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Prognostic Value of Pre radiotherapy ^{18}F -FDG PET/CT Volumetrics in Limited-stage Small Cell Lung Cancer

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Abstract

Background—Whether FDG PET/CT metrics predict outcome in limited-stage small cell lung cancer (LS-SCLC) has not been well established; most previous reports have only analyzed SUVmax. We investigated multiple pre-treatment PET metrics, including SUVmax, SUV mean, total lesion glycolysis (TLG), and metabolic tumor volume (MTV) in LS-SCLC patients undergoing chemoradiotherapy (CRT) and correlated them with survival and disease control outcomes.

Methods—All patients received platinum-based chemotherapy and a median radiation dose of 45 Gy. Kaplan-Meier and competing-risks analyses were performed to assess the prognostic value of PET metrics with respect to OS, DF, DFS, and LRF. Univariate and multivariate analyses were performed to account for the effect of other clinical factors on outcomes.

Results—A total of 120 patients with LS-SCLC had analyzable pre-CRT PET/CTs. The median follow up was 34 months. Median overall survival was 26.9 months. Overall survival was 53.2% at 2 years and 33.1% at 5 years. SUVmax, SUVmean, MTV, and TLG of the primary tumor were not significantly associated with OS, LRF, and DFS on univariate analysis. MTV was significantly associated with DF ($p=0.024$) on univariate but not multivariate analysis.

Conclusions—This is the largest reported series to date evaluating the prognostic value of baseline PET metrics in LS-SCLC. Neither SUVmax nor other analyzed PET metrics

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DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST:

The remaining authors declare that they have no conflict of interest.

demonstrated significant correlation with OS or LRF. MTV was correlated with DF and DFS, but this association was no longer significant after adjustment for other clinical factors. This analysis suggests that pre-treatment PET scans, even with the use of advanced metrics, do not have independent prognostic value for outcomes in LS-SCLC patients after CRT.

Keywords

Advanced PET metrics; overall survival; chemoradiotherapy; lung cancer; MTV

INTRODUCTION

In the United States, small cell lung cancer (SCLC) accounts for about 15% of all bronchogenic carcinomas and has poor prognosis¹. Patients with metastatic disease have a median survival of less than 1 year and for limited-stage SCLC (LS-SCLC), there is a 20–25% chance of cure². The main treatment for LS-SCLC is thoracic radiotherapy (RT) and chemotherapy (CT), typically with cisplatin plus etoposide³. Staging, age at diagnosis and performance status have been shown to have prognostic value⁴.

18F-FDG PET/CT (PET) is routinely used for initial staging in SCLC, but whether PET-CT also has independent prognostic value in LS-SCLC is not well established. Previously published data have demonstrated mixed results regarding prognostic value of pre-treatment PET parameters^{5,6}. There have been subsequent studies analyzing the role of PET, but these have often analyzed heterogeneous cohorts which included both extensive and limited-stage SCLC.

In general, maximum standardized uptake value (SUV), a quantitative parameter that measures the amount of FDG uptake into malignant tissues, has been used in most historical analyses⁷. One study had a subgroup analysis of limited-stage patients and found no significant association between SUVmax and PFS or OS (n=35)⁸. Another group analyzed a different PET metric and found MTV to be an independent prognostic factor for OS and PFS within their subgroup of LS patients (n=41)⁶. These examples indicate that there is currently no consensus regarding the prognostic role of PET metrics. We therefore sought to clarify the prognostic value of PET imaging in a larger, more rigorously-defined cohort of SCLC patients.

Besides SUVmax, other PET metrics of FDG avidity are available and may have more prognostic value compared to SUVmax in the pre-CRT setting. Therefore, we analyzed a large cohort of only LS-SCLC patients to determine whether a variety of PET metrics, in addition to SUVmax, would be predictive of survival and disease control. Our study also accounted for other clinically relevant factors to determine whether PET metrics had independent prognostic value.

METHODS

Patient Characteristics

All patients with LS-SCLC (n=156) treated with CRT with curative intent between 2003 and 2013 who had baseline PET-CT scans were identified. After obtaining a waiver of

authorization from our Institutional Review Board, patients' medical records were reviewed. Demographic information, stage, treatment, and disease-related outcomes were obtained from the medical records (Table 1). Patients were evaluated prior to initiation of therapy with chest CT and whole-body PET/CT scans. Of 156 patients, one hundred and twenty patients had analyzable PET/CTs. The remainder did not have re-analyzable scans on our picture archiving and communication system (PACs). Patients were staged according to the 7th Edition of the American Joint Committee on Cancer (AJCC) TNM staging system⁹ and all patients with up to Stage IIIB disease were considered as LS-SCLC. All patients had central pathological confirmation of SCLC. Patients were followed at regular intervals (every 3–6 months) after completion of therapy.

Treatment Protocol/Regimen

All patients received chemotherapy. All patients underwent CT simulation with custom immobilization in the supine position and were treated using either 3D-conformal or intensity-modulated radiation therapy. All PET-avid disease was included in the radiation treatment field.

PET/CT Imaging

Patients were imaged either on Advance, Discovery LS, or DSTE PET/CT scanners (General Electric Medical Systems, Milwaukee, WI) with attenuation, scatter, and other standard corrections applied by vendor provided algorithms. All patients had fasted for at least 4 hours prior to each scan. Images were acquired from the skull base to the upper thighs. All PET/CT scans were analyzed on AW Suite version 2.2 (Centricity AW Suite GE Healthcare) by an experienced nuclear medicine physician with all clinical and diagnostic imaging available. Images were reviewed in all standard planes along with maximum intensity projection images. Regions of interest were manually drawn around the visualized primary malignancy and nodes. To obtain SUV values, a determined cutoff established at our institution of 42% of threshold was used, and the values were normalized to body weight $[(\text{kBq/mL activity in region})/(\text{kBq injected activity/body mass in g})]^{10}$. From that threshold, SUVmax, MTV of only the primary tumor, and TLG (a calculated value of $\text{SUVmean} \times \text{MTV}$) were obtained. In the subsequent PET/CT scans, the region of interest was consistently drawn in the same general anatomic location.

Statistical Analysis

PET metrics were analyzed according to median splits and receiver operative characteristic (ROC) to allow for a more comparative analysis to other published data. SUVmax was also dichotomized for the distant failure endpoint using the method of optimal cut-point estimation, which uses a maximally selected Gray's statistic to choose the cut-point that best stratifies the cohort (Mazumdar et al). The endpoints of interest were OS, LRF (defined as progression [new, increased size or SUVmax] within the ipsilateral hemithorax), DF, and DFS. Overall survival was analyzed using the Kaplan-Meier method. LRF, DF, and DFS were analyzed using competing-risks methods. All endpoints were calculated from the date of the PET-CT scan. The risk of failure was estimated using a cumulative incidence function that accounted for death without failure as a competing event. Patients were censored if they were alive without a documented failure at the time of their most recent follow-up. The

differences in risk of failure between groups were assessed using the methods of Gray (univariate nonparametric analyses) and the Fine and Gray model for competing risks (multivariate analysis). Multivariate models were built using the significant variables and PET metrics in univariate analyses. All statistical tests were 2-sided, and p-values < 0.05 were considered significant. All analysis was done using R version 3.0.0 with survival and cmprsk packages.

RESULTS

The cohort's median age was 66 (range 45–93). One hundred and two patients had greater than 80% KPS, and 18 had less than 80%. The characteristics of the 120 patients are shown in Table 1. The majority of patients (65%) received platinum-based chemotherapy, with cisplatin and etoposide being the most common regimen. The median radiation therapy dose was 45Gy (range 45–70Gy). Forty-six patients received once-daily treatment while 74 received twice daily treatments. Sixty-three patients (53%) had prophylactic cranial irradiation (PCI) (Table 1). Average uptake time was 66 min (range 45–130). Injected dose was greater than 10 millicuries [mCi]. The average blood glucose level was 103 mg/dL (range 59–199). Median SUVmax, SUVmean, MTV, and TLG were 12.15, 7.5, 21.35, and 182.06, respectively (Table 2).

PET Parameters and Patient Outcomes

We analyzed various pretreatment PET/CT metrics as well as clinical factors to determine their prognostic value in regards to OS. Amongst the PET variables (SUVmax, mean, MTV, and TLG), no significant association was found in univariate analysis (Table 3). Clinical parameters including KPS (p=0.047), clinical stage IIIA vs. I/II (p=0.048) and IIIB vs. I/II (p=0.031) were significantly associated with OS in univariate analysis, while age and gender were not.

For univariate analysis, no PET/CT or clinical parameters were significantly associated with locoregional failure (Table 3).

MTV (p=0.024) was the only PET/CT metric that was significantly associated with DF (Table 3). There was a strong association between clinical parameters for distant failure; higher age (>65 vs. ≤65, p=0.036), clinical stage IIIA vs. I/II (p=0.007), and clinical stage IIIB vs. I/II (p<0.001). In a multivariate analysis, age and clinical stage (III vs I/II) remained independent predictors of distant failure, while MTV did not. Cutpoint analysis of SUVmax for DF did not identify any significant SUVmax threshold.

No PET metrics were significantly correlated with DFS (Table 3). Only clinical stage was strongly associated with DFS, and again, was found to be an independent predictor when adjusting for age and MTV.

DISCUSSION

In the existing literature, there are conflicting data about the prognostic role of PET/CT metrics in SCLC patients treated with definitive CRT. To further complicate the issue, many

of the studies analyzed LS and extensive-stage patients in the same cohort. This study attempted to identify the role of PET/CT metrics in a large and relatively uniform cohort of LS-SCLC patients treated with definitive CRT. We also adjusted for other possible clinical prognostic factors, to better isolate whether PET/CT metrics have independent prognostic value. We concluded that within our cohort, PET metrics of pre-treatment tumor metabolic activity do not have independent prognostic value for outcomes in LS-SCLC patients after CRT.

Most studies about the prognostic value of PET have focused exclusively on SUVmax, the most easily and commonly reported metric. We hypothesized that volumetric parameters may show a stronger correlation with outcome. Though less commonly reported, volumetrics may potentially be a more accurate prognostic factor since it also reflects the overall tumor burden.

Gomez et al. analyzed median values of SUVmax in the primary tumor, the nodal disease, and mean of the sum of the primary + nodal SUVmax in LS-SCLC, and concluded that SUVmax could not predict overall survival and locoregional recurrence¹¹. The majority of patients in their study received twice daily treatments, similar to our cohort. Our study confirms that for the examined LS-SCLC patients, pretreatment SUVmax of the primary malignancy is not predictive of OS or LRF.

In a mixed cohort of patients, the majority having extensive disease, van der Leest et al. subdivided their patients into high and low SUVmax based on the median value of 11.3. They discovered that SUVmax did not discriminate for either OS or progression-free survival (PFS) in their entire cohort (n=75)⁸. In addition, in their subset analysis of stage I–III disease (n=35), no association was found between SUVmax and OS or PFS.

A study by Oh et al. also included mostly patients with extensive-stage disease (n=106). They analyzed whole body MTV (WBMTV), defined as MTV of primary tumor, regional lymph nodes, and all distant metastases. In their univariate analysis under TNM staging, the median WBMTV was 127 cm³, and the median survival of patients with low WBMTV was significantly longer than that of patients with high WBMTV for OS and PFS. On multivariate analysis, high WBMTV was a significant predictor for OS and PFS. In a subgroup univariate analysis of limited-stage patients (n=45), their median WBMTV was 72 cm³, and patients with lower WBMTV had a significantly longer OS and PFS (p<0.001). They also looked at conventional staging with WBMTV and found that patients with LD and lower WBMTV had a significantly longer OS and PFS (p<0.001). Our analysis was similar, but utilized MTV of the primary tumor only. We observed a significant association with DF on univariate analysis but not on multivariate analysis. This re-affirms that MTV is highly correlated with disease burden, but suggests that it does not add additional value after adjusting for clinical stage.

Another group of investigators led by Zhu et al. determined through ROC analysis their optimal cutoff values for MTV, iSUV, SUVmean, and SUVmax of 64.6 cm³, 318.4, 6.9, and 7.8, respectively. In addition, they performed a subgroup analysis by stage and they were able to show a significant association between MTV and OS within LS patients. Larger

MTV in that cohort (n=11) showed a significantly shorter median OS than LS with smaller MTV (n=30) (14.5 months vs. 25.9 months) and PFS (7.8 months vs. 19.7 months)⁶. In our analysis, we used a median cutoff for MTV of 21.35 and contoured only the primary lesion. We found MTV to be significant for DF in univariate but not multivariate analysis. We did not, however, find significance with respect to OS, LRF, or DFS. We speculated that other SUVmax cutoff values might be more useful than the median. However, optimal cutpoint analysis of SUVmax for distant failure still yielded no meaningful cutpoint.

Compared to Zhu et al., there are subtle differences in our image analyses that could have affected our results. Mainly, their contouring margins around the target lesions used a circle encompassing regions equal or greater than SUV 2.5, all tumor foci were segmented, and they added all MTVs of each slice manually. We used a cube to contour our margins with a cutoff of 42% of SUVmax around the target lesion, which ultimately incorporates all 3 orthogonal planes of section.

Various limitations exist in this current study that should be highlighted. Like all previously referenced studies, this is a single-institution, retrospective analysis. There was some heterogeneity in treatment regimens, such as the use of twice-daily vs. once-daily thoracic radiation, the choice of chemotherapy regimen, and the use of prophylactic cranial irradiation. Furthermore, patients obtained PET-CT scans on a variety of different scanners, some of which were outside of our institution. Patients being scanned on different scanners can yield different SUV values because scan acquisition, image reconstruction, and data analysis settings can vary (Boellaard 2008).

Although our study failed to demonstrate prognostic utility of pre-treatment PET-CT parameters, which is consistent with most prior studies, this analysis does have some notable strengths. In particular, it is the largest series yet reported of PET in limited-stage SCLC. Prior studies were relatively small, and therefore may not have had the statistical power to demonstrate significance of PET-CT parameters, if they existed. More importantly, our study was among the first to analyze additional PET-CT parameters besides SUVmax. Since SUVmax is simply one measure of FDG avidity, it remained possible that other PET-CT parameters, particularly volumetric ones, might hold prognostic value even if SUVmax did not. However, we did not find any significant association with MTV, TLG, or SUVmean. Thirdly, we analyzed multiple disease control outcomes besides survival, in case PET-CT was predictive of patterns of failure such as locoregional or distant progression. Finally, we accounted for additional clinical and treatment parameters that might affect outcome and confound the relationship of PET-CT parameters to outcome. In particular, we limited our analysis to limited-stage patients and then controlled further for AJCC stage group.

Therefore, although our study did not generate any novel findings about the relationship of pretreatment PET-CT to outcome in LS-SCLC, the analysis of advanced PET metrics, size of our study cohort and the comprehensiveness of our analysis lead to a more definite conclusion, compared to the more limited size and methodology of previously published analyses.

It is possible to make some hypotheses about the lack of prognostic value of PET-CT in LS-SCLC. As noted above, the fact that clinical stage proved to be independently prognostic suggests that PET parameters may primarily be a reflection of overall disease burden. It is also possible that more FDG-avid tumors, even if they reflect a more biologically aggressive phenotype, are also more responsive to therapy. As such, any potential prognostic value of PET-CT would be negated by the greater efficacy of treatment. Ultimately, we conclude that pretreatment FDG avidity does not provide meaningful information about the prognosis or patterns of failure in LS-SCLC treated with definitive chemoradiation. Future studies could investigate post-treatment PET-CT parameters and changes in tumor activity (pre-versus post-treatment) as it is possible that these could have more prognostic value. In conclusion, this is the largest series of patients with limited-stage disease and a pre-treatment PET/CT. Despite a suggestion that MTV may be prognostic for distant failure, after adjustment for other clinical factors, notably stage, our results indicate that pretreatment PET-CT parameters have no independent prognostic value in LS-SCLC.

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REFERENCES

1. Oh J-R, Seo J-H, Chong A, et al. Whole-body metabolic tumour volume of 18F-FDG PET/CT improves the prediction of prognosis in small cell lung cancer. *European journal of nuclear medicine and molecular imaging*. 2012; 39:925–935. [PubMed: 22270509]
2. Ceresoli GL. FDG PET/CT metabolic tumour volume in small-cell lung cancer: better staging and prognostic stratification for an improved therapeutic strategy. *European journal of nuclear medicine and molecular imaging*. 2012; 39:921–924. [PubMed: 22426828]
3. Turrisi AT 3rd, Kim K, Blum R, et al. Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. *The New England journal of medicine*. 1999; 340:265–271. [PubMed: 9920950]
4. Paesmans M, Sculier JP, Lecomte J, et al. Prognostic factors for patients with small cell lung carcinoma: analysis of a series of 763 patients included in 4 consecutive prospective trials with a minimum follow-up of 5 years. *Cancer*. 2000; 89:523–533. [PubMed: 10931451]
5. Gomez DR, Gladish GW, Wei X, et al. Prognostic Value of Positron Emission Tomography/Computed Tomography Findings in Limited-stage Small Cell Lung Cancer Before Chemoradiation Therapy. *American journal of clinical oncology*. 2012
6. Zhu D, Ma T, Niu Z, et al. Prognostic significance of metabolic parameters measured by (18)Ffluorodeoxyglucose positron emission tomography/computed tomography in patients with small cell lung cancer. *Lung cancer*. 2011; 73:332–337. [PubMed: 21292341]
7. Shirvani SM, Komaki R, Heymach JV, Fossella FV, Chang JY. Positron emission tomography/computed tomography-guided intensity-modulated radiotherapy for limited-stage small-cell lung cancer. *International journal of radiation oncology, biology, physics*. 2012; 82:e91–e97.
8. van der Leest C, Smit EF, Baas J, et al. SUVmax during 18FDG-PET scanning in small cell lung cancer: similar information as in non-small cell lung cancer? *Lung cancer*. 2012; 76:67–71. [PubMed: 21996089]
9. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Annals of surgical oncology*. 2010; 17:1471–1474. [PubMed: 20180029]
10. Erdi YE, Mawlawi O, Larson SM, et al. Segmentation of lung lesion volume by adaptive positron emission tomography image thresholding. *Cancer*. 1997; 80:2505–2509. [PubMed: 9406703]

11. Gomez DR, Gladish GW, Wei X, et al. Prognostic value of positron emission tomography/computed tomography findings in limited-stage small cell lung cancer before chemoradiation therapy. *American journal of clinical oncology*. 2014; 37:77–80. [PubMed: 23111360]

CLINICAL PRACTICE POINTS

- PET-CT has proven value in distinguishing limited-stage from extensive-stage small cell lung cancer, but it remains unclear whether PET metrics also have prognostic value in limited-stage disease.
- Conflicting data has been published regarding the prognostic value of SUVmax. Little has been published about the prognostic value of other PET-based metrics.
- This analysis of a large cohort of limited-stage disease, which examined multiple PET metrics and adjusted for other clinical confounders, indicates more clearly that PET metrics do not have independent prognostic value in limited-stage SCLC that is treated with chemoradiation.

Table 1

Patient demographic and clinical characteristics (n=120)

Factor	N (%)
Gender	
Male	52 (43)
Female	68 (57)
KPS	
< 80	18 (15)
80	102 (85)
Clinical stage	
I/II	32 (27)
IIIA	56 (47)
IIIB	32 (27)
Fractions per day	
Once-daily	46 (38)
Twice-daily	74 (62)
PCI given	
No	57 (48)
Yes	63 (53)
Age at pre-RT PET	65.5 (45–93)*

* Median (range)

Table 2

PET Metrics (n=120)

	Median	Range	IQR
SUV _{max}	12.15	2.90–70.50	9.60–14.95
SUV _{mean}	7.50	1.50–43.60	5.90–9.03
MTV	21.45	1.44–782.00	9.22–65.65
TLG	182.06	3.46–2258.02	56.42–551.10

Table 3

Association of SUV metrics with clinical outcomes

	Hazard Ratio for OS (95% CI) (p-value)	Hazard Ratio for DF (95% CI) (p-value)	Hazard Ratio for DFS (95% CI) (p-value)	Hazard Ratio for LRF (95% CI) (p-value)
SUV _{max}	0.91 (0.57–1.45) (p=0.68)	1.4 (0.83–2.37) (p=0.21)	1.22 (0.76–1.96) (p=0.41)	1.15 (0.55–2.39) (p=0.72)
SUV _{mean}	0.8 (0.50–1.29) (p=0.36)	1.12 (0.66–1.89) (p=0.68)	1.0 (0.63–1.61) (p=0.98)	0.86 (0.41–1.80) (p=0.69)
MTV	1.22 (0.76–1.96) (p=0.41)	1.85 (1.08–3.15) (p=0.024)	1.48 (0.92–2.38) (p=0.1)	1.18 (0.56–2.48) (p=0.66)
TLG	1.0 (0.63–1.61) (p=0.99)	1.53 (0.90–2.62) (p=0.12)	1.23 (0.77–1.98) (p=0.39)	1.2 (0.57–2.51) (p=0.63)