Prognostic significance of semi-quantitative FDG-PET/CT parameters in stage I non-small cell lung cancer (NSCLC) treated with Carbon-ion radiotherapy

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BACKGROUND

Carbon ion (C-ion) radiotherapy: an emerging treatment modality for stage I NSCLC

- for those unfit or unwilling for surgery
- available in a few centers around the world
- Very costly
- No efficient prognostic study to-date till this study

OBJECTIVES

- To evaluate the prognostic significance of volumetric parameters of FDG PET/CT in stage I NSCLC patients treated with C-ion radiotherapy (RT), and need of histology-wise separate cut-offs for risk stratification

METHODS

- **Patients:** 39 patients (29 men, 10 women)
- pathologically confirmed stage I NSCLC patients
- between June 2010 and October 2016,
- having PET/CT performed in our hospital before C-ion RT
- > 6 months follow up
- No other anti-cancer therapy before C-ion RT
- Age: 71.9+/-8.3 years old, range: 54-85 years

- **FDG parameters** (measured using Syngo.via software)
- Standardized uptake values (maximum – SUVmax, mean – SUVmean, peak – SUVpeak)
- Metabolic tumor volume (MTV): calculated by using SUV of 2.5 or greater within the isocountour line
- Total lesion glycolysis (TLG) values: calculated as MTV multiplied by SUVmean by using SUV of 2.5

- **Prognostic study** using Cox proportional hazards regression analysis
- Comparison of medians of significant parameters between adenocarcinoma and Squamous cell carcinoma using Mann-Whitney test
- Kaplan Meier curves for median based low and high-risk groups
- Accuracy of predictive performance of the significant parameters analyzed using area under the curve (AUC) in receiver operating characteristic (ROC) curve analysis
- Correlation and regression analyses to calculate intraobserver and interobserver variabilities between two observers
- SPSS ver. 25 was used for statistical analysis, $p<0.05$ considered significant

RESULTS

- Median follow up time: 44.8 months (8.9 – 83.8)
- 23 Adenocarcinoma , 16 Squamous cell carcinoma patietns
- 29 stage IA and 10 stage IB patients

Survival Rates	1-year	2-year	3-year
Overall Survival (OS)	94.9%	84.3%	70.8%
Progression Free Survival (PFS)	82.1%	69.2%	58.4%
Local Control (LC)	97.3%	85.7%	82.3%

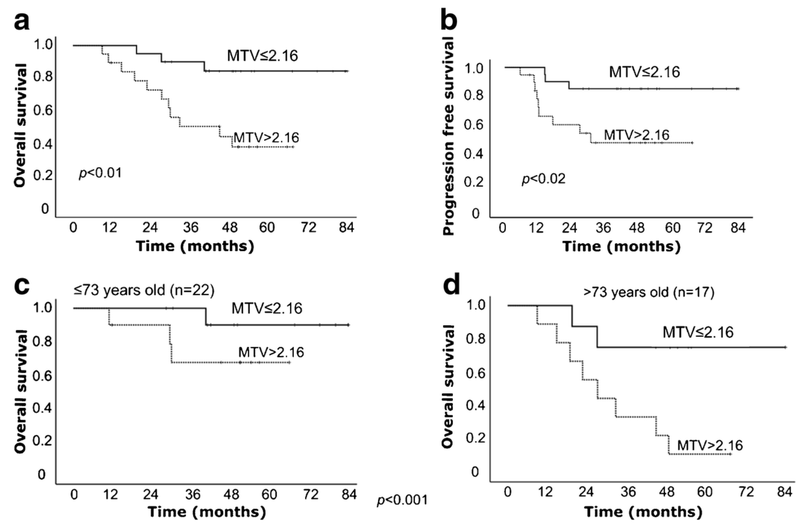
- OS : 1st day of the C-ion RT till the day of death or last follow-up.
- PFS: 1st day of the C-ion RT to the day of recurrence or metastasis.
- LC : 1st day of the C-ion RT to the day of a local recurrence.

Univariate and Multivariate Cox proportional Hazard Regression Analysis

Univariate Analysis Independent variable	OS HR	95% CI	*p*-value	PFS HR	95% CI	*p*-value
Age	1.087	1.008, 1.172	**0.030**			n.s.
Male Sex			n..s.			n.s.
Tumor size (continuous, cm)			n.s.			n.s.
Tumor size (categorical, based on median)						
Stage IA			n.s.			n.s.
Adenocarcinoma	0.279	0.093, 0.834	**0.022**			n.s.
Irradiation dose (52.8 Gy)			n.s.			n.s.
Operability			n.s.			n.s.
Categorical FDG variables (based on median)						
SUVmax			n.s.			
SUVpeak			n.s.			
SUVmean			n.s.			
MTV	5.199	1.447,18.675	0.012	4.634	1.250, 17.179	0.022
TLG	5.199	1.447,18.675	**0.012**	3.032	0.910,10.1.5	0.071
Multivariate Analysis						
MTV	4.832	1.211, 19.274	0.026	5.302	1.316, 21.359	0.019
TLG	3.728	0.842, 16.510	0.083			
Age	1.092	1.001, 1.190	**0.048**			

For LC: all parameters non-significant

Kaplan-Meier curves of **a** OS and **b** PFS stratified by MTV, and **c**, **d** OS stratified by age-adjusted MTV in stage I NSCLC patients treated with C-ion RT



ROC curve Analysis showed

- MTV had greatest accuracy among all, for OS (AUC=0.74, p<0.02) and PFS (0.72, p<0.04)
- Tumor size had the lowest and insignificant AUC compared to other parameters for OS (0.63, p>0.1) and PFS (0.62, p>0.2)

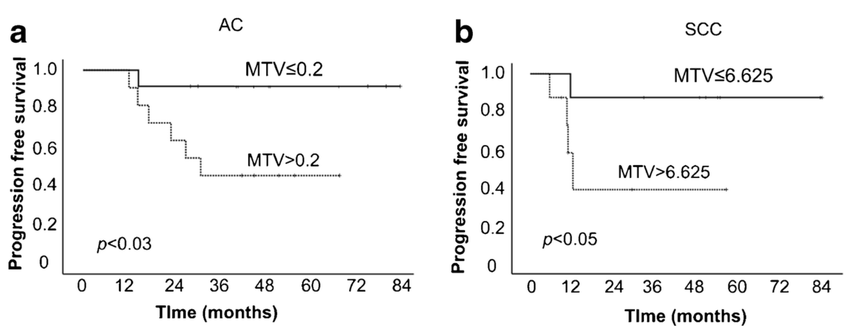
Median MTVs between AC and SCC, p<0.01

- AC – 0.2 cm^3 (range, 0-43.7 cm^3)
- SCC : 6.625 cm3 (0 -70.6 cm3)

KM curves for PFS in AC and SCC using overall median of MTV 2.16 as cut-off

- significant only for AC, but insignificant for SCC.
- However, using MTV median values of each histology, they were found significant.

Kaplan-Meier curves of PFS stratified by MTV in **a** stage I lung adenocarcinomas and **b** SCC treated with C-ion RT



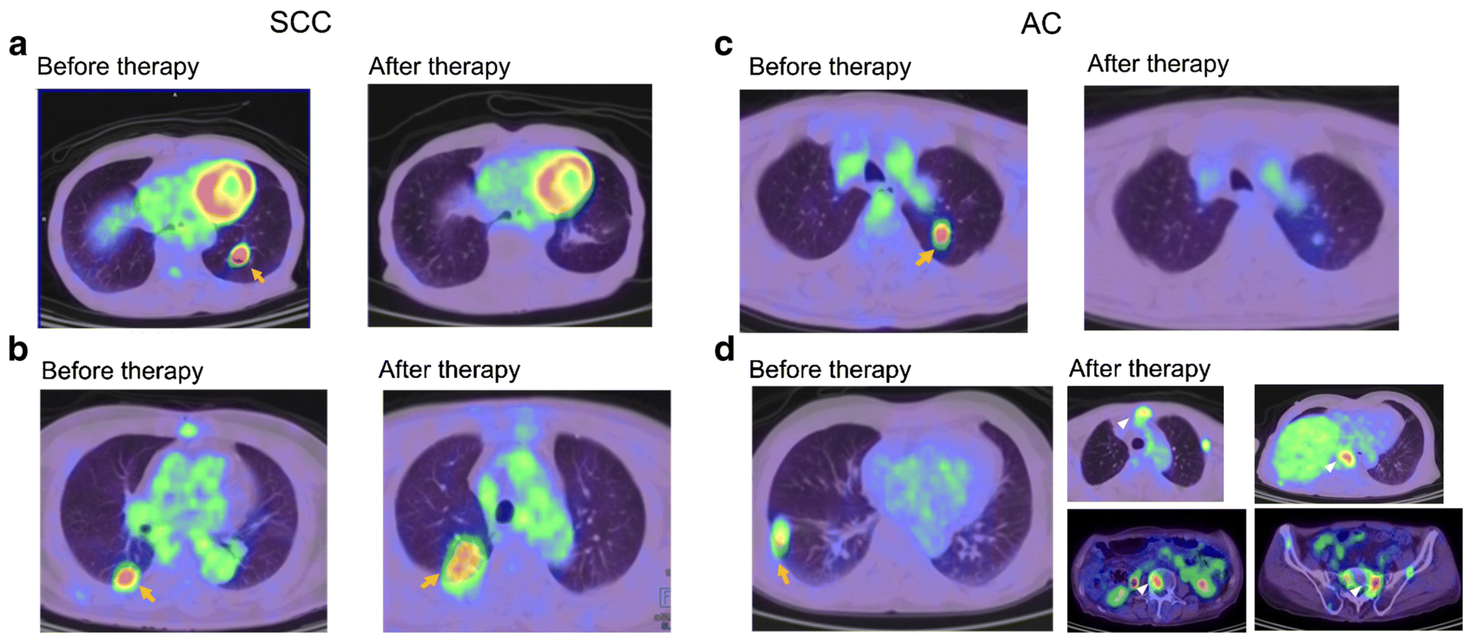
Reliability and Reproducibility of MTV compared to tumor size

Pearson correlation (r) and regression analysis between two reading times (intraobserver) and between two observers (interobserver) showed

- very high reproducibility for MTV (r = 0.998–1, intercept = 0.04–0.2%, slope = 0.98–1.04)
- and lowest for tumor size (r = 0.85–0.92, intercept = 1.39–3.99, slope = 0.76–0.99).

Intraclass correlation coefficient (ICC) values:
- high for MTV (ICC = 0.99–1)
- compared to tumor size (ICC = 0.94–0.95).

Representative Cases:



Lung tumor lesions indicated by yellow arrows, and bone metastases indicated by white arrowheads.

SCC patients:
a 80-year-old male having tumor with SUVmax 10.34 and MTV 5.78 cm3, with 48.6 months PFS/OS, and
b 76-year-old male having tumor with SUVmax 7.04 and MTV 7.96 cm3 with 5.5 months PFS and 27.1 months OS;

AC patients:
c 77-year-old male having tumor with SUVmax 5.85 and MTV 1.59 cm3 with 55.4 months PFS/OS, and
d 73-year-old male having tumor with SUVmax 4.28 and MTV 2.51 cm3 with 17.2 months PFS and 29.7 months OS.

In both SCC and AC, **MTV correlated better than SUVmax with survival outcomes**

CONCLUSIONS

Among FDG PET parameters studied, MTV was the only independent significant parameter with high reproducibility and reliability and superior to tumor size, for prognosis of OS and PFS in NSCLC stage I patients treated with C-ion therapy, and histology may also need to be considered in determining the cut-off for stratifying the low and high MTV groups.

This study has been accepted by EJNMMI and can be accessed openly by the readers.

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ORIGINAL ARTICLE

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