4.40	0.19
Age (≥65 vs. <65 years)	1.16	0.46 - 2.94	0.75	1.21	0.51 - 2.90	0.66
Stage of disease (SST/T4 vs. N2/N3)	0.81	0.30 - 2.23	0.69	0.75	0.29 - 1.93	0.55
BMI at baseline (≥25 vs <25 kg/m^2)	1.75	0.70 - 4.38	0.23	1.41	0.59 - 3.36	0.45
FEV_1 (%)	1.00	0.98 - 1.03	0.97	1.00	0.97 - 1.02	0.66
Induction scheme (cisplatin-docetaxel vs other)	1.21	0.46 - 3.22	0.70	0.67	0.24 - 1.90	0.45
ASA score (III vs. I/II)	1.17	0.49 - 2.80	0.72	0.64	0.26 - 1.53	0.31
Extent of lung resection (pneumonectomy vs. other)	2.32	0.55 - 9.73	0.25	4.91	1.40 - 17.18	0.02 [a]
Completeness of resection (R0 vs. R1)	1.83	0.51 - 6.57	0.35	2.28	0.59 - 8.73	0.233
Complete pathological remission (yes vs. no)	0.32	0.10 - 1.08	0.07	0.26	0.08 - 0.88	0.03 [a]
Weight loss ≥5% between baseline and surgery	2.80	1.10 - 7.13	0.03 [a]	1.77	0.75 - 4.16	0.19
BMI ≥25 and ≥5% weight loss between baseline and surgery	4.63	1.58 - 13.56	0.005 [a]	6.03	1.65 - 22.11	0.007 [a]

Cox regression for progression-free and overall survival, adjusted for confounding factors.
[a] $p < 0.05$. HR, hazard ratio; CI, confidence interval; SST, sulcus superior tumor; BMI, body mass index; FEV_1, forced expiratory volume in 1 second; ASA, American Society of Anaesthesiologists; R0, complete resection; R1, microscopic residual disease.

Figure 1. Overall survival. Kaplan Meier overall survival curve of overweight patients (BMI ≥25) experiencing ≥5% weight loss during induction period (n = 7) compared with other study patients (n = 44) (log-rank p = 0.04).



Discussion

In this study, a well-defined group of 51 stage III NSCLC patients underwent trimodality treatment, consisting of concurrent CRT followed by surgery. The nutritional status of patients was not only determined at baseline but also monitored continuously during CRT and thereafter until surgery. A high number of postoperative complications were observed, which is in line with other series of lung resections after induction CRT.[1,2,21] However, most complications were minor, and postoperative mortality was lower than in other studies.[1,21] None of the preoperative risk factors, including nutritional status, were predictive for postoperative complications. In general, obese patients are thought to be at higher risk for postoperative complications due to more difficulty in mobilization, impaired wound healing, and atelectasis.[22] However, several studies found that only morbidly obese patients have a higher risk of major complications or mortality after general surgical procedures and major intra-abdominal oncological resections. A low risk was observed for moderately obese patients.[17] BMI has not been found to be a risk factor for complications of mortality in patients operated for esophageal cancer or lung cancer.[23–25]

Several studies have indicated a higher risk for postoperative complications and death in malnourished patients.[3,14,17,26] Although all patients in our study received intensive nutritional support during induction treatment, the percentage of malnourished patients at time of surgery was 39% compared with 24% at baseline, indicative of the toxicity of induction treatment with CRT. Malnutrition measured at different phases of the treatment, however, was not associated with outcome in terms of postoperative complications or mortality. This is in line with previous studies showing that nutritional support in malnourished surgical patients, as was given in our study group, reduces postoperative morbidity and mortality.[5,14] Our study shows that in general, surgery can be performed safely after CRT despite worsening of the nutritional status during induction treatment, provided that patients receive adequate nutritional support throughout the treatment period.

Next to the observation that weight loss ≥5% during induction period predicted for shorter OS, a remarkable finding was that especially the combination of overweight and weight loss ≥5% during induction treatment predicted for both poor OS and PFS, suggesting that the development of malnutrition during induction CRT in overweight patients impairs not only surgical outcome but also long-term oncological outcome. Therefore, the nutritional status of (overweight) patients treated with CRT and surgery for NSCLC should be monitored throughout the entire treatment period and not only at the start of the treatment.

Obesity leads to central fat deposition, disordered energy use by cell mitochondria, especially in muscle and liver, and malfunctioning immune, coagulation, endothelial, and other systems.[27] Patients with a high BMI, experiencing undesired weight loss, might also develop malnutrition. However, little is known about the consequences of malnutrition on body composition in obesity. Probably the relatively low fat-free mass in obese patients might result in altered metabolic pathways, which might influence the response to surgery after CRT and the hosts' immune response to the malignant tumor. In daily practice, recognition of malnutrition in patients with overweight, who do not appear to be malnourished at first sight, rarely takes place. Therefore, recognition by regular weighing during the induction period and treatment of malnutrition in patients with overweight or obesity may be beneficial.

The main limitation of this study is a small, selected study population. The toxicity of trimodality treatment makes careful patient selection imperative. As a result, statistical power is low and the importance of other risk factors might have been overlooked.

In conclusion, this study, focusing on the significance of nutritional status in stage III NSCLC patients undergoing trimodality treatment did not identify predicting factors for general postoperative complications. Despite nutritional support throughout the treatment period, especially overweight patients (BMI ≥25) who suffered from weight loss ≥5% during induction treatment had a significantly shorter OS and PFS. These findings indicate that (mal)nutrition during aggressive trimodality treatment is an important factor with potentially negative impact on outcomes in stage III NSCLC, not only in underweight patients but also in those with overweight at initial diagnosis.

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