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Greater Reduction in Mid-treatment FDG-PET Volume May Be Associated with Worse Survival in Non-Small Cell Lung Cancer

Feng-Ming (Spring) Kong, M.D., Ph.D.[1,2,*], **Ling Li, M.D., Ph.D.**[2,3], **Weili Wang, M.D. Ph.D.**[1,2], **Jeff Campbell, Ph.D.**[4], **Jennifer L. Waller, Ph.D.**[4], **Morand Piert, M.D., Ph.D.**[5], **Milton Gross, M.D.**[5,6], **Monica Cheng, MS, MD Candiate**[7], **Dawn Owen, M.D.**[2], **Matthew Stenmark, M.D.**[2], **Colin Huang, Ph.D.**[7], **Kirk A. Frey, M.D.**[5], **Randall K. Ten Haken, Ph.D.**[2], and **Theodore S Lawrence, M.D., Ph.D.**[2]

[1]Department of Radiation Oncology, Seidman Cancer Center, Case Western Reserve University School of Medicine, University Hospitals Cleveland Medical Center, Cleveland, OH

[2]Department of Radiation Oncology, University of Michigan, Ann Arbor, MI

[3]Department of Radiation Oncology, Cancer Hospital, Fudan University, Shanghai

[4]Department of Biostatistics & Epidemiology, Augusta University, Augusta, GA

[5]Department of Radiology, University of Michigan, Ann Arbor, MI

[6]Department of Radiology, Ann Arbor Veteran Affairs Hospital, Ann Arbor, MI

[7]Department of Radiation Oncology, IU Simon Cancer Center, Indiana University School of Medicine, IN

Abstract

Background and purpose: This study tested the hypotheses that 1) changes in mid-treatment fluorodeoxyglucose (FDG)-positron emission tomography (PET) parameters are predictive of overall survival (OS) and 2) mid-treatment FDG-PET-adapted treatment has a potential to improve survival in non-small cell lung cancer (NSCLC).

Material and methods: Patients with stage I-III NSCLC requiring daily fractionated radiation were eligible. FDG-PET-CT scans were obtained before radiotherapy and mid-treatment at 40–50 Gy. The normalized maximum standardized uptake value (NSUVmax), normalized mean SUV (NSUVmean), PET-metabolic tumor volume (MTV), total lesion glycolysis (TLG), and computed tomography-based gross tumor volume (CT-GTV) were consistently measured for all patients. The primary study endpoint was OS.

[*]Feng-Ming (Spring) Kong, MD, PhD, FACR, Department of Radiation Oncology, Seidman Cancer Center, Case Western Reserve University School of Medicine, University Hospitals Cleveland Medical Center, Cleveland, OH 44106, Tel: 1-216-844-2530.

Conflict of interest: None

Results: The study included a total of 102 patients who received 3-dimensional conformal radiotherapy, with 30 patients who received mid-treatment PET-adapted dose escalation radiotherapy. All PET-CT parameters were decreased significantly (P<0.001) mid-treatment, with greater reductions in FDG-volumetric parameters compared to FDG-activity factors. Mid-treatment changes in MTV (P=0.053) and TLG (P=0.021) were associated with OS, while changes in NSUVmax, NSUVmean, and CT-GTV were not (all Ps>0.1). In patients who received conventional radiation (60–70 Gy) and had MTV reductions greater versus less than the median, the median survival times were 14 versus 22 months, respectively. In contrast, in patients who received mid-treatment PET-adapted radiation and had MTV reductions greater versus less than the median, the corresponding median survival durations were 33 versus 19 months, respectively. Overall, PET-adapted treatment resulted in a 19% better 5-year survival than did conventional radiation.

Conclusion: Changes in mid-treatment PET-volumetric parameters were significantly associated with survival in NSCLC. A greater reduction in the mid-treatment MTV was associated with worse survival in patients treated with standard radiation, but with better survival in patients who received mid-treatment PET-adapted treatment.

Summary

In addition to validating the significance of PET and CT tumor volumes, this study demonstrated that the metabolic tumor volume on PET and its changes mid-treatment were significantly associated with overall survival after radiation therapy in patients with non-small cell lung cancer. A greater reduction in mid-treatment PET tumor volume was associated with worse survival in patients treated with standard radiation therapy, but with better survival in those who received mid-treatment PET-adapted treatment.

Keywords

FDG-PET; metabolic tumor volume; mid-treatment; non-small cell lung cancer

Introduction

While several promising radiotracers have become available for tumor-specific imaging, Fluorodeoxyglucose (FDG)-positron emission tomography (PET) remains the most widely utilized FDA-approved tumor imaging modality in our daily practice. An extensive amount of literature has demonstrated that FDG-PET imaging improves staging accuracy and provides an approximately 20% improvement in staging accuracy over computed tomography (CT) in non-small cell lung cancer (NSCLC) [1-3]. The application of FDG-PET in radiation treatment planning improves the accuracy of target definition [4].

FDG-PET can be used to monitor the response of tumors to radiation therapy [5, 6]. The magnitude of FDG uptake in primary lesions correlates with tumor growth rate and survival in NSCLC [7]. FDG activity following treatment is associated with the response to treatment [3, 7–10]. A high metabolic uptake after completion of radiotherapy (RT) is associated with poor tumor control [8], while a return of the FDG standardized uptake value (SUV) to background was shown to be an accurate predictor of complete response and a sensitive

indicator of a favorable prognosis [7]. For the detection of residual and recurrent disease, FDG-PET has a reported sensitivity of 100% and specificity of 92% [8].

PET is typically performed at 1–3 months after RT, and post-treatment inflammatory changes observed in normal tissues do not appear to confound therapeutic response evaluation [10, 11]. However, post-treatment PET does not provide an opportunity for the individual patient to receive more effective treatment. PET imaging during the course of treatment may provide an earlier assessment of treatment response and an opportunity to apply an alternative therapy that may be more efficacious or to identify unnecessary radiation toxicity related to less effective or ineffective therapies. We have previously demonstrated that FDG activity and FDG-avid tumor volumes change remarkably during the course of fractionated RT, and that mid-treatment FDG activity correlates with post-RT response, which is predictive of overall survival (OS) [12-14]. This study aimed to test the hypotheses that mid-treatment FDG-PET parameters or changes in tumor metabolic parameters can directly predict long-term survival, and that an effective mid-treatment PET-adapted therapy may improve survival in patients with locally advanced NSCLC.

Materials and Methods

Study population

This work was part of the prospective Institutional Review Board-approved studies (including NCT00603057 & NCT1190527) conducted at two centers, the University of Michigan and the Veterans Affairs Medical Center, Ann Arbor, MI, using functional imaging to predict treatment outcomes (non-therapeutic study) and to guide personalized adaptive treatment (therapeutic study). Adult patients with histologically confirmed or clinically diagnosed FDG-avid stage I to III NSCLC requiring definitive RT with or without chemotherapy were eligible. Patients with a history of prior thoracic RT, small cell lung cancer or mixed small cell/non-small cell histology, pericardial effusion or pregnancy were excluded from the study.

Study design

Patients received one of two treatment regimens: 1) daily conventionally fractionated 3D conformal radiotherapy (3DCRT) to 60–74 Gy at 2 Gy per fraction in the imaging study or 2) 2.2–3.8 Gy daily fractionated 3DCRT to NTCP of 17.2% with dose up to 88 Gy according to PET-adapted radiation (PART) dose escalation protocols. Patients with stage III disease in imaging study were treated with concurrent chemoradiation or radiotherapy alone according to the decision of the treating physician. The details of the specific prospective trials are summarized in Table S1. The dose of RT for the treatment protocol was based on an estimated normal lung complication probability of 15–17% [15]. The details of radiation treatment, such as target definition, dose prescription and organ at risk limitation, were as previously described [12, 13, 16].

FDG PET/CT scans were performed 7 days (range 0–29) prior to the start of treatment (pre-RT) and 30 days (range 19-54) after the start of treatment (mid-treatment), that was after the delivery of approximately 40–50 Gy in 2-Gy equivalents of 3DCRT, as described previously

[13]. The time of attainment of approximately 40–50 Gy of the total prescribed dose was chosen for the mid-treatment scan, as this dose may have allowed control of microscopic disease, and a reasonable amount of the remaining treatment time would allow for an alteration in the treatment plan for an additional RT boost. When radiation was administered in fractions other than 2 Gy, the tumor dose was converted to a biologic equivalent dose in 2-Gy fractions (EQD2).

PET/CT Image Acquisition

FDG PET/CT scans were performed at two institutions between 2003 and 2013. The ^{18}F-FDG PET/CT imaging protocols used at both institutions were standardized throughout this time period and the details were published previously [17]. At one center, PET/CT imaging was performed on a Siemens Biograph Classic (Siemens Medical Solutions, Hoffman Estates, IL, USA) from 2003 to 2006 and on a Siemens Biograph T6 from 2006 to 2013. All PET/CT studies at another medical center were performed on a Siemens Biograph T6. FDG-PET/CT scanning was performed in a standardized fashion on a flat table top, with patients' arms raised above the head in the treatment position. The CT images (5-mm slices) for the PET/CT study typically were obtained during shallow breathing. Emission PET images were obtained beginning 60 minutes after administration of 8–10 mCi of [^{18}F]FDG. For the PET scan, the blood glucose level was required to be less than 150 mg/mL.

FDG-PET/CT images from the diagnostic radiology department were transferred to the Functional Image Analysis Tool (FIAT, in house system) and the UM-Plan system (in-house planning systems). Imaging data sets were co-registered according to anatomic match (CT of PET/CT registered to CT simulation based on CT anatomy).

Quantitative FDG-PET Parameters

PET metabolic tumor volumes (MTVs) of FDG-avid tumors were delineated by auto-segmentation at tumor/aorta ratio of 1.5 followed by knowledge-based manual editing according to CT anatomy, as previously described [12, 13]. In brief, a sphere 1.2 cm in diameter (approximate to 1 cc) was first drawn in the center of the aortic arch on the same scan. The mean intensity obtained from this sphere was used as the background for the aorta as a surrogate of the normal tissue. This methodology minimized the confounding effect from variance in the standardized update value (SUV) from imaging by different machines and the variability of the intervals between injection and image acquisition in the same patient. Primary tumor and nodal disease were contoured in a consistent manner. PET tumor parameters of interest included:

1) FDG activity factors: NSUVmax and NSUVmean, both normalized to median SUVs of the above-specified sphere in the middle of the aortic arch.

2) FDG volumetric factors: MTV and total lesion glycolysis (TLG $=NSUV_{mean}*MTV$).

As a reference, CT-based gross tumor volume (CT-GTV) was contoured on the CT component of the PET-CT with visual guidance from the PET scan.

Radiation Treatment

All patients received 3-dimensional conformal radiotherapy (3DCRT), and among them, 30 patients received mid-treatment PET-adapted dose escalated radiotherapy. The gross tumor volume (GTV) included the primary tumor, any hilar or mediastinal lymph nodes with a short-axis diameter of at least 1 cm on CT, and any abnormal findings detected on bronchoscopy or mediastinoscopy, and PET MTV. The clinical target volume (CTV) was uniformly created by expanding the GTV by 0.5 cm. Clinically uninvolved hilar, mediastinal, and supraclavicular nodal regions were not purposely included in the CTV. In patients with free breathing treatment, an internal margin was added to CTV to form the internal target volume (ITV). The planning target volume (PTV) was created by expanding the CTV for breathing controlled treatment, ITV for free breathing treatment, by a minimum of 0.5 cm for setup error for treatment under active breathing control. An in house plan (UMPlan) was used for treatment planning, and the treatments were delivered using Varian EX or trilogy linear accelerators. PET at baseline was used to guide treatment decision and GTV delineation. MTVs were delineated consistently from PET scans as previously prescribed [12, 16]. The treatment technique and number of fields of initial and mid-treatment FDG-PET/CT-guided adaptive radiation plans were individually tailored for each patient. Dose volume histograms (DVHs) were evaluated to limit doses for normal organs and to provide objective criteria for the selection of an appropriate treatment plan. Suitable treatment plans were those that maximized target doses while constraining the lung NTCP to 17.2% or less and limiting doses to other critical organs at risk to the standard limits. Organs at risk, such as lung, heart, esophagus, spinal cord, and brachial plexus, were contoured in the treatment planning system when they were included in the field of irradiation. If any of these tolerance doses could not be met, the prescription doses were decreased heterogeneously according to these limits.

Patient follow-up and statistical consideration

Patients were prospectively evaluated for treatment outcome weekly during the course of RT, with follow-up evaluation at 1 month after completion of RT, every 3 months for the first year, every 6 months the second year, and then yearly afterward. At each follow-up, patients underwent a history and physical examination, a CT scan of the chest, and PET-CT as needed.

The primary endpoint was OS from the start of RT. The MTV and GTV values were scaled by a factor of 10, i.e., the hazard ratio is per 10 cc instead of 1 cc for continuous variable analysis. Survival analysis was performed using Cox proportional hazards modeling. The P values presented are from a multivariate Cox proportional hazard analysis unless otherwise specified. Two-tailed tests were performed to test for statistical significance at a level of $P<0.05$.

Results

A total of 102 patients with inoperable and unresectable NSCLC were enrolled in this study between 2003 and 2012 (Table 1). The median follow-up was 58 months (95% CI, 48–68 months). The majority of subjects were male (76%), Caucasian (99%), and current or former

smokers (96%). The median age was 65 years (range, 45–85 years). Eighty-three percent of patients with locally advanced disease were treated with chemotherapy in combination with definitive RT (dose range 60–88 Gy). The median OS was 23 months (95% CI, 14–32 months).

As shown in Table 1, gender, histology, Karnofsky Performance Status (KPS), EQD2 and treatment modality were significant clinical factors: specifically, female gender, adenocarcinoma, higher KPS, higher EQD2, and mid-treatment PART were associated with better OS. These factors were thus selected as clinical co-variables for further multivariate analysis of the PET variables.

The results for the significance of all PET-CT parameters pre-treatment for OS are shown in Table 2. Under either univariate or multivariate analyses, none of the FDG activity parameters including pre-treatment or mid-treatment NSUVmax or NSUVmean or changes in NSUVmax or NSUVmean was significantly associated with OS. However, all baseline volumetric factors including MTV, GTV and TLG were significant under univariate analysis (all $P<0.05$). After adjustment for clinically significant variables, only pre-treatment TLG remained significant. A greater TLG was associated with worse OS (hazard ratio [HR] for each 10 units =1.006; 95% CI, 1.001–1.010; P=0.023). The median survival times were 18 and 30 months for patients with greater or less than the median pre-RT TLG, respectively.

Of 87 patients with recoverable mid-treatment PET scans, NSUVmax, NSUVmean, PET-MTV, PET-TLG and CT-GTV were all decreased significantly (all $Ps<0.001$). The waterfall plots of changes in PET-MTV and CT-GTV for individual patients in Figure 1 show the greater magnitude of reductions in PET-MTV and PET-TLG comparing to CT-GTV as well as the individual differences of the change. According to the mid-treatment PET and CT, 8% (7/87) patients had a complete metabolic response, 3% (3/87) had metabolic progressive disease, and 89% (77/87) had partial response and stable disease. To explore whether the response differed according to histological type, we analyzed the changes in PET parameters in cases of squamous cell carcinoma (SCC; n=37) versus adenocarcinoma (ADC; n=24). Compared to ADC patients, SCC patients had a significantly larger MTV (104 cc versus 59 cc) and CTGTV (154 cc versus 86 cc). For mid-treatment changes, SCC patients had greater reductions in NSUVmean (1.2 versus 0.7) and TLG (290 versus 131) than ADC patients (both $P<0.05$). To explore whether the response differed related to baseline tumor volume, we analyzed the changes in volumetric parameters in cases of greater than (n=42) versus less than median change (n=45). Patients with greater than median change had a significantly larger PET-MTV (174 cc versus 26 cc) and CT-GTV (236 cc versus 53 cc) (both $P<0.05$).

Of FDG activity parameters, neither NSUVmax or NSUVmean nor changes in either one was significant for survival (Table 2).

Of the mid-treatment PET-CT volumetric parameters, MTV (P=0.021) and GTV (P=0.026) were significantly associated with survival under univariate analysis. A smaller mid-treatment tumor was associated with better survival: the median survival times were 19 and 33 months for patients who had a mid-treatment CT-GTV greater or less than the median of 51 cc, respectively. However, only MTV remained significant (HR for each 10 cc =1.059;

95% CI, 1.009–1.111, P=0.020) and CT-GTV (P=0.051) was borderline significant under multivariate analysis (Table 2).

Of changes in the mid-treatment PET-CT volumetric parameters, both of MTV and TLG were significant under univariate analyses (all P<0.05). Greater changes in MTV (P=0.016) and TLG (P=0.012) were associated significantly with worse survival: for example, the median survival times were 18 versus 30 months for greater versus less than the median change in MTV, respectively. However, only changes in TLG remained significant (HR for each 10 cc =1.008; 95% CI, 1.001–1.114, P=0.021) and changes in MTV were borderline significant (P=0.053) under multivariate analysis (Table 2).

To generalize our results to the current standard dose range, the significance of PET-CT parameters were further tested in patients who received doses of 60–70 Gy in 2-Gy fractions (Table 3). Similar to the results for all patients presented above, none of the FDG activity parameters, including pre-treatment or mid-treatment NSUVmax or NSUVmean or changes in either one, was significantly associated with OS. MTV, TLG, and CTV at pre-treatment and their changes were significant or borderline significant under univariate analysis (all P<0.05). After adjustment for other significant variables, only TLG at pre-treatment was significant (P=0.041). Although some had significances under univariate analysis, none of the mid-treatment volumetric factors was significant under multivariate analysis. Of the changes in PET-volumetric factors, both MTV and TLG were significant under univariate analysis, but only TLG remained significant after multivariate adjustment: a greater change in TLG (HR for each 10 units =1.006; 95% CI, 1.000–1.011; P=0.041) was associated with worse OS. The median survival times were 14 versus 28 months for patients with changes greater versus less than the median change in TLG.

Of patients treated with mid-treatment PET-adapted 3DCRT, none of PET parameters, including all of the volumetric factors, were significantly associated with OS (data not shown). In contrast to those treated with standard care, numerically better long-term survival was seen in patients who had a greater volumetric reduction at mid-treatment, with median survival times of 33 versus 19 months for patients with greater versus less than the median changes, respectively. The long-term survival was considerably better in patients treated with adaptive treatment compared with standard care 3DCRT, with a 19% difference in the 5-year survival rates (Figure 2). There were no significant differences in patient and tumor characteristics between these two groups.

Discussion

This large study, a retrospective pooled analysis of data acquired in four prospective clinical trials, examined the predictive effect of mid-treatment PET-CT on OS in NSCLC patients treated with definitive RT. It demonstrated that changes in FDG volumetric parameters instead of absolute values of the activity parameters at mid-treatment were significantly associated with OS. Interestingly, greater changes in PET volumetric factors mid-treatment were associated with significantly worse survival in patients treated with standard radiation of 60–70 Gy, after adjusting for clinical factors, but with better survival in those treated with mid-treatment PART.

Tumor volume is a known prognostic factor. Our findings on the significance of pre-treatment volumetric factors such as TLG are consistent with previous findings regarding the effect of tumor volume on survival in patients with NSCLC after 3DCRT [14, 17-19]. A recent meta-analysis of 1473 patients across 10 studies revealed that patients with a GTV greater than 112 cc had significantly worse survival ($P<0.01$) than patients with smaller tumors [17]. Our findings regarding the effect of CT-GTV on survival are consistent with reports from Asia, Washington University, RTOG and recently, a large multicenter effort [17-19]. Studies on the survival effect of baseline MTV are relatively limited. Investigators from the University of Chicago concluded that PET-MTV was more important than AJCC staging, and PET-MTV can further predict survival for each stage group such as IIIA [20, 21]. Another study reported that a smaller MTV on FDG-PET was associated with epidermal growth factor receptor (EGFR) mutations and better survival [22]. Our study differs from these previous studies because we examined the influence of both CT-GTV and PET-MTV on survival as well as the product of activity with MTV, i.e., TLG, showing a statistical significance of only TLG under multivariate analysis (Table-2, MTV was borderline with p value of 0.05, CTGTV was not). It is not clear to us, however, whether MTV serves as a better predictor than CT-GTV. Further studies with larger sample sizes are needed to determine whether PET-MTV provides additional prognostic value beyond CT-GTV and whether sophisticated PET radiomics can be truly theranostic for guiding precision treatment in NSCLC [23].

Importantly, this study examined the significance of mid-treatment tumor volume for survival prediction, which has only been studied in a limited series [24, 25]. A small retrospective study from Denmark (n = 21) reported significantly longer progression-free survival in patients with locally advanced NSCLC who demonstrated a partial response according to qualitative assessment during the course of treatment [26]. Earlier studies from the Netherlands and Stanford reported correlations between progression-free survival and PET-MTV and investigated the effect of TLG, but did not study the effect of changes in MTV and TLG [27-30]. A recent study of 28 patients from the Netherlands reported a significant association between TLG and the change in TLG at the second week with progression-free survival without providing details on SUV and MTV as well as MTV delineation [24, 25]. A study of 28 patients from Sweden reported no significant association between PET parameters at the third week during-treatment and 2-year OS, with inclusion of MTV defined to 40–50% of the lesion maximum [30]. Using a consistent tumor background ratio for MTV definition to minimize the effects of PET scanner and technique variance, our study of 102 patients is unique, also as it investigated the effect of multi-dimensional factors including PET-MTV, TLG and CT-GTV on long-term survival. We demonstrated that all of these volume-related factors were significant for OS under univariate analysis, though only TLG remained significant under multivariate analysis after adjustment for the clinically significant factors. Although the lack of statistical significance for GTV and MTV could be a result of the “small” sample size, it is also possible that the effect of tumor volume is correlated with other factors such as tumor stage and histology. An exploratory analysis for the responses according to histology showed that SCC patients had greater reduction than ADC patients, which is consist with the previous study. [31] Future

studies are needed to address the volumetric effects in cases of the same stage and same histology. The significance of the TLG effect warrants further independent validation.

Contrary to our expectations, this study demonstrated superior survival in patients with a lesser absolute reduction in tumor volume after treatment with otherwise standard care. The underlying etiology is unclear, and we speculate that this could be a result of multiple factors. It is possible that tumors with less reduction mid-treatment have a longer potential tumor doubling time (i.e., they are less aggressive, thus requiring a longer time to demonstrate the effects of radiation). Importantly, greater tumor shrinkage at mid-treatment may shift more normal tissue into high-dose regions (original treating target) for the remaining uniform treatment. These normal tissues may be infiltrated with lymphocytes that are primed for the tumors, and this is partially supported by a recent study from RTOG617 showing the effective dose to immune cells as the most important factor for survival [32]. This hypothesis is supported by the fact that patients treated with mid-treatment PART by reducing RT volume had an inverse volume-reduction and survival relationship: A greater reduction in PET volume was associated with a trend of superior survival after treatment with PART (Figure 2), which reduced doses to these normal tissues. Indeed, this differential association of mid-treatment PET volumes between patients who received standard and PET-adapted treatment confirmed the potential benefit of a mid-treatment adaptive trial [33]. These results suggest the promise of mid-treatment PART, which has been recently shown to be feasible [34-37]. Our approach of applying PART at around 40–50 Gy is being tested in randomized fashion under RTOG1106/ACRIN 6697.

Notably, although SUVmax is the most commonly used measure of FDG activity, it has been a commonly studied important factor for its prognostic value under many different settings [38, 39]. However, SUVmax was not found to be a significant factor in our study neither pre- nor mid-treatment. Our findings differ from a study from Maastricht University in which 34 patients showed a correlation between survival and SUV during-treatment [30]. This inconsistency is most likely multifactorial including small sample size effect, timing of during-treatment scanning and the variation in SUV. Indeed, it can be influenced by multiple factors such as the FDG dose used for imaging, the time of imaging after FDG injection, and blood glucose levels. Importantly, SUVmax only looked into one voxel of maximum activity without accounting for the remaining tumor or overall tumor burden. SUV could also be confounded by inflammation from non-tumor etiologies. We believe our method of using an internally normalized SUV is most resistant to these technical variations, and the mean SUV from a consistently outlined MTV would have provided a more robust estimate of tumor activity. Our data are consistent with the largest series on baseline PET from the University Chicago, which showed that SUV is not a significant factor for survival while MTV is [40].

In this study, we were unable to examine differences in survival based on radiation dose fractionations due to small sample sizes of the various radiation regimens. The study was also limited by the fact that we only had imaging data available for 30 out of 42 patients who underwent PET-adapted 3DCRT for this analysis, although the results for these patients were interestingly different from those treated with the standard of care, suggesting a need for a future trial [33].

In summary, this study demonstrated that changes in FDG volumetric factors during-treatment were significantly predictive of OS, while FDG activity parameters were not either at baseline nor at mid-treatment in patients with NSCLC treated with radiotherapy. Great changes in the metabolic active volume at mid-treatment were associated with worse survival after standard 3DCRT, but not after PART, suggesting the promise of using mid-treatment PART to improve OS in patients with NSCLC. This study supports the need for future phase III trials of a PET-CT volume-based radiation adaptive plan to improve survival.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Highlights

In addition to validating the significance of PET and CT tumor volumes, this study demonstrated that the metabolic tumor volume on PET and its changes mid-treatment were significantly associated with overall survival after radiation therapy in patients with non-small cell lung cancer. A greater reduction in mid-treatment PET tumor volume was associated with worse survival in patients treated with standard radiation therapy, but with better survival in those who received mid-treatment PET-adapted treatment.

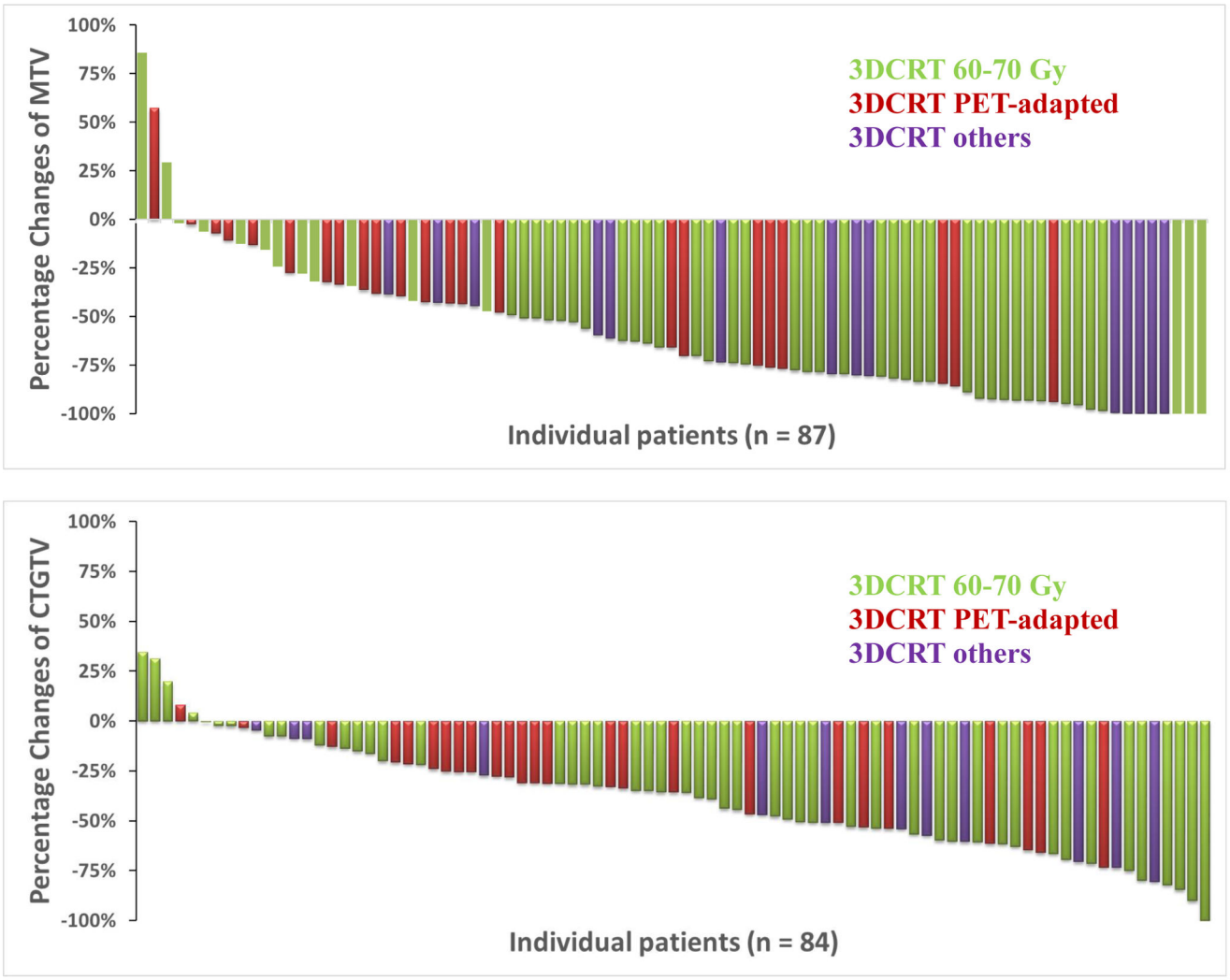

Figure 1.
Waterfall plots for tumor responses at mid-treatment.

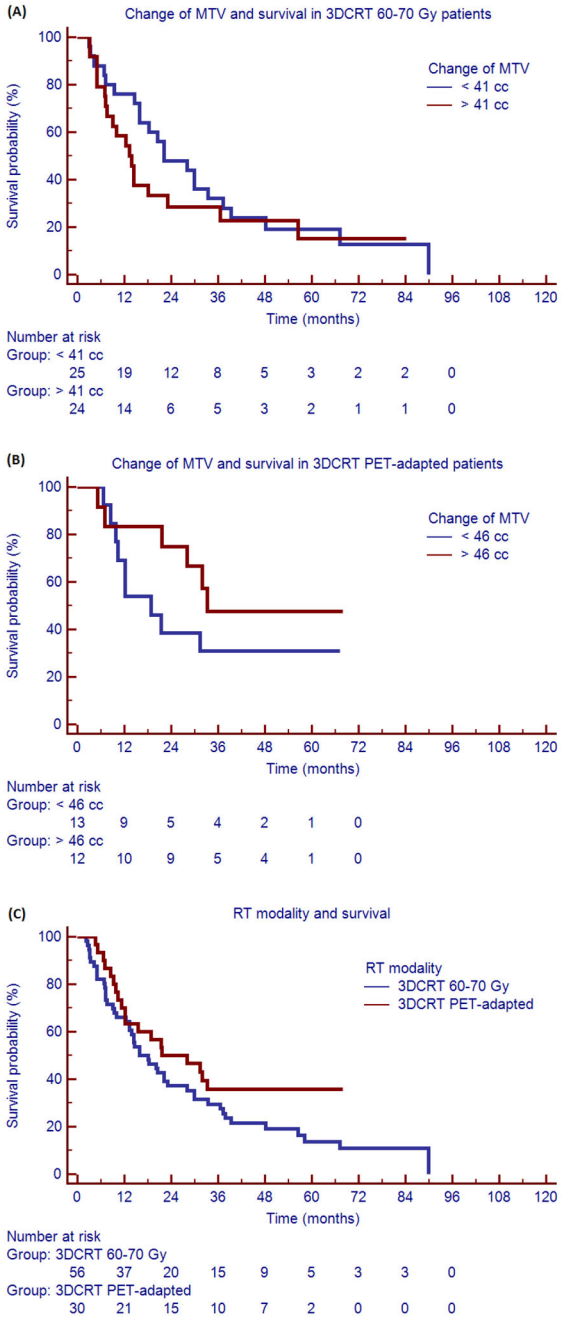

Figure 2.

Mid-treatment changes in PET-MTV, overall survival and radiation therapy modality.

Table 1

Patients Characteristics and Overall Survival.

Clinical factors	Patients (N)	Overall Survival			
		Death N (%)	MST (months) (95% CI)	P*	HR (95% CI)*
Age (years)					
≥65	51	33 (65)	31 (22-41)	0.074	1.000 (reference)
>65	51	44 (86)	16 (11-20)		1.021 (0.998-1.045)
Gender					
Male	78	64 (82)	21 (16-27)	**0.033**	1.000 (reference)
Female	24	13 (54)	39 (13-66)		0.521 (0.286-0.948)
Race					
Caucasian	101	76 (75)	25 (17-34)	0.126	1.000 (reference)
Others	1	1 (100)	7 (−)		4.803 (0.643-35.887)
Smoking					
No	4	1 (25)	-	0.104	1.000 (reference)
Yes	98	76 (78)	22 (13-31)		5.136 (0.713-37.021)
Histology					
Adenocarcinoma	24	13 (54)	56 (25-88)	**0.032**	1.000 (reference)
Squamous cell	37	29 (78)	21 (7-36)		2.092 (1.082-4.045)
Large cell	1	1 (100)	7 (−)		11.303 (1.399-91.325)
NOS	40	34 (85)	22 (12-32)		2.100 (1.104-3.994)
Clinical stage					
1	14	12 (86)	39 (12-66)	0.989	1.000 (reference)
II	12	12 (100)	12 (7-17)		2.745 (1.197-6.291)
III	76	53 (70)	22 (13-31)		1.220 (0.646-2.301)
KPS					
≤80	39	34 (87)	14 (7-22)	**0.022**	1.000 (reference)
>80	63	43 (68)	33 (24-43)		0.972 (0.949-0.996)
EQD2 (Gy)					
≤70	56	48 (86)	16 (9-23)	**0.005**	1.000 (reference)
>70	46	29 (63)	33 (17-49)		0.964 (0.940-0.989)
Chemotherapy					
No	17	16 (94)	18 (0-37)	0.308	1.000 (reference)
Yes	85	61 (72)	25 (17-34)		0.749 (0.430-1.305)
Radiation Modality					
3DCRT 60-70 Gy	56	48 (86)	16 (9-23)	**0.009**	1.000 (reference)
3DCRT PET-adapted	30	19 63	22 5-38		0.656 0.384-1.121
3DCRT others	16	10 (62)	58 (42-74)		0.360 (0.181-0.717)

Abbreviations: NOS, non-otherwise specified; MST, median OS; KPS, Karnofsky performance status; EQD2, the 2 Gy-per-fraction equivalent dose; HR, hazard ratio; 95% CI, 95% confidence interval.

*By univariate analysis. Age, KPS and EQD2 were analyzed as continuous variables.

Table 2

PET parameters and overall survival in all 102 patients.

Time points	PET Variable	Patients (N)	Death N (%)	MST (months) (95% CI)	Univariate P	aHR#	95% CI#	Multivariate P#
Pre-RT	**NSUVmean**							
	≤ median	51	41 (80)	29 (20-38)	0.877	1.000		0.935
	> median	51	36 (71)	21 (14-29)		1.102	0.109-11.163	
	NSUVmax							
	≤ median	51	38 (74)	28 (19-38)	0.536	1.000		0.982
	> median	51	39 (76)	22 (8-35)		1.007	0.568-1.783	
	MTV							
	≤ median	51	41 (80)	30 (22-38)	**0.008**	1.000		0.055
	> median	51	36 (71)	20 (11-29)		1.016	1.000-1.033	
	TLG							
	≤ median	51	41 (80)	30 (22-38)	**0.007**	1.000		**0.023**
	> median	51	36 (71)	18 (10-26)		1.006	1.001-1.010	
	CT-GTV							
	≤ median	51	39 (76)	30 (24-36)	**0.047**	1.000		0.230
	> median	51	38 (74)	14 (5-24)		1.008	0.995-1.021	
Mid-treatment	**NSUVmean**							
	≤ median	45	33 (73)	30 (24-37)	0.702	1.000		0.653
	> median	42	32 (76)	22 (11-32)		2.249	0.066-77.097	
	NSUVmax							
	≤ median	44	31 (70)	30 (25-36)	0.433	1.000		0.834
	> median	43	34 (79)	22 (17-26)		1.150	0.312-4.237	
	MTV							
	≤ median	44	32 (73)	33 (26-41)	**0.021**	1.000		**0.020**
	> median	43	33 (77)	21 (14-29)		1.059	1.009-1.111	
	TLG							
	≤ median	43	31 (72)	33 (25-42)	0.073	1.000		**0.046**
	> median	44	34 (77)	19 (11-27)		1.019	1.000-1.037	
	CT-GTV							
	≤ median	42	30 (71)	33 (22-45)	**0.026**	1.000		0.051
	> median	42	34 (81)	19 (10-28)		1.021	1.000-1.043	
Change (Pre-Mid)	**NSUVmean**							
	≤ median	43	33 (77)	29 (19-39)	0.555	1.000		0.363
	> median	44	33 (73)	22 (5-38)		0.262	0.015-4.702	
	NSUVmax							
	≤ median	43	32 (74)	29 (18-40)	0.907	1.000		0.583
	> median	44	33 (75)	22 (9-35)		0.804	0.369-1.751	
	MTV							
	≤ median	45	36 (80)	30 (26-34)	**0.016**	1.000		0.053
	> median	42	29 (69)	18 (8-29)		1.026	1.001-1.053	

Time points	PET Variable	Patients (N)	Death N (%)	MST (months) (95% CI)	Univariate P	aHR[#]	95% CI[#]	Multivariate P[#]
	TLG							
	≤ median	43	35 (81)	30 (26-34)	**0.012**	1.000		**0.021**
	> median	44	30 (68)	22 (9-34)		1.008	1.001-1.014	
	CT-GTV							
	≤ median	42	33 (79)	30 (24-36)	0.326	1.000		0.650
	> median	42	31 (74)	19 (8-29)		1.007	0.978-1.037	

Abbreviations: MST, median OS; aHR, adjusted hazard ratio; 95% CI, 95% confidence interval; SUV, standard update value; MTV, metabolic tumor volume; TLG, total lesion glycolysis; CT-GTV, CT based gross tumor volume.

[#]From multivariate Cox proportional hazards regression models by adjusting for gender, histology, KPS and EQD2. All PET parameters were analyzed as continuous variables.

Table 3

PET Parameters and overall survival in 56 patients treated with 60-70 Gy.

Time points	PET Variable	Univariate P	aHR[#]	95% CI[#]	Multivariate P[#]
Pre-RT	SUVmean				
	≤ median	0.558	1.000		0.900
	> median		0.827	0.042-16.125	
	SUVmax				
	≤ median	0.284	1.000		0.676
	> median		1.157	0.584-2.292	
	MTV				
	≤ median	**0.035**	1.000		0.092
	> median		1.016	0.998-1.034	
	TLG				
	≤ median	**0.015**	1.000		**0.041**
	> median		1.006	1.000-1.011	
	CT-GTV				
	≤ median	0.090	1.000		0.258
	> median		1.009	0.993-1.025	
Mid-treatment	SUVmean				
	≤ median	0.777	1.000		0.809
	> median		0.555	0.005-65.614	
	SUVmax				
	≤ median	0.195	1.000		0.960
	> median		1.043	0.201-5.407	
	MTV				
	≤ median	**0.044**	1.000		0.194
	> median		1.048	0.977-1.124	
	TLG				
	≤ median	0.084	1.000		0.229
	> median		1.020	0.987-1.054	
	CT-GTV				
	≤ median	0.060	1.000		0.216
	> median		1.016	0.991-1.041	
Change (Pre-Mid)	SUVmean				
	≤ median	0.895	1.000		0.690
	> median		0.450	0.009-22.921	
	SUVmax				
	≤ median	0.184	1.000		0.518
	> median		1.349	0.544-3.348	
	MTV				
	≤ median	**0.026**	1.000		0.063
	> median		1.024	0.999-1.051	

Time points	PET Variable	Univariate P	aHR[#]	95% CI[#]	Multivariate P[#]
	TLG				
	≤ median	**0.022**	1.000		**0.041**
	> median		1.007	1.000-1.014	
	CT-GTV				
	≤ median	0.210	1.000		0.338
	> median		1.015	0.984-1.047	

Abbreviations: MST, median OS; aHR, adjusted hazard ratio; 95% CI, 95% confidence interval; SUV, standard update value; MTV, metabolic tumor volume; TLG, total lesion glycolysis; CT-GTV, CT based gross tumor volume.

[#]From multivariate Cox proportional hazards regression models by adjusting for KPS. All PET parameters were analyzed as continuous variables.