

Tumor volume combined with number of positive lymph node stations is a more important prognostic factor than TNM stage for survival of Non-small cell lung cancer patients treated with (chemo)radiotherapy

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CONFLICT OF INTEREST NOTIFICATION

No actual or potential conflicts of interest.

ABSTRACT

Purpose: The current TNM system needs refinement in order to improve its ability to predict survival of non-small cell lung cancer (NSCLC) patients treated with (chemo)radiation. In this study we investigated the prognostic value of tumor volume and N-status, assessed by FDG-PET scans.

Patients and Methods: Clinical data from 270 consecutive inoperable NSCLC patients, stage I-IIIb, treated radically with (chemo)radiation was collected retrospectively. Diagnostic imaging was performed either with an integrated PET-CT or with CT-scan and PET-scan separately. The Kaplan-Meier method as well as Cox regression were used to analyse the data.

Results: Univariate survival analysis showed that number of positive lymph node stations (PLNSs) as well as N-stage on PET-scan were significantly associated with survival. The final multivariate Cox model consisted of the number of PLNSs, gross tumor volume (i.e. volume of the primary plus lymph nodes) , gender, World Health Organization (WHO) performance status and equivalent radiation dose corrected for time ($EQD_{2,T}$); N-stage was no longer significant.

Conclusions: The number of PLNSs, assessed by FDG-PET scans, was a significant factor for survival of patients with inoperable NSCLC treated with (chemo)radiation. Risk stratification for this group of patients should be based on gross tumor volume, number of PLNSs, gender, WHO-performance status and $EQD_{2,T}$.

INTRODUCTION

It is widely recognized that the tumor, node, metastasis (TNM) staging system has its shortcomings when used for risk stratification of patients with non-small-cell lung cancer (NSCLC) treated with radiotherapy. The staging system, developed by Mountain [1], is primarily based on resectability of the tumor.

Tumor size is taken into account only partially. However, technical and medical progress have led to an improvement in nonsurgical treatment options, thereby changing the marginal role of radiotherapy and chemotherapy for the survival of NSCLC patients into one of significant importance. Identification of prognostic factors for this specific patient population is needed.

At present, generally accepted prognostic factors for patients with inoperable disease are performance status (PS) [2-4], weight loss [2-4], presence of comorbidity [5,6], use of chemotherapy in addition to radiotherapy [2,7] radiation dose [2,8] and tumor size [9-12]. For other factors such as gender and age the literature shows inconsistent results, making it impossible to draw definitive conclusions [3].

In these studies computed tomographic (CT) scans were used as the major staging tool. Since then, the introduction of fluorodeoxyglucose (FDG)-positron emission tomography (PET) has led to significant improvements in the detection of positive lymph nodes and distant metastases, leading to stage migration [13]. In a recent study, comparing PET-based or non-PET based TNM stage, PET staging was the best predictor for overall survival [14]. However, because the study population was very heterogeneous, it was not possible to draw any

conclusions for patients treated with (chemo)radiotherapy. For patients treated with surgery, number of pathologically positive lymph node stations (PLNSs) also was shown to be a predictive factor for survival [15]. All this taken into account, we hypothesized that the gross tumor volume (GTV), the volume of the primary tumor and the lymph nodes, as well as the number of involved nodal areas quantified by means of PET, would have a prognostic value for survival in patients with inoperable NSCLC, treated radically with (chemo)radiation. We therefore decided to investigate the prognostic value of stage, GTV and number of PLNSs for the survival of patients with inoperable NSCLC treated radically with (chemo)radiation, by using information from FDG-PET-scans and taking into account other known prognostic factors.

METHODS AND MATERIALS

Patient population

From January 2002 to December 2005 a total of 312 patients with inoperable NSCLC, stage I-IIIb, were referred to MAASTRO clinic to be treated with curative intent. Clinical data for these patients were collected retrospectively by reviewing the clinical charts. If PET was not used as staging tool, patients were excluded from the study. This resulted in the inclusion of 270 patients. The primary gross tumor volume (GTV_{primary}) and nodal gross tumor volume (GTV_{nodal}) were calculated, as delineated by the treating radiation oncologist, using a commercial radiotherapy treatment planning system (Computerized Medical Systems, Inc, St. Louis, MO). The sum of GTV_{primary} and GTV_{nodal} resulted in the GTV. For patients

treated by means of sequential chemotherapy, these volumes were calculated using postchemotherapy imaging information. Creation of volumes was based on information from PET and CT only; bronchoscopic findings were not taken into account. The number of PLNSs was assessed by the nuclear medicine specialist using either an integrated FDG-PET-CT scan or a CT-scan combined with FDG-PET-scan. T-stage and N-stage were assessed using pre-treatment CT, PET and mediastinoscopy, when applicable. For patients treated with sequential chemotherapy stage as well as number of PLNSs were assessed by using prechemotherapy imaging information.

Radiotherapy treatment

All patients were treated at MAASTRO clinic. No elective nodal irradiation was performed [16,17] and irradiation was delivered 5 days/week. Radiotherapy planning was performed using a Focus (Computerized Medical Systems, Inc.) system, taking into account lung density and according to ICRU 50 guidelines [18].

Three different radiotherapy treatment regimes were applied.

1) Forty-two patients were included in a Phase I dose-escalation study. They received a total radiation dose ranging from 61.2 to 68.4 Gy, delivered twice daily in fractions of 1.8 Gy. An 8-hour interval between fractions was respected.

2) The second group consisted of 191 patients, who were treated according to the standard protocol, used until May 2005. They received either 70 Gy (stage I-II) or 60 Gy (stage III), in daily fractions of 2 Gy.

3) Finally, 37 patients were treated according to the new standard protocol which was introduced in June 2005. The radiation dose ranged from 54.0 to 79.2 Gy, delivered in fractions of 1.8 Gy, twice daily, depending on the mean lung dose or the spinal cord dose constraint. An 8-hour interval between fractions was respected.

The equivalent dose in 2-Gy fractions, corrected for overall treatment time (EQD_{2,T}) was used as a measure for the intensity of chest radiotherapy [19].

Adjustment for dose/fraction and time factors were made as follows:

$$\text{EQD}_{2,T} = D * \left(\frac{d + \alpha/\beta}{2 + \alpha/\beta} \right) - \gamma * (T - Tk)$$

where D = the total radiation dose, d = dose per fraction, $\alpha/\beta = 10$ Gy, T = overall treatment time, Tk (accelerated repopulation kick-off time) = 28 days, and γ (the loss in dose per day due to repopulation) = 0.66 Gy/day.

Chemotherapy

One hundred fifty-one patients received chemotherapy before radiotherapy treatment started. The regimen consisted of carboplatin (AUC 5) on day 1 and gemcitabine 1250 mg/m² on day 1 and 8. The majority of the patients received 3 cycles (range, one to six cycles). No concurrent chemo-radiation was used.

Statistical analysis

Survival status was evaluated in December 2006. Overall survival was calculated from the start of radiotherapy. The Kaplan-Meier method was used for univariate survival analysis. Groups were compared using the log-rank test for trend. The Cox proportional hazards model was applied to perform multivariate analysis. Variables were considered statistically significant if the likelihood ratio test resulted in a p-value <0.05. A stepwise backward method was used to select a relevant set of predictors. In addition, interaction terms were tested. The Cox proportional hazards assumption was tested by adding time-dependent covariates to the model. Hazard ratios and the 95% confidence intervals (CIs) were reported. The concordance index (Harrell's C) was used to assess the performance of the models. The interpretation of the concordance index is similar to the interpretation of the area under the curve (AUC) of the receiver operator curve (ROC) and can be applied to Cox regression models. The maximum value of the concordance index is 1.0; indicating a perfect prediction model. A value of 0.5 indicates that patients are correctly classified in 50% of the cases, e.g. as good as chance. Bootstrapping techniques were used to validate the model, that is, to adjust the estimated model performance for overoptimism or overfitting [20,21]. The concordance index of the final multivariate model, corrected for optimism, was reported. In addition, Akaike's information criterion (AIC) was calculated [22]. The AIC takes into account how well the model fits the data as well as the complexity of a model, thereby reducing the risk of overfitting. The preferred model is the one with the lowest AIC value. To assess the relative merits of a model compared with others, the difference is interpreted as follows: a

decrease by 4-7 indicates weak support, ≥ 10 indicates strong support for a model. For the multivariate analyses, we imputed the mean value of a variable if the value was missing. Logarithmic transformation was applied to obtain more symmetrically distributed data for the GTV, GTV_{primary} and GTV_{nodal} . Statistical tests were performed using SPSS version 15.0 (SPSS inc., Chicago, IL) and R (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Univariate analysis

Table 1 lists characteristics of the study population. At the time of analysis, 64 patients were still alive. The median follow-up of surviving patients was 29 months (range 11-55). The median survival was 15 months (95% CI: 13 - 17 months), with a 2-year survival of 36% (95% CI: 24%-48%) for stage I, 29% (95% CI: 10%-48%) for stage II, 24% (95% CI: 14%-34%) for stage IIIA and 31% (95% CI: 22%-40%) for stage IIIB. Differences among stage groups were not significant. The number of PLNSs assessed by PET was split into 3 subgroups: (1) no PLNS, (2) 1-2 PLNSs, (3) ≥ 3 PLNSs. Survival of patients in the three lymph node groups showed a statistically significant difference ($p \leq 0.001$; Fig. 1A). Clinical N-stage was also split into three subgroups: (1) N0, (2) N1-N2, (3) N3. The grouping of N1 with N2 was caused by the small number of patients with an N1 stage. Survival, shown in Fig. 1B, shows a significant difference between the groups ($p= 0.014$). The influence of GTV, GTV_{primary} and GTV_{nodal} on survival was assessed using univariate Cox regression. GTV and GTV_{primary} were

statistically significant factors, but GTV_{nodal} was not ($p < 0.001$, $p < 0.001$ and $p = 0.107$ respectively).

Multivariate analysis

The initial multivariate model consisted of age, gender, weight loss, WHO performance status (PS), Charlson's comorbidity index, clinical overall stage, T stage, N stage, number of PLNSs, GTV, $EQD_{2,T}$ and chemotherapy. After the stepwise backward selection procedure the final model consisted of gender, $EQD_{2,T}$, GTV, PLNSs and WHO-PS (Table 2). N-stage was removed from the model, but PLNSs remained a statistically significant predictor for survival with a hazard ratio of 1.51 (95% CI: 1.09 - 2.09) and 1.95 (95% CI: 1.34 - 2.85) for the groups with one or two and three or more positive lymph node stations compared to the group with no positive lymph node stations, respectively. The concordance index of the final model was 0.68. After the bootstrap procedure the concordance index, corrected for optimism, was 0.67. To investigate the difference between the prognostic value of stage, T stage and N stage, tumor volume and PLNSs three multivariate analyses were performed, each consisting of gender, WHO PS, and $EQD_{2,T}$, and only one of the following combinations (1) stage, (2) T stage and N stage, (3) GTV and PLNSs. The concordance indices as well as the AIC showed a benefit for the model with PLNSs and GTV (Table 2.). Finally, the coefficients of the Cox regression model were used to create a probability graph for 2-year survival, taking into account GTV, PLNSs and gender (Figure 2A and 2B). The WHO-PS as well as the $EQD_{2,T}$ were kept constant; the WHO-PS was

assumed to be 1 (median value of the population) and the $EQD_{2,T}$ was greater than 55 Gy.

DISCUSSION

To our knowledge, this is the first study investigating the prognostic value of number of PLNSs, by using PET-CT information for patients with inoperable NSCLC. Our results show that information from FDG-PET scans offers the possibility to use new prognostic factors such as number of PLNSs. Furthermore, we show that risk stratification should be based on multiple factors including WHO PS, gender, $EQD_{2,T}$, number of PLNSs, and GTV.

Risk stratification based on TNM stage has shown to be useful to predict survival for the entire NSCLC population [1,23], whereas for the radiotherapy population, treated with curative intent, results are disappointing [8,24,25]. Two studies found that T stage and N stage were not statistically significant predictors for survival in patients with inoperable disease treated with radiotherapy [10,11]. One of these studies investigated the influence of overall stage, which also was not significant¹¹. In a recursive partitioning analysis of 1999 patients Werner-Wasik [26] identified five prognostic groups which differed with regard to survival, using performance scale, chemotherapy, pleural effusion, age and histologic state. Staging information was not included in the final model, because T stage, as well as N stage was not statistically significant. Bradley et al [9] concluded that T stage was a predictor for survival whereas overall stage and N stage were not. However, 75% of their patients had stage T1 or T2. In this case, tumor size is

reflected in the staging system, which might explain why T stage was found to be statistically significant. All studies mentioned above showed that variables based on overall stage were of limited predictive value for survival of patients with inoperable NSCLC treated with radical (chemo)radiation.

In all previous series, CT was used for staging, whereas at present, FDG-PET scan is considered the best noninvasive tool to detect distant metastasis other than brain, and is superior to CT scan for staging of the mediastinum [13]. In our study, on purpose, we selected patients who were PET-staged. Although this certainly lead to a better selection of patients eligible for radical (chemo)radiotherapy treatment, N stage as a predictor of survival for this specific group did not improve the multivariate analysis.

Although there are no randomized data, retrospective studies suggest that a higher radiation dose led to improved local control and better survival rates [3,8]. Our results are in line with this, showing a survival benefit for patients receiving higher doses of radiation therapy.

Until now the prognostic value of the number of PLNSs was assessed only in surgical series, where pathological examination of lymph nodes was possible [27,28]. Our study shows that number of PLNSs on FDG-PET is also an important risk factor for patients with inoperable disease. However, we are aware that FDG uptake in mediastinal lymph nodes may be caused by conditions other than cancer, such as inflammation or anthraco-silicosis. In our hands, and in our patient population, false positive FDG-PET scans were observed in 12% of patients [29]. This should be taken into account when interpreting our results.

Several groups concluded that the primary tumor volume was a highly significant factor for the prediction of survival [9,11,12]. In addition, Basaki et al [11] found that total tumor volume (primary tumor + nodal volume) and primary tumor volume were significant predictors for, but nodal volume had no independent effect on, survival. Our results led to the same conclusions.

Theoretically, it is possible that the number of PLNSs correlates with lymph node volume and thus the effect of number of PLNSs on survival might be caused by lymph node volume. We therefore checked the influence of nodal volume on survival by performing univariate Cox regression, which led to the conclusion that GTV_{nodal} was statistically not significant.

In agreement with the literature, where performance scale, regardless of resectability of the tumor, consistently was identified as an important predictor for survival [3,4,8], we found that worse performance is associated with shorter survival.

The variety of definitions used for the assessment of weight loss obviously does not conceal its prognostic importance for survival [3,8,30]. However, our final model did not include weight loss, which can be explained by the fact that the majority of waspatients had no or limited weight loss.

The presence of severe comorbidity was associated with a worse survival [5,6]. Although comorbidities were present in a large group of our study population, the final model did not include this factor. It can be assumed that comorbidities, especially chronic obstructive pulmonary disease (COPD), can lead to a higher score on the WHO PS, which was included in the final multivariate analysis.

Moreover, we included a large group of potential predictive factors, while other groups limited their multivariate analyses to a few variables[5] or did not include performance status [6].

There are indications that female gender is a favorable factor for survival [2,23,31,32], whereas several studies that consisted of patients treated with (chemo)radiation showed no influence of gender [26,33]. Gender was statistically significant in our multivariate analysis; the hazard ratio for female patients was 0.45 (95% CI: 0.31 - 0.66).

Several other studies showed that the maximum standardized uptake value (SUV) of FDG is a prognostic factor for survival [34-36]. In the present series, we could not use the SUV because PET was performed in different hospitals in which, at the time, no standardization between centers was done. Moreover, in most radiation oncology centers, PET scans are used that are not standardized for SUV measurements from patients referred from different hospitals, making our results widely applicable.

We did not incorporate tumor volume assessed by using PET in this study.

Although the primary lung tumor volume, assessed by means of PET, was validated with pathologic evaluation [37], this is not the case for the nodal tumor volume. Instead, we used CT volumes which are also used in standard clinical care.

CONCLUSIONS

In this study, we show that the best prediction for survival of patients with inoperable NSCLC treated with radical (chemo)-radiation is based on GTV, number of PLNSs, gender, WHO PS and EQD_{2,T}. Substitution of tumor volume and number of positive lymph node stations by T, N, or overall stage decreased the performance of the multivariate model, thereby emphasizing the limited predictive value of the TNM stage for this specific group of patients.

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Table 1. Patient characteristics (n=270)

Male/female	210 / 60
Age	36-90 years (mean, 69 years)
WHO-PS: 0 / 1 / 2 / 3 / 4	85 / 142 / 33 / 3 / 0
CCI: 0 / 1 / 2 / 3 / 4 / 5	87 / 86 / 54 / 22 / 9 / 3
weight loss: <10% / ≥10%	173 / 32
FEV1 (%)	17-139 (mean, 70%)
SCC/adenoca/large/other/no histology	98 / 38 / 91 / 9 / 34
clinical stage I / II / IIIA / IIIB	66 / 21 / 68 / 112
T-stage: T1 / T2 / T3 / T4 / Tx	53 / 105 / 31 / 78 / 2
N-stage: N0 / N1 / N2 / N3 / Nx	107 / 14 / 93 / 49 / 4
GTV _{primary} (cc)	mean 93 (SD, 99)
GTV _{nodal} (cc)	mean 32 (SD, 42)
positive nodal stations (0 / 1-2 / ≥ 3)	127 / 90 / 53
EQD _{2,T} (Gy)	mean 55.8 (SD, 6.6)
overall treatment time (days)	mean 37 (SD, 9)
fractionation (once/twice daily)	195 / 75
chemotherapy (no/sequential)	119 / 151

Abbreviations: WHO-PS= world health organization - performance scale;

CCI= Charlson comorbidity index; FEV1 = forced expiratory volume in 1s;

SCC = squamous cell carcinoma; EQD_{2,T} = equivalent radiation dose at 2 Gy,

corrected for time

Table 2. Multivariate cox regression models

Model	Variable	Hazard Ratio	95% CI	p	AIC	Harrell's C
Model 1 (final)	gender				1965.8	0.68
	male	1 (ref)				
	female	0.45	0.31 - 0.66	<0.001		
	WHO-PS					
	0	1 (ref)				
	1	1.53	1.10 - 2.11	0.01		
	≥ 2	1.84	1.19 - 2.85	0.006		
	PLNS					
	0	1 (ref)				
	1-2	1.51	1.09 - 2.09	0.014		
	≥ 3	1.95	1.34 - 2.85	0.001		
	EQD _{2,T}					
	≤ 55	1 (ref)				

	> 55	0.70	0.51	-	0.96	0.025		
	ln GTV (cc)	1.49	1.26	-	1.75	<0.001		
Model 2	gender, WHO-PS, EQD _{2,T} , T-stage, N-stage						1989.9	0.65
Model 3	gender, WHO-PS, EQD _{2,T} , overall stage						2001.2	0.62

abbreviations: WHO-PS=World Health Organisation performance scale, PLNS= number of positive lymph node stations; EQD_{2,T} = equivalent dose (2 Gy) corrected for time; ln= natural logarithm; GTV = gross tumor volume; AIC= Akaike's information criterion; Harrell's C= Harrell's concordance index

Figure 1. Overall survival according to

A. The number of positive lymph node stations on FDG-PET scan: no, 1-2 and ≥ 3 .

B. N-stage

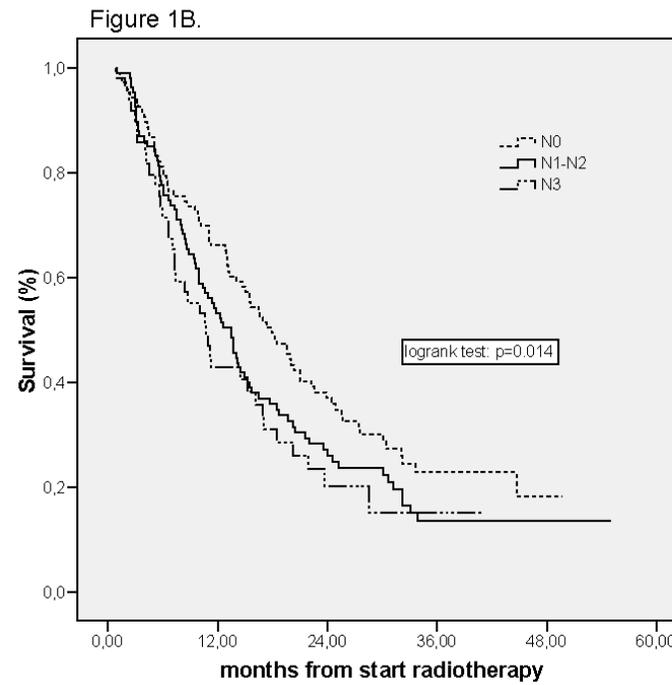
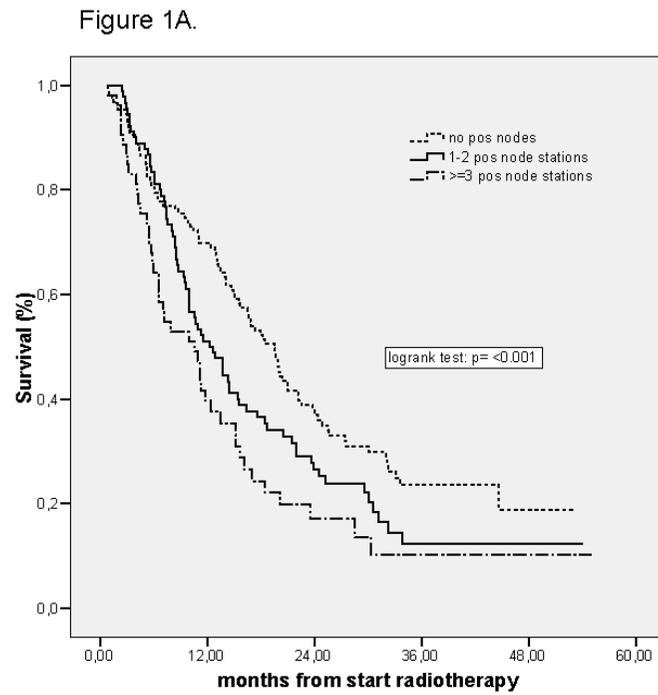


Figure 2. Predicted probability for 2-year survival based on the multivariate Cox regression model. Patients received a high equivalent radiation dose, at 2 Gy, corrected for time (> 55 Gy) and WHO-performance score was 1 (median value of the population). The natural logarithm (ln) of the GTV was used.

A. males B. females

Figure 2A.

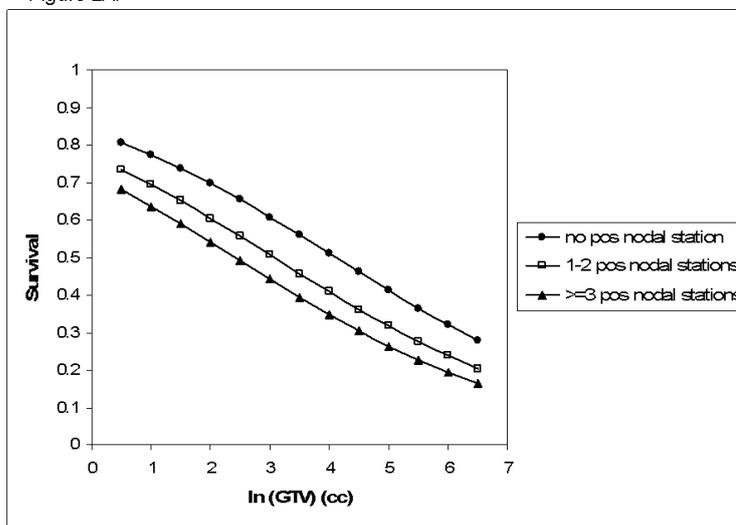


Figure 2B.

