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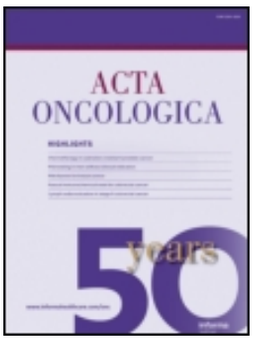

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ORIGINAL ARTICLE

Prediction of residual metabolic activity after treatment in NSCLC patients

EMMANUEL RIOS VELAZQUEZ, HUGO J. W. L. AERTS, CARY OBERIJE, DIRK DE RUYSSCHER & PHILIPPE LAMBIN

Department of Radiation Oncology (MAASTRO), GROW- School for Oncology and Developmental Biology, Maastricht University Medical Center (MUMC+), Maastricht, The Netherlands

Abstract

Purpose. Metabolic response assessment is often used as a surrogate of local failure and survival. Early identification of patients with residual metabolic activity is essential as this enables selection of patients who could potentially benefit from additional therapy. We report on the development of a pre-treatment prediction model for metabolic response using patient, tumor and treatment factors. *Methods*. One hundred and one patients with inoperable NSCLC (stage I-IV), treated with 3D conformal radical (chemo)-radiotherapy were retrospectively included in this study. All patients received a pre and post-radiotherapy fluorodeoxyglucose positron emission tomography-computed tomography FDG-PET-CT scan. The electronic medical record system and the medical patient charts were reviewed to obtain demographic, clinical, tumor and treatment data. Primary outcome measure was examined using a metabolic response assessment on a post-radiotherapy FDG-PET-CT scan. Radiotherapy was delivered in fractions of 1.8 Gy, twice a day, with a median prescribed dose of 60 Gy. *Results*. Overall survival was worse in patients with residual metabolic active areas compared with the patients with a complete metabolic response ($p=0.0001$). In univariate analysis, three variables were significantly associated with residual disease: larger primary gross tumor volume ($GTV_{primary}$, $p=0.002$), higher pre-treatment maximum standardized uptake value (SUV_{max}, $p=0.0005$) in the primary tumor and shorter overall treatment time (OTT, $p=0.046$). A multivariate model including $GTV_{primary}$, SUV_{max}, equivalent radiation dose at 2 Gy corrected for time ($EQD_{2,T}$) and OTT yielded an area under the curve assessed by the leave-one-out cross validation of 0.71 (95% CI, 0.65–0.76). *Conclusion*. Our results confirmed the validity of metabolic response assessment as a surrogate of survival. We developed a multivariate model that is able to identify patients at risk of residual disease. These patients may benefit from an individualized and more adequate therapeutic approach, thereby improving local control and survival.

Lung cancer is an important cause of cancer-related deaths worldwide [1]. In 2008, lung cancer was the most common cause of death from cancer with an estimate of 342 000 deaths in Europe [1]. Non-small cell lung cancer (NSCLC) accounts for at least 80% of all lung cancer cases [2]. The majority of these NSCLC patients present advanced-stage disease (stage III and IV), which are considered inoperable [3]. For these patients, the combination of radiotherapy and chemotherapy shows improved treatment outcome [4,5], however local tumor failure is still observed in approximately 70% of patients [6]. Therefore early identification of patients with a high risk of local treatment failure is important, as these patients may potentially benefit from additional therapy. One method of investigating local treatment failure, is assessing metabolic response within the primary tumor after treatment with ^{18}Fluorodeoxyglucose (FDG) positron emission tomography (PET) imaging [7]. Several studies indicated that patients with metabolically active residual masses after treatment have a poorer prognosis compared to patients without residual metabolic activity [8,9]. Although, other studies have shown that FDG uptake before treatment is prognostic for residual metabolic activity within the tumor [9–11], other pre-treatment clinical factors were not investigated for their prognostic capability. Therefore, we hypothesize that also other

Correspondence: Emmanuel Rios Velazquez, Department of Radiation Oncology, (MAASTRO), Maastricht University Medical Center, Maastricht, The Netherlands and Maastro Clinic, Dr. Tanslaan 12, 6229 ET Maastricht, The Netherlands. Tel: +31 43 3882909. Fax: +31 43 3884540. E-mail: emmanuel.rios@maastro.nl

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pre-treatment factors, including demographic, tumor and treatment characteristics, can have prognostic value for predicting metabolic response after treatment. In the present study we examined the association between commonly used prognostic factors in NSCLC patients and metabolic response after treatment in a univariate and multivariate analysis.

Materials and methods

Patient characteristics

The electronic medical record system and the medical patient charts were retrospectively reviewed to obtain demographic, clinical, tumor and treatment data. One hundred and one patients (40 women and 61 men) with inoperable non-small cell lung cancer (NSCLC), stage I-IV, were included in this study. Their age ranged from 43 to 86 years (mean: 65.6 years). All patients were treated with curative intent at MAASTRO Clinic with sequential chemo-radiotherapy (82 patients) or with radical radiotherapy alone (19 patients) between December 2004 and September 2007. All patients received a pre and post-treatment FDG-PET-CT scan. For patients receiving sequential chemo-radiotherapy the pre-treatment scan was performed after chemotherapy. The average time interval between the last radiotherapy and the second FDG-PET-CT scan was 99 days (range: 49–184 days). No treatment was given between the end of radiotherapy and the post-treatment scan.

FDG-PET-CT Imaging

Pre and post-treatment FDG-PET-CT scans were performed using a Siemens Biograph (Siemens, Knoxville, TN). All patients were instructed to fast at least six hours before the intravenous administration of FDG (Tyco Health Care, Amsterdam, The Netherlands), followed by physiologic saline (10 ml). The total injected activity of FDG was dependent on the patient weight: (weight*4) + 20 Mbq. After a period of 45 minutes, during which the patient was encouraged to rest, PET and CT imaging were performed [12].

Treatment characteristics

The radiotherapy treatment was delivered in fractions of 1.8 Gy, twice a day, with a mean lung dose (MLD) restricted to 19 Gy and a maximal allowed total tumor dose (TTD) of 79.2 Gy [12]. Patients with stage III disease, who where physically fit enough received sequential chemo-radiotherapy, consisting of three courses of gemcitabine in combination with cisplatin or carboplatin, followed by radiotherapy as described for stage I/II. No concurrent chemo-radiotherapy was given. The biologic equivalent dose was used as indication of the intensity of chest RT delivered to the tumor and was calculated using the quadratic model [13] and corrected for overall treatment time.

Metabolic response

Metabolic response was assessed for all patients with a FGD-PET-CT scan after treatment. Residual disease was defined as residual metabolic activity within the primary tumor, i.e. areas with FDG uptake higher than in the aortic arch ($SUV > SUV_{AORTA}$) [7,8]. If there was no activity within the tumor, patients were defined as with a complete metabolic response [10]. Survival data were obtained by reviewing the Dutch Communal Data register. Survival time was defined as the date from the start of radiotherapy until the date of death or last follow-up. Survival status could not be retrieved for one patient.

Statistical analysis

All data are expressed as means $\pm$ SD. Because the distribution of the continuous variables was rather skewed, the Mann-Whitney U test was used to determine statistical differences between the patients with and without residual disease. For categorical variables the χ^2 test was used. Differences were considered to be significant when the p-value was lower than 0.05. The area under the curve (AUC) of the receiver operating characteristic (ROC), a plot of the true positive rate (correctly classified positive samples) and false positive rate (incorrectly classified negative samples) was used to analyze the association between the variables and residual disease in univariate analysis using a proximal-support vector machine (p-SVM) [14]. A p-SVM was also used to build a multivariate prediction model, using metabolic residual disease as outcome measure. Combinatorial feature selection was performed to obtain an optimal subset of features. The set of variables with the highest AUC of the ROC curve was included in the multivariate predictive model. The Kaplan-Meier method was used to estimate survival probabilities and statistical differences were assessed using the log-rank test. Data were considered right-censored if patients were alive at the time of last follow-up. All the analyses were performed in Matlab 2008b (The MathWorks Inc, Natick, MA, USA) and SPSS (Version 15.0 for Windows, Chicago, IL).

Results

Patients characteristics

To assess the power of clinical parameters for the prediction of metabolic response, commonly known

prognostic factors were collected before treatment and correlated with metabolic response after treatment. A total of 101 NSCLC patients were included in this analysis, of which 56 (55%) patients showed persistent residual FDG uptake on the post-radiotherapy CT-PET scan and 45 (45%) patients had a complete metabolic response (CMR) indicating no residual FDG uptake within the tumor post-radiotherapy. Patient, tumor and treatment characteristics for both groups are listed in Table I. The median follow-up duration was 23.9 months (range: 3.8–55.5 months). The patients with residual active areas post-treatment had a significantly worse survival (median survival: 13.4 months) compared to patients with a complete metabolic response (median survival not reached) (Figure 1; 95% CI, 38.9–49.8 months, p=0.0001). The hazard ratio for death for patients with residual areas compared to individuals without was 3.701 (95% confidence interval: 1.92 to 7.13; p=0.0001 by the log-rank test, two-sided).

Univariate analysis

To assess the association between patient, tumor and treatment characteristics with post-radiotherapy outcome, a univariate analysis was performed. The area under the ROC curve of a univariate model for each parameter was estimated. These results are summarized in Table I. The volume of the primary tumor ($GTV_{primary}$), maximum FDG uptake and OTT had the highest predictive power, while other commonly used predictors such as FEV_1, WHO-performance status or clinical stage showed a low predictive ability. $GTV_{primary}$ was significantly higher for patients with residual areas than for patients with a complete metabolic response (103 cm^3 ± 126.13 cm^3 vs. 48.3 cm^3 ± 55.5 cm^3, p = 0.008). Similarly, the maximum FDG uptake on the pre-RT scan was significantly higher for patients with residual disease compared to patients with a complete metabolic response (10.5 ± 5 vs. 7.7 ± 5.2, p = 0.007). The overall treatment time (OTT) was longer for patients with a complete metabolic response in comparison with patients with residual disease (27 ± 6 days vs. 24 ± 5 days, p = 0.013).

Kaplan-Meier survival curves for subgroups determined by the median for selected variables are shown in Figure 2. Survival was significantly higher for patients with a tumor volume smaller than the median ($GTV_{primary}$= 46.6 cm^3) (p=0.001). In patients with a SUV_{max} higher than the median (SUV_{max} = 8.4) in the pre-treatment scan, survival was significantly shorter, compared to patients with a SUV_{max} lower than the median (p=0.040). Significant differences in survival were also observed for OTT, with a more prolonged survival for patients with a treatment time longer than the median of 25

Table I. Patient characteristics and their association with post-RT outcome in univariate analysis. Comparison of groups with residual disease and with complete metabolic response.

Variable	Residual disease (n = 56)	Complete metabolic response (n = 45)	p*	AUC
Age, years				
Mean	65	65	0.907	0.54
SD	10.6	7.5		
Gender				
Female	21 (38)	19 (42)	0.480	0.54
Male	35 (62)	26 (58)		
Stage				
I	8 (14)	7 (16)	0.882	0.54
II	1 (2)	1 (2)		
IIIA	13 (23)	9 (20)		
IIIB	33 (59)	28 (62)		
IV	1 (2)			
Histology				
SCC	17 (30)	7 (16)	0.327	0.54
Adenocarcinoma	9 (16)	11 (24)		0.56
Large cell	20 (36)	17 (38)		0.54
NSCLC, NOS	10 (18)	10 (22)		0.47
FEV 1				
Mean	75.3	72.2	0.454	0.52
SD	16.8	22.5		
WHO-PS				
0	15 (27)	14 (31)	0.468	0.54
1	32 (57)	24 (53)		
≥ 2	9 (16)	7 (16)		
$GTV_{primary}$ (cm^3)				
Mean	103.0	48.3	0.008	0.62
SD	126.13	55.5		
GTV_{nodal} (cm^3)				
Mean	24.9	34.4	0.368	0.54
SD	37.3	66.5		
Tumor load (cm^3)				
Mean	127.8	82.2	0.047	0.60
SD	124.6	97.5		
Chemotherapy				
Yes	45 (80)	37 (82)	0.813	0.54
No	11 (20)	8 (18)		
PLNS				
0	12 (21)	12 (27)	0.929	0.54
1	13 (23)	12 (27)		
2	22 (39)	11 (24)		
3	6 (11)	4 (9)		
≥ 4	3 (5)	6 (13)		
SUV_{max}				
Mean	10.5	7.7	0.007	0.64
SD	5.0	5.2		
OTT (days)				
Mean	24	27	0.013	0.60
SD	5	6		
$EQD_{2,T}$ (Gy)				
Mean	60.6	62.0	0.468	0.47
SD	9.5	9.2		
Prescribed TTD (Gy)				
Mean	61.0	61.5	0.809	0.54
SD	10.7	11.1		

Abbreviations: TTD = Total tumor dose; OTT = Overall Treatment Time; SUV_{max} = Standardized Uptake Value; $EQD_{2,T}$ = Equivalent radiation dose at 2 Gy corrected for time; FEV_1 = Forced expiratory volume in 1 s; SCC = Squamous cell carcinoma; NOS = Not specified otherwise; WHO-PS = World Health Organization-performance status; PLNS = Positive lymph node stations.

*Comparison between residual disease group vs. complete metabolic response group for variables. The Mann-Whitney U test was used for continuous variables and the Chi-square test for categorical variables.

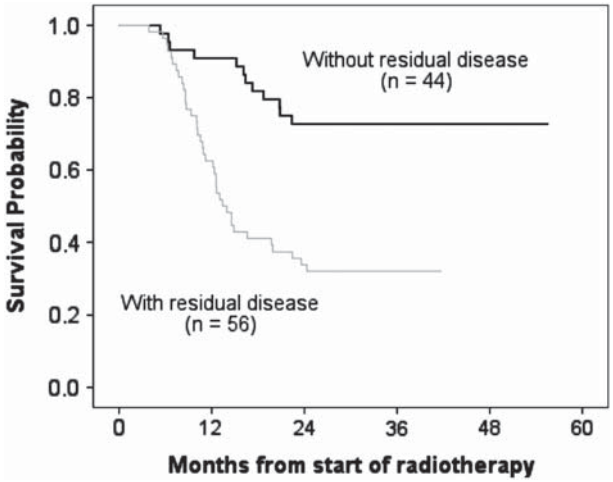

Figure 1. Kaplan-Meier estimates of overall survival of patients with residual metabolically active areas and with complete metabolic response on the post-radiotherapy PET-CT scan. Patients with residual metabolically active areas had significantly worse survival (p = 0.0001).

days (p=0.042). Survival differences in patients stratified according to TNM stage, were statistically not significant (p=0.266). The same result was obtained for age. Older patients did not have different survival compared to younger patients (p=0.998). Higher equivalent radiation dose was associated with better survival, however the difference was not statistically significant (p=0.056).

Multivariate analysis

For the multivariate analysis, all the available variables were subjected to a combinatorial feature selection procedure. The combination with the highest AUC assessed by the leave-one-out cross validation approach was selected for the multivariate model. The variables included in the final multivariate p-SVM model were $GTV_{primary}$, maximum standardized FDG uptake, OTT and equivalent dose corrected for treatment time ($EQD_{2,T}$). Addition of other parameters to this model did not improve its performance. The area under the curve of the final predictive model was 0.71 (95% CI, 0.65–0.76; Figure 3). The variables included in the multivariate model showed also a significant association with the post-radiotherapy outcome in univariate analysis.

Discussion

In this study we investigated the relationship of clinical parameters, including demographic, tumor and treatment characteristics, with metabolic response post-treatment. Our primary endpoint was defined as residual metabolic disease on a post-treatment PET-CT scan. Previous studies have shown that patients with residual metabolically active areas after treatment have a poorer prognosis compared with patients without [10,15,16]. In agreement with these studies, also our results showed that patients with residual disease had a significantly worse survival (p=0.0001), compared to patients with a complete metabolic response, thus supporting the importance of our primary endpoint as surrogate for survival.

Previous studies examined the value of pre-treatment FDG-PET alone to determine treatment response after radiotherapy [17] and chemotherapy [18]. In our study, we explored not only the prognostic capability of FDG-PET but also the additional value of other clinico-pathological prognostic factors. Some of them, i.e. age, gender, tumor size, WHO performance status have been included in predictive models for survival in NSCLC patients [19–21]. In a retrospective study with a large patient population of NSCLC patients (stage I and II) which received resection with curative intent, Agarwal et al., reported that age and gender, tumor volume and type of surgery were important for the prediction of survival [22]. However, we did not find a significant association between age and metabolic response. Similarly, other studies have shown a relation between female gender and a favorable outcome [23]. We did not find a significant difference based on gender between responders and non-responders.

WHO performance status and FEV_1, have been cited as predictors of survival [19,21], in which worse performance status and impaired lung function measurements are associated with shorter survival. We could not identify an association between these parameters and the post-treatment outcome. Although the tumor-node-metastasis (TNM) staging system is an important tool to estimate prognosis and choose the best treatment modality, several studies have reported that TNM has a poor predictive capability for survival in NSCLC patients [24]. In our cohort, the majority of patients were diagnosed with stage IIIA (22%) and IIIB (61%) disease. Therefore, stage was not a good predictor for residual disease, as differences in stage between the responding and the non-responding groups were not observed. Great interest has been given to the use of FDG-PET as a tool for tumor detection, staging and particularly for response assessment after radical radiotherapy or chemo-radiation [25,26]. The maximum FDG uptake in the primary tumor measured on a pre-treatment scan has consistently been shown as an important prognostic factor for survival in NSCLC [15,18,25]. Our results showed that patients with residual metabolically active areas had a significantly higher FDG uptake on the pre-treatment scan, compared to patients with a complete metabolic response. A high pre-treatment FDG uptake within the primary tumor

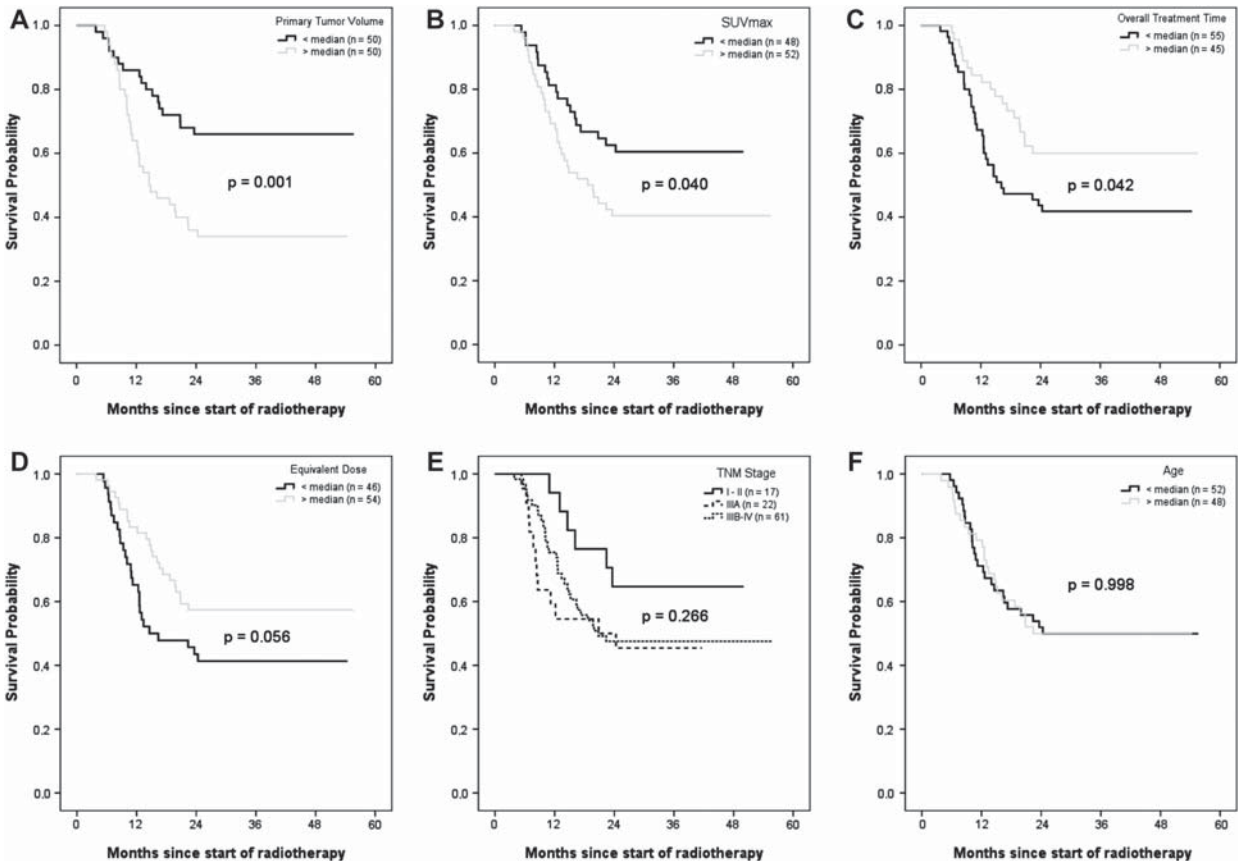

Figure 2. Survival among patients with advanced NSCLC for selected variables. For continuous variables, the cut-off value to stratify the patients was defined at the variable median. Shown are Kaplan-Meier curves for $GTV_{primary}$, SUV_{max}, OTT, $EQD_{2,T}$, TNM stage and age. In panel E, patients with stage I and II were grouped together due to the small number of cases. Stage IV (1 patient) was grouped with Stage IIIB.

was also significantly associated with worse survival ($p=0.040$). Furthermore, the SUV_{max} showed a good predictive capability in univariate analysis.

Tumor volume also emerged as one of the most important predictors of residual disease. Our results are consistent with recently published studies, which have identified tumor size as an important prognostic factor of survival [27]. Here we confirmed the predictive capability of tumor size in assessment of metabolic response. This might indicate that specially for larger tumors, an effective dose could not be reached due to the dose constraints of the current protocol. The total tumor load ($GTV_{primary}$ + GTV_{nodal}) showed a strong association with the post-treatment outcome (Table I). This association is due to the primary tumor volume, and perhaps enhanced by the addition of secondary volumes, however GTV_{nodal} alone did not show a predictive capability. A similar result was obtained for the number of positive lymph node stations on a pre-treatment PET-CT scan. Although the number of PLNSs is an important risk and staging factor for non-surgical patients [28], and has been included

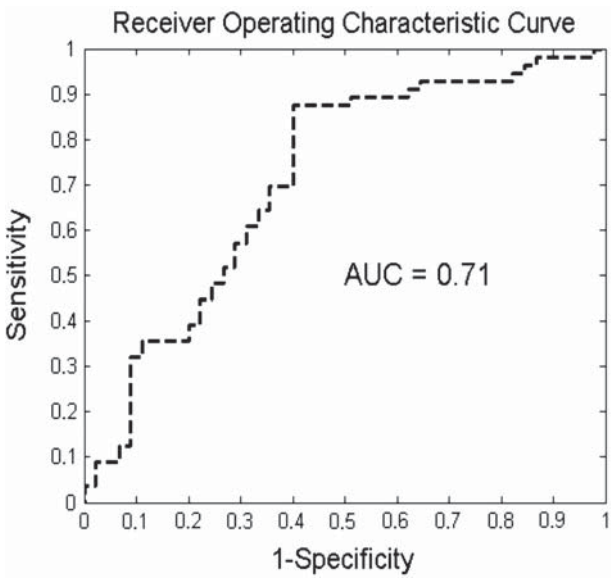

Figure 3. Area under the ROC curve assessed by the leave-one-out method for the multivariate model consisting on $GTV_{primary}$, SUV_{max}, OTT and $EQD_{2,T}$. A classifier with sensitivity of 1 and (1-specificity) of 0, point (0, 1) in graph, is ideal.

in multivariate models for survival in NSCLC, we did not find an added prognostic value for residual disease, perhaps because the outcome was defined in the primary tumor.

Despite an overall difference of two days, overall treatment time was significantly higher for patients with complete metabolic response in comparison with patients with residual disease. OTT was also significantly associated with the outcome in univariate analysis. It is generally accepted that a short treatment time should be chosen, to minimize the effect of accelerated repopulation [29]. The fact that we observe a longer treatment time in patients with a positive outcome is because those patients received a higher dose. Higher total treatment dose has been associated with improved local tumor control and better survival [27,30]. In the present study, the prescribed total dose was not different for patients with a complete response compared to patients with residual disease ($p=0.809$).

Several predictive models of survival have been published for NSCLC patients, reporting different values of the area under the ROC as performance measurement, ranging from 0.65 to 0.86. These models were developed on populations that underwent different treatment modalities such as surgery [31], chemotherapy [28], radiotherapy or a combination [32] and consisted of patients with different tumor and patient characteristics. Thus, application of those models to different scenarios is still subject of research. Here we presented a multivariate model for prediction of residual disease. The final model consisted on tumor volume, overall treatment time, SUV_{max} and equivalent dose corrected for treatment time. This model yielded an AUC of 0.71 (95% CI, 0.65–0.76). This may have clinical relevance for patients identified at risk of treatment failure that may benefit from additional therapy. We were not able to analyze potential prognostic variables such as molecular markers or imaging surrogates [33–35] that may improve the ability of the presented model to predict the post-treatment failure. The lack of an external cohort to validate the presented model and confirm our results is an important limitation to our study. Our results may require validation according to the treatment modality to avoid possible confounding effects associated with multiple treatment modalities.

In conclusion, our results demonstrated that patients who do not respond to radiotherapy can be identified early in the course of their treatment. To our knowledge, this is the first study that examines different clinico-pathological predictors of residual disease. We identified important prognostic factors of residual disease and developed a multivariate model that identified patients at risk of treatment failure. Furthermore, we confirmed the validity of residual disease as a surrogate of survival. Our results could assist clinicians in the treatment decision-making process and in stratification of patients for clinical trials.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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