# Intratumoral Metabolic Heterogeneity and Other Quantitative FDG PET/CT Parameters for Prognosis Prediction in Esophageal Cancer

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## Introduction

FDG PET/CT is routinely performed in patients with esophageal cancer for initial staging and during restaging after induction chemoradiation prior to surgery. One of the roles of PET/CT performed at initial staging is that it can give prognostic information to the physician which can tailor treatment. The most popular quantitative variables that have been used are standard uptake volume max (SUVmax), metabolic tumor volume (MTV) and total lesion glycolysis (TLG) (Han et al 2018).

In esophageal cancers, some studies showed lower survival rates with increased MTV and TLG, but no association with SUV max (Rizk et al 2009). However, none of these variables have been great at predicting prognosis, which has spiked an interest to look for novel approaches. Metabolic heterogeneity has garnered interest as one of the markers that could more accurately predict prognosis (Eary et al 2008).

Intratumoral metabolic heterogeneity reflects the distribution of uptake across a lesion. This value is obtained by creating a cumulative SUV-volume histograms by plotting the percent volume of the tumor greater than different thresholds of percentage of SUVmax. The area of the histogram or area under the curve (AUC-CSH) gives a numeric value for heterogeneity, with a lower area under the curve corresponding to a higher degree of heterogeneity (Van Velden et al 2011).

## Objective

To evaluate the impact of heterogeneity as well as the other quantitative parameters for predicting progression free survival and overall survival in patients with esophageal cancer

## References

Han, S et al. Prognostic Value of Volumetric Parameters of Pretreatment 18F-FDG PET/CT in Esophageal Cancer: A Systematic Review and Meta-analysis. Clin Nucl Med 2018 43(12): 887-894.
Rizk, NP et al. Predictive value of initial PET-SUVmax in patients with locally advanced esophageal and gastroesophageal junction adenocarcinoma. J Thorac Oncol. 2009 Jul;4(7):875-9.
Eary JF et al. Spatial heterogeneity in sarcoma 18F-FDG uptake as a predictor of patient outcome. J Nucl Med. 2008 Dec;49(12):1973-9.
Van Velden FH et al. Evaluation of a cumulative SUV-volume histogram method for parameterizing heterogeneous intratumoural FDG uptake in non-small cell lung cancer PET studies. Eur J Nucl Med Mol Imaging. 2011 Sep;38(9):1636-47.

## Methods

This IRB and HIPPA compliant retrospective study included a total of 71 patients with biopsy proven adenocarcinoma or squamous cell carcinoma of the esophagus who had a FDG PET/CT for initial staging.

Automated gradient-based segmentation method was used to assess the primary tumor standardized uptake value maximum and peak (SUV max and SUV peak), metabolic tumor volume (MTV) and metabolic intratumoral heterogeneity index, calculated as the area under cumulative SUV-volume histograms (AUC-CSH), with lower AUC-CSH indexes corresponding to higher degrees of tumor heterogeneity. Patient's demographics and tumor staging were also collected. Median follow up time was 28.2 ± 30.3 months. Overall survival (OS) and progression free survival (PFS) were calculated using univariate cox regression with the adjustment of age, gender, staging, treatment and histological grade. All PET measurements were normalized and the hazard ratios change was equivalent to one standard deviation.

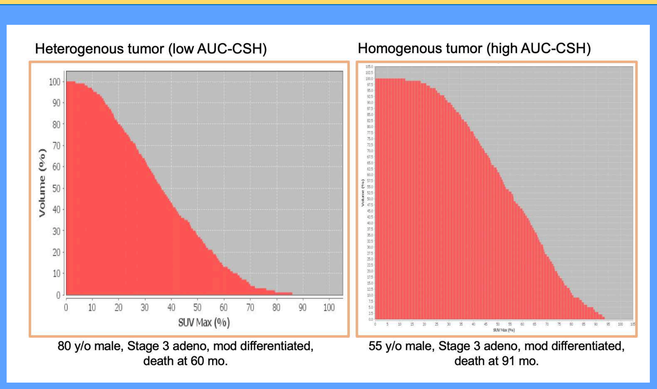
## Results

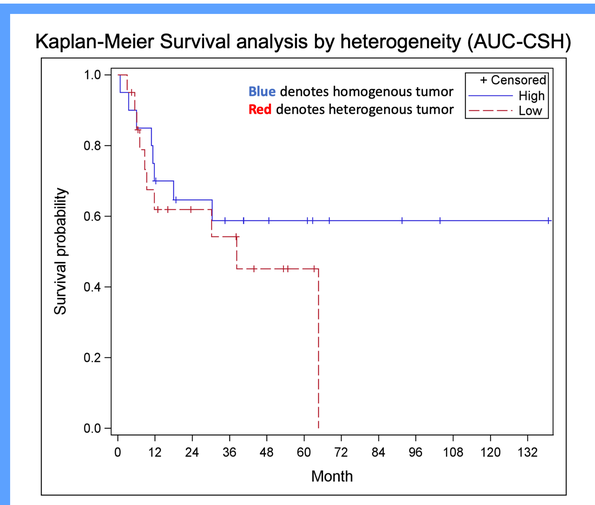
The patients' mean age was 64 ± 10.3 years and there were 6 patients with stage I, 11 with stage II, 31 with stage III, 21 with stage IV disease, and 2 with unknown staging.

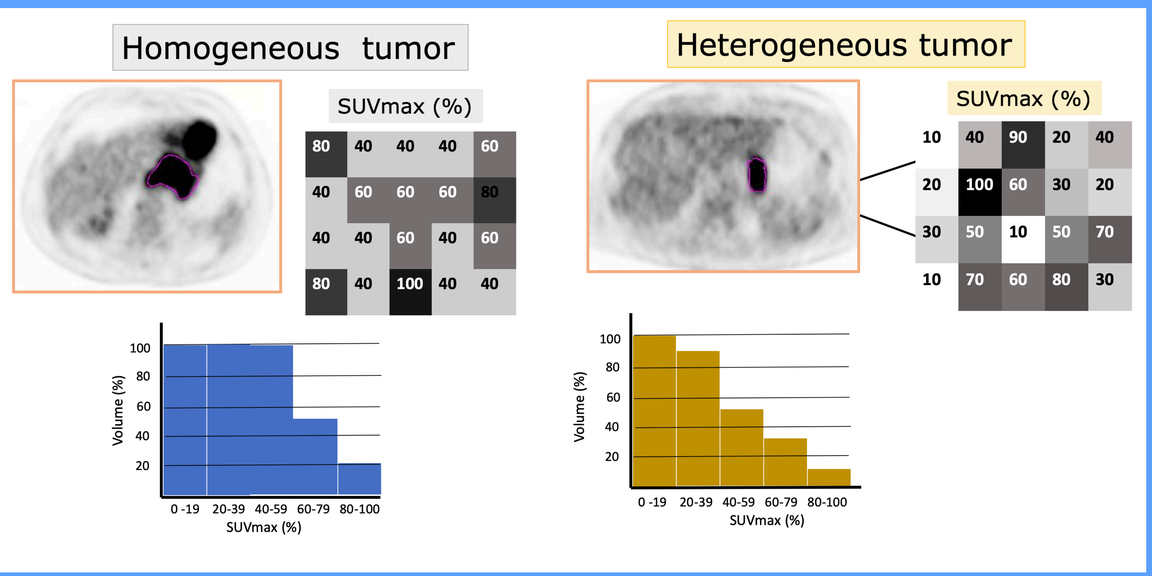
Median survival was 16.1 months. Forty-six patients died and 15 were alive as of the end of the study (for 10 patients no recent information on survival was available). Eighteen patients had recurrence as of the end of the study.

Higher MTV was significantly associated with reduced PFS for every standard deviation increase (HR=0.193, 95% CI=0.052-0.711, p=0.0134). Higher AUC-CSH (lower tumor heterogeneity, homogeneous tumor) was significantly associated with increased PFS for every standard deviation increase in the area under the curve (HR=10.779, 95% CI=1.306-88.957, p=0.0272). In multivariable cox regression, with only AUC_CSH (heterogeneity) selected, no other variable has significant incremental contribution in PFS.

There was no significant correlation of any of the parameters with overall survival (OS).




## Discussion

There was a significant association of MTV and tumor heterogeneity with progression free survival for patients with esophageal cancer. While our findings are promising for using heterogeneity as a prognostic indicator, there are some notable limitations of our retrospective study. We used a public registry to search for patient death, which can have variable accuracy compared to patients that were followed closely by our hospital until death. Additionally, few patients were altogether lost to follow up which limited our sample size of useable patients.

Our study showed a significant association of tumor heterogeneity and metabolic tumor volume on initial staging FDG PET/CT with progression free survival for patients with esophageal cancer. PET/CT quantitative parameters on initial staging scan can provide prognostic information, potentially leading to a more personalized approach for patient's treatment.