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ORIGINAL ARTICLE

Pretreatment metabolic tumour volume in stage IIIA/B non-small-cell lung cancer uncovers differences in effectiveness of definitive radiochemotherapy schedules: analysis of the ESPATUE randomized phase 3 trial

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Abstract

Purpose According to the ACRIN 6668/RTOG 0235 trial, pretreatment metabolic tumour volume (MTV) as detected by ^{18}F-fluorodeoxyglucose PET/CT is a prognostic factor in patients with stage III non-small-cell lung cancer (NSCLC) after definitive radiochemotherapy (RCT). To validate the prognostic value of MTV in patients with stage III NSCLC after RCT, we analysed mature survival data from the German phase III trial ESPATUE.

Methods This analysis included patients who were staged by PET/CT and who were enrolled in the ESPATUE trial, a randomized study comparing definitive RCT (arm A) with surgery (arm B) after induction chemotherapy and RCT in patients with resectable stage IIIA/IIIB NSCLC. Patients refusing surgery and those with nonresectable disease were scheduled to receive definitive RCT. MTV was measured using a fixed threshold-based approach and a model-based iterative volume thresholding approach. Data were analysed using proportional hazards models and Kaplan-Meier survival functions.

Results MTV as a continuous variable did not reveal differences in survival between the 117 patients scheduled to receive definitive RCT and all 169 enrolled patients who underwent pretreatment PET/CT ($p > 0.5$). Five-year survival rates were 33% (95% CI 17–49%) in patients scheduled for definitive RCT with a high MTV (>95.4 ml) and 32% (95% CI: 22–42%) in those with a low MTV. The hazard ratio for survival was 0.997 (95% CI 0.973–1.022) per 10-ml increase in MTV and the slope was significantly shallower than that in the ACRIN 6668/RTOG 0235 trial (random effects model, $p = 0.002$). There were no differences in MTV size distributions between the ACRIN and ESPATUE trials ($p = 0.97$).

Conclusion Patients with stage III NSCLC and a large MTV in whom definitive RCT had a particularly good survival in the ESPATUE trial. Treatment individualization according to MTV is not supported by this study. The ESPATUE and ACRIN trials differed by the use of cisplatin-containing induction chemotherapy and an intensified radiotherapy regimen that were particularly effective in patients with large MTV disease.

Keywords MTV · Prognostic marker · Stage III · Induction · NSCLC

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Introduction

The introduction of ^{18}F-fluorodeoxyglucose (FDG) PET/CT changed the prognosis of stage III non-small-cell lung cancer (NSCLC) in the period between 2000 and 2015 because of stage migration [1]. As a result of the higher sensitivity of PET/CT in detecting distant metastases, the proportion of patients with distant metastases increased, whereas the proportion of patients with stage III NSCLC decreased. There are few prospective studies of definitive radiochemotherapy (RCT) in patients with stage III NSCLC, the majority staged with PET/CT. However, these studies show that the long-term results of treatment have improved over time [2–7].

Definitive RCT is a standard treatment option in patients with stage III NSCLC [8, 9]. According to a recent analysis of the US National Cancer Database, 85% of patients with stage IIIA NSCLC were treated with definitive RCT, whereas the remaining 15% underwent trimodality treatment [10]. According to a survey of German lung cancer centres certified on the basis of the requirements of the German Cancer Society, 57% of patients with stage IIIA NSCLC and 9% of patients with stage IIIB NSCLC underwent surgery as one component of their treatment [11]. Therefore, there are large transatlantic differences in the inoperability criteria for stage III NSCLC, and objective prognostic factors for treatment selection and intensification are urgently needed.

The size of the primary tumour is an important prognostic variable of the T descriptor in NSCLC without lymph node or distant metastases, according to the IASLC Lung Cancer Staging Project in patients treated with surgery or stereotactic radiotherapy [12, 13]. An exploratory analysis of data from the ACRIN 6668/RTOG 0235 trial suggested that the metabolic tumour volume (MTV) of the primary tumour and involved lymph nodes, as determined by ^{18}F-FDG PET/CT before definitive RCT, is a predictor of overall survival in patients with stage III NSCLC. Patients with MTV higher than 95.4 ml had a 5-year survival rate of less than 10% [2–4].

This study was undertaken to validate the findings from the ACRIN 6668/RTOG 0235 trial data in an independent cohort. The present analysis used the data from the prospective, randomized ESPATUE trial to investigate the prognostic value of pretreatment MTV as determined by ^{18}F-FDG PET/CT in patients with locally advanced stage IIIA/IIIB NSCLC [6]. This analysis included all patients scheduled for treatment with definitive RCT, as there were patients who were not randomly assigned to surgery (study arm A), patients who refused random assignment, and patients whose cancer was not resectable.

Materials and methods

Patients

The basis for this analysis was the dataset obtained from all patients enrolled in the ESPATUE trial who were treated at the University Hospital Essen and underwent a PET/CT scan for initial staging before or up to 9 days after enrolment. The ESPATUE trial is a randomized multicentre study in patients with ECOG performance status 0 or 1 and potentially resectable stage IIIA (N2) or selected patients with stage IIIB NSCLC, according to the UICC TNM classification, sixth edition [6]. Three cycles of cisplatin/paclitaxel were given as induction chemotherapy, followed by neoadjuvant thoracic RCT (1.5 Gy twice daily, 5 days per week, up to 45 Gy; concurrent cisplatin/vinorelbine). After this treatment, patients medically rated as fit for surgery with resectable tumours were randomly assigned either to immediate continuation of RCT (up to 65–71 Gy; concurrent cisplatin/vinorelbine) or to resection. Patients with nonresectable tumours were scheduled to receive definitive RCT. Accrual of patients started in January 2004 and ended in January 2013. The closing date for survival follow-up of patients undergoing definitive RCT was January 2018.

PET/CT imaging

PET/CT scans were acquired using a Biograph mCT system (Siemens Healthcare, Erlangen, Germany) or a Siemens Biograph Duo scanner. The details of the PET/CT acquisition and ^{18}F-FDG administration have been reported elsewhere [14]. The MTV of the primary tumour and of ^{18}F-FDG-avid lymph node metastases, as well as the maximal and mean tracer activity values within the tumour volume in terms of standardized uptake values (SUV) were determined by visual inspection and were measured separately for each lesion. Two methods were used to determine the MTV: a fixed-threshold enclosed maximal activity method (method 1), and an automatic model-based iterative thresholding method (method 2) using a delineation-averaged signal and a background signal, implemented as a tumour volume segmentation tool in PMOD software (PMOD Technologies LLC, Zurich, Switzerland) [15, 16].

Method 1 was performed using the “PET Subvolume Thresholding” contouring tool of the VARIAN eclipse treatment planning system (Varian Medical Systems, Palo Alto, CA, USA). The MTVs of all visible thoracic hypermetabolic lesions in each patient were determined by a single experienced observer, who was blinded to all clinical outcomes. The resulting MTVs were approved by a second observer. The default fixed threshold in this study was set at 40% of the maximum intensity within the tumour lesion, as in other studies analysing targets with low background activity [15].

For tumour volumes abutting background regions with a higher activity concentration, such as the heart, large vessels and diaphragm, the respective threshold was adapted as follows:

$$SUV_{maxBackground} + 0.4\left(SUV_{maxTumour} - SUV_{maxBackground}\right)$$

to take into account the normal tissue background activity concentration in the segmentation of the MTV.

For method 2 PMOD software was used to select a background activity-corrected boundary and the method reproduced the activity threshold relative to the delineation-averaged activity concentration within the tumour volume. It required selection of an initial tumour region of interest and a manually defined background shell, as well as the reconstructed PET spatial resolution [16].

Data analysis

Survival and freedom from distant metastases as a component of first relapse and pathological complete response (pCR) were used as primary and secondary endpoints. Survival time was defined as the time from study enrolment to death. Proportional hazard analyses were performed with the procedure PHREG in SAS statistical software, version 9.4 (Cary, NC, USA). A Kolmogorov-type supremum test was performed to test the proportional hazard assumption for MTV and the linearity assumption of the dependence of the log hazard function on MTV. The product limit method was used to estimate the survival curves, and a two-sided log-rank test was used to compare survival curves between MTV groups (procedure LIFETEST in SAS).

Analyses of the ACRIN 6668/RTOG 0235 trial data suggested that the likelihood of survival in patients with a pretreatment MTV higher than 95.4 ml and stage III NSCLC treated with definitive RCT was worse than in patients with a lower MTV [2–4]. All patients recruited for the ESPATUE trial not randomly assigned to surgery were considered to be scheduled for definitive RCT. The ratio of median survival times between the high and low MTV groups in the ACRIN 6668/RTOG 0235 trial was 1.76, obtained in an exploratory analysis after selection of an optimal cut-off point ($p < 0.001$, log-rank test). This hazard ratio equals the inverse ratio of the median survival times between groups assuming exponential survival curves, obtained from the original publication [17].

First, the power of our analysis of the ESPATUE trial data for determining the prognostic value of MTV at the preset cut-off value of 95.4 ml, assuming exponential survival curves and an associated hazard ratio of 1.76 between the high and low MTV groups, was assessed. This analysis was performed with the procedure POWER in SAS. The information used for the power analysis was the accrual duration of the ESPATUE trial (9 years) and the minimum follow-up duration after the end of recruitment (5 years). A one-sided log-rank test with statistical significance set at $\alpha = 0.05$ was used. Median survival times in the high and low MTV groups were determined from the observed median survival of all patients scheduled to receive definitive RCT. If the power of the ESPATUE trial data at the preset MTV cut-off value was found to be higher than 80%, then further analysis of the associations between MTV and survival and freedom from distant metastases were planned. The power of proportional hazard analysis using MTV as a continuous covariable should be even higher than that using a cut-off value if the assumptions of proportional hazard analysis are fulfilled [18].

Hazard ratios for MTV as a continuous prognostic variable from multivariable analysis were compared between this and the ACRIN 6668/RTOG 0235 trial, which used the meta-analytic tools of R (package 'meta') [19]. Spearman rank-order correlations using Fisher's Z-transformation and analysis of two-way tables were performed with SAS procedures CORR and FREQ.

Role of the funding source

The randomized ESPATUE trial was supported by Deutsche Krebshilfe (German Cancer Aid; grant no. 70-3070-Eb). The sponsor had no role in analysing the data, writing the report, or submitting the manuscript for publication.

Results

A total of 246 patients were recruited for the ESPATUE trial, 183 of them at the University Hospital Essen. Of these patients, 169 had undergone PET/CT before or up to 9 days after enrolment. PET/CT scans from the other participating institutions with more than three recruited patients were no longer available for quantitative MTV analysis. Of these 169 patients, 117 were scheduled to undergo definitive RCT, i.e. they were not randomly assigned to surgery. Patient characteristics are shown in Table 1. There were only small differences in the distribution of total MTV values as determined by methods 1 and 2 ($p = 0.043$, Wilcoxon signed-ranks test). The median total MTV value as determined by method 1 was 57.6 ml (first quartile 30.0 ml, third quartile 107.5 ml), and by method 2 was 57.7 ml (first quartile 33.9 ml, third quartile 98.4 ml). The Spearman rank-order correlation coefficient between the total MTV values determined by methods 1 and 2 was 0.94. In addition, there were no differences between the distributions of MTV values from the ESPATUE and ACRIN trials [2]. The median, and lower and upper quartiles of the MTV distribution from the ACRIN study were 57.2 ml, 28.1 ml and 104.5 ml, respectively. There was agreement between the two studies in the grouping of the MTV value frequency

distributions according to the above quartile classes ($p = 0.97$, chi-squared test).

With 117 patients scheduled to receive definitive RCT, the power of this analysis was found to be 0.85 for detecting a hazard ratio of 1.76 at a MTV cut-off value of 95.4 ml. The survival curves of patients with high and low total MTV as determined by method 1 who received definitive RCT are shown in Fig. 1 with the predefined cut-off value of 95.4 ml. This cut-off value was close to the third quartile value of the total MTV distribution. No trend toward a lower survival rate in patients with a high total MTV was observed.

In patients with a high MTV, the median survival time was 31.0 months (95% CI 17.4–59.3 months) and the 5-year survival rate was 33% (95% CI 17–49%). In patients with a low MTV, the median survival time was 28.8 months (95% CI 19.5–36.5 months) and the 5-year survival rate was 32% (95% CI 22–42%; $p = 0.62$, log-rank test). Determination of MTV by method 2 led to reclassification of five patients from low to high total MTV and of four patients from high to low total MTV. Median survival times and 5-year survival rates in the high and low total MTV groups differed by less than 1 month or 1%. There were no differences between the survival curves of the two groups ($p = 0.73$, log-rank test).

Table 1 Patient, tumour and treatment characteristics of the patients treated at the University Hospital Essen within the ESPATUE trial who had undergone a pretreatment PET/CT scan

Characteristic	Value
Sex (women/men)	46/123
ECOG performance status (0/1)	112/57
Age (years), median (range)	59 (33–74)
T stage	
T1/2	99
T3	12
T4	58
N stage	
N0/1	57
N2	90
N3	22
Histology	
Squamous cell carcinoma	75
Adenocarcinoma	65
Other	29
Treatment arm	
A	56
B	52
All remaining patients	61
Total MTV (ml)[a]	
Median (range)	54.2 (1.3–514.7)
Interquartile range	28.8–96.1

ECOG Eastern Cooperative Oncology Group, *MTV*, total metabolic volume

[a] The MTV of the primary tumour together with the MTV of the lymph nodes (lymph node MTV). The values shown were determined according to method 1

In addition, we analysed the prognostic value of total MTV in patients who were scheduled to receive definitive RCT and in those who received it according to the protocol with acceptable deviations in total radiation dose. Thus, the total doses amounted to less than 45 Gy, which is less than 70% of the protocol-specified total dose. In the 27 patients with a high MTV as determined by method 1, the median survival time was 31.4 months (95% CI 17.4–71.2 months) and the 5-year survival rate was 33% (95% CI 17–51%). In contrast, in the 74 patients with a low MTV who received the intended definitive RCT with acceptable dose deviations, the median survival time was 29.6 months (95% CI 20.4–39.6 months) and the 5-year survival rate was 31% (95% CI 21–42%; $p = 0.76$, log-rank test; Fig. 2). The remaining 16 patients scheduled for definitive RCT received less than 70% of the total dose according to the protocol for several reasons: discontinuation of therapy during induction chemotherapy (death, one patient), distant metastases (one patient), toxicities (one patient), withdrawal (three patients), death during RCT (one patient), and crossover to surgery after neoadjuvant RCT (nine patients).

Univariable and multivariable proportional hazards analyses using the pretreatment MTV and patient characteristics from Table 1 showed no association between total MTV as determined by method 1 as a continuous variable and survival in patients scheduled for definitive RCT, in patients scheduled for definitive RCT with acceptable dose deviations, or in all patients who had undergone an initial PET/CT scan (Table 2). In all included patients, no important deviations from the proportional hazards assumption ($p = 0.27$, supremum test) or from the linearity assumption of the log hazard dependence on MTV ($p = 0.66$, supremum test) were observed for MTV. These results were independent of the method of MTV determination, because similar results were obtained for MTV as determined by method 2. The hazard ratio for patients scheduled for definitive RCT associated with a 10-cm^3 increase in MTV was significantly lower (0.997, 95% CI 0.973–1.022; $p = 0.81$) than the hazard ratio of the ACRIN 6668/RTOG 0235 trial (1.04, 95% CI 1.03–1.06; $p < 0.001$; random-effects model, $p = 0.002$, chi-squared test).

Figure 3 shows the survival curves for all 169 patients included in the ESPATUE trial for whom the results of the initial PET/CT scan were available, including those patients randomly assigned to surgery after neoadjuvant RCT. No association between MTV as determined by method 1 and survival was observed when the resulting survival curves were compared using either the log-rank test ($p = 0.27$) or the multivariable proportional hazards analysis (Table 2). These results did not depend on the method of MTV determination.

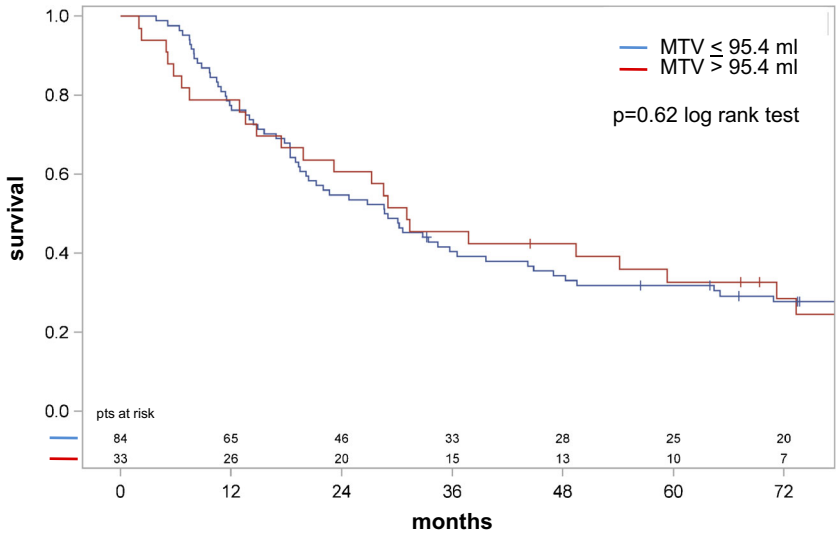

Fig. 1 Overall survival of patients in the ESPATUE trial treated at the University Hospital Essen who had undergone an initial PET/CT scan and were scheduled to receive definitive radiochemotherapy. Patients were grouped according to metabolic tumour volume (MTV) with a the predefined cut-off value of 95.4 ml

The effect of induction chemotherapy followed by concurrent RCT but only to a dose of 45 Gy could also be determined on the endpoint of pCR in the 53 patients in this study who underwent tumour resection. There was no association between MTV and the probability of observing a pCR (Fisher-Spearman correlation coefficient $r = 0.07$, 95% CI 0.33–0.21; $p = 0.62$). Among the patients in whom MTV was determined by method 1, pCR was achieved in 4 of 12 resected tumours with a high MTV (>95.4 ml) and in 17 of 41 tumours with a low MTV (relative risk of no pCR in the high vs. low MTV groups 1.14, 95% CI 0.71–1.83). Distant metastases as sites of first recurrence were found in 11 of the 33 patients scheduled for definitive RCT with a high MTV (>95.4 ml) and in 43 of the 84 patients with a low MTV. These distant metastases were the most common sites of relapse (relative risk of distant metastases in the low vs. high MTV group, 1.22; 95% CI 0.98–1.53).

Discussion

The present study showed that long-term survival in patients with locally advanced NSCLC from the prospective ESPATUE trial scheduled to receive induction chemotherapy followed by definitive RCT with a large pretreatment MTV of >95.4 ml was favourable, and not different from survival in patients with a smaller MTV. MTV as a continuous variable was also not a significant predictor of survival, in either the univariable analysis or the multivariable proportional hazards analysis.

This study was performed to validate the findings of an exploratory analysis of the data from the ACRIN 6668/RTOG 0235 trial, which indicated that MTV is a predictor of survival after definitive RCT [2–4]. The null hypothesis, that MTV has no prognostic significance for survival after definitive RCT, could not be rejected. In addition, intention-to-treat analyses of the ESPATUE trial data and the ACRIN 6668/

Table 2 Total metabolic tumour volume (MTV) as a prognostic factor for survival and time to progression among patients treated with definitive radiochemotherapy

	Hazard ratio[b]	95% confidence interval	*p* value
Patients scheduled for definitive radiochemotherapy ($n = 117$)			
Univariable analysis	1.007	0.988–1.025	0.49
Multivariable analysis[a]	0.997	0.973–1.022	0.81
Patients who received definitive radiochemotherapy ($n = 101$)			
Univariable analysis	1.007	0.988–1.026	0.49
Multivariable analysis[a]	0.999	0.974–1.024	0.94
All patients included in this study ($n = 169$)			
Univariable analysis	1.004	0.986–1.022	0.70
Multivariable analysis[a]	0.996	0.975–1.019	0.75

[a] Multivariable proportional hazard analysis of the effect of total MTV on survival, as determined by method 1, adjusted for gender, ECOG status, age, T stage, N stage, histological subgroup, and eligibility for random assignment as decided by a tumour conference after neoadjuvant radiochemotherapy

[b] Hazard ratios are given per 10 ml increase in MTV

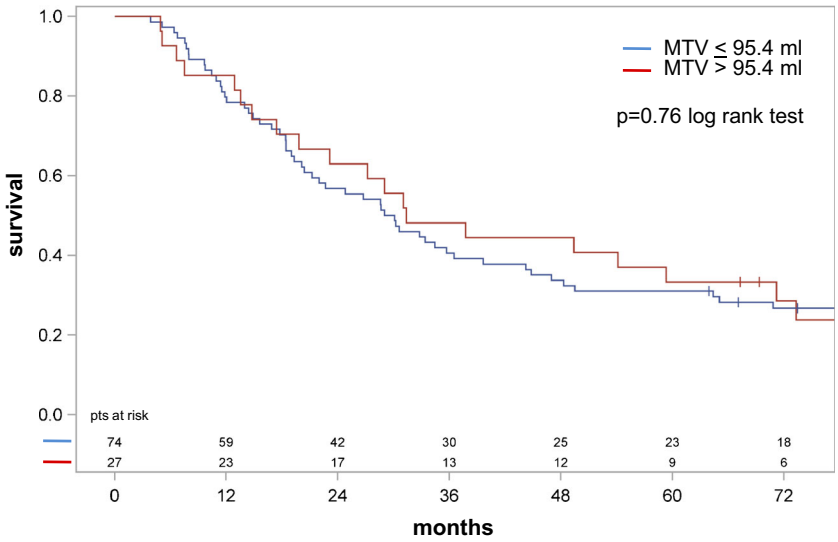

Fig. 2 Overall survival of patients in the ESPATUE trial treated at the University Hospital Essen who underwent an initial PET/CT scan and were scheduled to receive definitive radiochemotherapy without substantial dose deviations. Patients were grouped according to metabolic tumour volume (MTV) with a predefined cut-off value of 95.4 ml

RTOG 0235 trial data showed that the hazard ratios associated with an increase in MTV of 10 ml after definitive RCT were significantly different in the two studies.

This study used two separate methods for MTV delineation, both of which are known to result in metabolic target volumes similar to GTVs (GTV) as determined by CT scanning or in histopathological studies [20]. The MTV distribution in the ESPATUE trial was very similar to that observed in the ACRIN 6668/RTOG 0235 trial, but the ESPATUE trial included a higher percentage of patients with stage IIIB disease.

In addition to the ACRIN 6668/RTOG 0235 trial, some retrospective studies on definitive RCT in patients with stage III NSCLC have found an inverse association between macroscopic tumour volume and overall survival [21, 22]. In the latter studies, the macroscopic tumour volume was determined on CT. These studies found a poor survival rate in patients with a high-tumour volume (>100 ml): the 5-year survival rate was lower than 20% in the studies by Koo et al. [21] and Warner et al. [22], and <10% in the ACRIN 6668/RTOG 0235 trial [2]. On the other hand, a secondary analysis of phase II studies by Stinchcombe et al. using induction chemotherapy before radical radiotherapy or RCT in patients with stage III NSCLC did not show that pretreatment GTV on CT is a prognostic factor [23]. A retrospective study by Ahmed et al. found a better survival in patients with locally advanced NSCLC with GTVs >150 ml receiving induction chemotherapy in addition to concurrent RCT than in those receiving concurrent RCT alone [24]. Postinduction chemotherapy PET/CT metrics were better predictors of survival than pretreatment characteristics. These findings establish a decrease in ^{18}F-FDG SUV as an important predictor of survival in patients with stage III NSCLC [14, 24]. Two small to medium-sized randomized studies on induction chemotherapy before definitive RCT did not demonstrate a survival benefit of induction chemotherapy in patients with stage III NSCLC not selected according to GTV [25, 26]. In these studies, PET/CT was not consistently used for staging. The present analysis

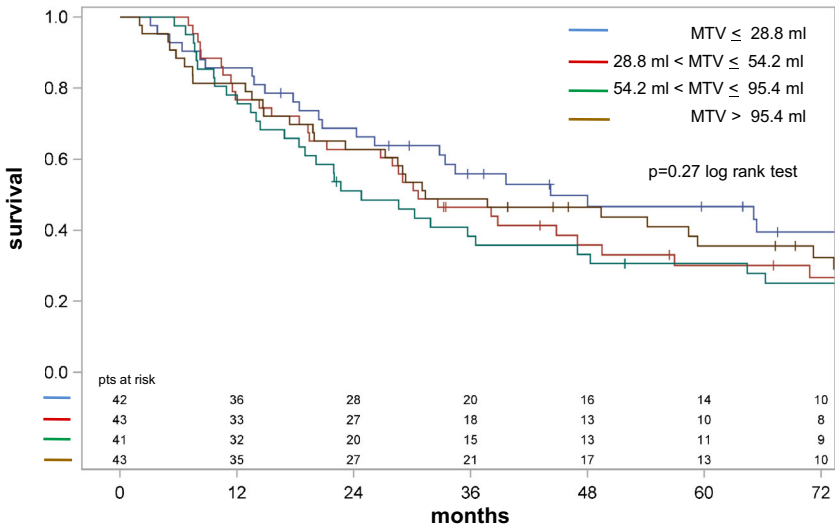

Fig. 3 Overall survival of all patients in the ESPATUE trial treated at the University Hospital Essen who underwent an initial PET/CT scan. Patients were grouped according to metabolic tumour volume (MTV) with a predefined value of 95.4 ml, a first-quartile MTV of 28.8 ml, and a median MTV of 54.2 ml as cut-off values

together the studies by Stinchcombe et al. and Ahmed et al. support the view that induction chemotherapy can be particularly effective prior to definitive RCT in patients with stage III NSCLC with large macroscopic tumour volumes [22, 24].

One biological reason why MTV may not be a strong predictor of survival after definitive RCT is the finding that even small tumours can seed lymph nodes and form distant metastases. Distant metastases may occur early during the clonal evolution of lung cancer, as shown by reconstructions of the mutational history of NSCLC, which use whole-exome sequencing to compare mutational patterns in the primary tumour and in the metastases [27]. Early intratumoral heterogeneity through chromosome instability might support this process [28]. We also found no relationship between total MTV and the incidence of distant metastases as a component of first relapse; such distant metastases are the most important sites of failure in locally advanced NSCLC. In addition, high-risk subvolumes within the macroscopic tumour, e.g. the most metabolically active or hypoxic areas, not the total MTV, may carry the prognostic information [29, 30]. Pathological complete response is a strong prognostic marker for survival after trimodality treatment and directly indicates the locoregional effectiveness of induction chemotherapy followed by neoadjuvant RCT as determined by histopathological analysis of the resected tumour [31]. The current study showed no association between initial MTV and pCR in patients undergoing trimodality treatment, a further indication that cure after induction chemotherapy followed by neoadjuvant chemotherapy followed by concurrent RCT depends predominantly on factors other than MTV.

To provide a reliable prediction, any set of parameters needs to represent a specific model of the tumour class under a specific therapy, and should have the same dimensionality or number of dominant independent factors as the tumour class itself for a full description [32]. The lack of correlations between MTV and the incidence of distant metastases or the histopathological tumour response or long-term survival after induction chemotherapy and definitive RCT shows the limitations of MTV as a major prognostic factor, and indicates that research on parameters related to relevant factors promoting resistance to the specific therapy is necessary. PET tracers specific for mechanisms associated with resistance to therapy, e.g. hypoxia or programmed cell death ligand-1 [33], together with genetic profiling and response assessment during a specific therapy offer the chance to find better prognostic models in the future.

In conclusion, this study found no general validity for the hypothesis that the survival rate of patients with stage III NSCLC after definitive RCT is dependent on pretreatment total MTV when induction chemotherapy is given. The difference in the influence of MTV on outcome found in the ESPATUE trial and the ACRIN 6668/RTOG 0235 trial can be explained by differences in the treatment schedules: cisplatin-containing induction chemotherapy and an intensified radiation fractionation schedule were used in the ESPATUE trial. The data from the present analysis indicate that patients with a large MTV of >95.4 ml might particularly benefit from these modifications.

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Compliance with ethical standards

Conflicts of interest W. Eberhardt received honoraria from Eli Lilly, Boehringer Ingelheim, Pfizer, Novartis, Roche, Merck, Bristol-Myers Squibb, Amgen, GlaxoSmithKline, Aestellas, Bayer, Teva, Merck Serono, Daichi Sankyo and Hexal, and is a consultand or advisor to Eli Lilly, Boehringer Ingelheim, Novartis, Pfizer, Roche, Merck, Bristol-Myers Squibb, Aestellas, Bayer, Teva, Daichi Sankyo. Research Funding and Eli Lilly (Inst).

T. Gauler received Honoraria from Eli Lilly, Boehringer Ingelheim, Merck Serono, Novartis, Roche, Pfizer, Bayer, MSD Oncology, Bristol-Myers Squibb, Symphogen and GlaxoSmithKline, is a consultand or advisor to MSD Oncology, Merck Serono, Novartis, and Eli Lilly, and received travel, accommodation and other expenses from Boehringer Ingelheim and Merck Serono.

M. Schuler received honoraria from Alexion Pharmaceuticals, Boehringer Ingelheim, Celgene, GlaxoSmithKline, Eli Lilly, Novartis and Pfizer, is a consultant or advisor to AstraZeneca, Boehringer Ingelheim, Celgene, Bristol-Myers Squibb, Novartis, IQWiG and Eli Lilly, and received research funding from Boehringer Ingelheim (Inst), Novartis (Inst) and Bristol-Myers Squibb (Inst). Patents, Royalties, Other intellectual property: patents (University Hospital Essen).

D. Theegarten is an advisory board member of E. Lilly.

C. Pöttgen received honoraria from Roche Pharma and Boehringer Ingelheim (speakers bureau).

All other authors declare no conflicts of interest.

Ethical approval All procedures performed were in accordance with the ethical standards of the institutional research committee and with the principles of the 1964 Declaration of Helsinki and its later amendments. This secondary analysis was approved by the lead ethics committee of the Medical Faculty of the University Duisburg-Essen in September 2016.

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