Current Trends in
Clinical & Medical Imaging
ISSN: 2573-2609

Juniper Publishers
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Research Article
Volume 3 Issue 3 - June 2019
DOI: 10.19080/CTCMI.2019.03.555613

Curr Trends Clin Med Imaging

Metabolic Tumor Volume Predicts Overall Survival in Patients with Stage III and IV Small Cell Lung Cancer

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Received date: May 29, 2019; **Published date:** June 13, 2019

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Abstract

Objective: This study aimed to determine the relationship between the pre-operative metabolic tumor volume (MTV) and the overall survival (OS) of patients with stage III and IV small cell lung cancer (SCLC) using F-18 2-fluoro-2-deoxy-D-glucose (FDG) positron-emission tomography–computed tomography (PET-CT) scanning.

Methods: Forty patients with pathologically proven stage III and III SCLC had FDG PET-CT scans before concurrent chemoradiotherapy. Computer-aided MTV measurement was performed using RT-Image, an open-source software application. A maximum-intensity projection view of the images permitted rapid visual identification of the hypermetabolic lesions (primary tumor and lymph nodes). Each tumor interactively identified by the user was then volumetrically segmented by the automatic software algorithm, which defines the segmented volume as all connected voxels with intensity greater than a lesion-specific adaptive threshold of 60% of the peak SUV within the lesion. The software then calculates the MTV by summing the volumes of all segmented lesions. Kaplan-Meier curves and Cox proportional hazards regression models were used to associate MTV with OS.

Results: A total of 40 patients were analyzed and follow-up in 3 years. The mean of survival time was 12.6 months (95%CI: 9.5 – 15.5 months). Only one case survived up to 36 months (3.1%). The median pretreatment MTV was 36.2 mL (range, 0.05-529.2 mL). Patients were divided into higher (≥36.2 ml) and lower (<36.2 ml) MTV groups. The higher MTV group exhibited a significantly worse OS compared with the lower MTV group. Resession revealed a significant inverse relationship between MTV and affected survival rate.

Conclusion: Higher pretreatment MTV is associated with significantly worse OS in inoperable stage III and IV SCLC treated with concurrent chemoradiotherapy.

Keywords: Prediction; Overall Survival; Small Cell Lung Cancer; MTV

Abbreviation: 18FDG PET-CT: [18F] Fluoro-D-Glucose Positron-Emission Tomography; SCLC: Small Cell Lung Cancer;CCRT: Concurrent Chemoradiotherapy; SUVmax: Maximum Standardized Uptake Value; MTV: Pre-operative Metabolic Tumor Volume; OS: Overall Survival; TNM: Tumour Node Metastasis; VALSG: Veterans Administration Lung Study Group

Introduction

Lung cancer is the major cause of death in the developing countries, with an incidence of about 65–70 new cases per 100.000 [1]. Lung cancer is histologically divided into 2 main types: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). SCLC is an aggressive disease that accounts for approximately 14% of all lung cancers. Unlike NSCLC, in which major advances have been made using targeted therapies, there are still no approved targeted drugs for SCLC. Consequently, the 5-year survival rate remains low at <7% overall, and most patients survive for only 1 year or less after diagnosis [2-4]. [18F] fluoro-D-glucose positron-emission tomography (18F-FDG PET/CT) is widely used in lung cancer for staging, restaging and evaluation of the treatment response [5,6]. Multiple studies demonstrate that PET/CT is more sensitive and specific than PET alone in evaluating the lung cancer since it provides combined morphological and functional information of the tumour [7-10]. High accuracy of PET/CT has been observed in the early assessment of response to therapy, showing a close correlation between the reduction of tumour metabolic activity measured after a course of therapy and the clinical outcome of patients after the previewed cycles of therapy in patients in advanced stage [11,12].

Maximum SUV (SUVmax) is a long-established value in clinical practice for quantifying a lesion's metabolism.

However, as it is based on a single voxel value, SUVmax may not represent total tumor metabolism. By contrast, PET metabolic parameters, such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG), are volumetric indices, and are thus more reliable reflections of tumor burden and aggressiveness [13]. Furthermore, these metabolic parameters are potentially useful prognostic markers for various malignancies examined by 18F-FDG PET [14-16]. The aim of this study was to evaluate the correlation between the pre-operative metabolic tumor volume (MTV) and overall survival (OS) in patients with small cell lung cancer after concurrent chemoradiotherapy (CCRT).

Material and Methods

Clinical Data

We prospectively analyzed the 18F-FDG PET-CT findings of 40 newly diagnosed SCLC patients between December 2010 and April 2019. They were selected according to the following criteria: (1) pathologically proven stage III and IV SCLC; (2) PET-CT was applied before any therapy. These patients were followed up for 3 years. Patients Were enrolled by convenient sampling method. The patients were referred to Bach Mai Nuclear Medicine and Oncology Center for initial staging with PET-CT scan and treated with CCRT. The tumor-node-metastasis (TNM) stage was determined according to the TNM 7th edition [17]. TNM staging was obtained via information gathered through patient's chart including physical examination and total-body 18F-FDG PET/CT scan. Survival and death information were obtained from the hospitals databases and through phone calls to the patient families. The research proposal was approved by Institutional Review Board and Ethics Committee. The inclusion criteria were histologically proven SCLC, glycaemia lower than 140 mg/dl at the time of the exam, availability of FDG-PET/CT and tumour size > 20 mm to minimize the underestimation of MTV. Exclusion criteria were as follows: (a) poor performance status; (b) diabetes (due to poor uptake of FDG); (c) pregnancy.

Concurrent Chemoradiation Therapy

All patients were treated with CCRT. Chemotherapy consisting of 1–4 cycles of cisplatin (20 mg/m2) given on days 1–5 (or days 1–3) and vinorelbine (25 mg/m2) given on days 1, 8, paclitaxel (150 mg/m2 d) given on days 1, 8, or docetaxel (75 mg/m2 d) given on days 1, 8. The first cycle of chemotherapy was applied the next day after the start of the radiotherapy. The second cycle of chemotherapy was applied 4 weeks after the first cycle. The radiotherapy was delivered by three-dimensional conformal radiotherapy technique. After setting up the patients in the vacuum bag, CT for treatment planning was performed in 4-mm slices, usually with intravenous contrast medium. Three-dimensional treatment planning was performed using the ADAC Pinnacle 7.4

FGD-PET-CT Imaging

PET/CT imaging was performed with a median of 4 days (minimum 2 days, maximum 7 days) before starting treatment. Patients were asked to fast at least 6 h before the FDG-PET-CT scan. All patients had a glucose level below 180 mg/dl and were injected intravenously with 0.15-0.20 mCi /kg (7-12mCi) FDG. At 45–60 min after the injection, data were acquired from the vertex to the upper thigh. Immediately after CT, a PET scan (PET/CT Biograph True Point – Siemens, Germany) was performed for about 25 min, with seven to eight bed positions and 3 min/position. PET images were reconstructed iteratively with CT data for attenuation correction, using an inline integrated Siemens Esoft Workstation system. Computerized tomography integrated positron emission tomography fusion images in transaxial, sagittal, and coronal planes were evaluated visually.

MTV Definition and Measurement

MTV values were measured from attenuation-corrected F-18 FDG-PET-CT images using an SUV-based automated contouring program (Advantage Workstation Volume Share version 2, GE Healthcare). Initially, the F-18 FDG-PET data were introduced into the workstation in a DICOM format, and these images were reviewed to localize the target lesions that had been confirmed by two nuclear medicine physicians. MTV was defined as the sum of the metabolic volumes of the primary tumors. Computer-aided MTV measurement was performed using RT-Image, an open-source software application. A maximum-intensity projection view of the images permitted rapid visual identification of the hypermetabolic lesions (primary tumor and lymph nodes). Each tumor interactively identified by the user was then volumetrically segmented by the automatic software algorithm, which defines the segmented volume as all connected voxels with intensity greater than a lesion-specific adaptive threshold of 60% of the peak SUV within the lesion. The software then calculates the MTV by summing the volumes of all segmented lesions.

Statistical Analyses

Continuous variables were summarized by mean and standard deviation, and categorical variables were summarized by frequency and percentage. Cox proportional hazard model was used to correlate continuous independent variables with survival. Survival functions of different populations were estimated by Kaplan-Meier estimator and compared by log-rank test. Multivariate Logistic resession was applied to assess the association between survival of patients and clinical factors. All analyses were performed by SPSS 20.0 (Chicago, Illinois, USA).

Results

Table 1: Positron Emission Tomography–Computed Tomography Scan Results.

Variables	PET Stage III	PET Stage IV	P Value
N	21	19	
Tumor size, mean	2.61 ± 0.88 (cm)	7.88±1.96 (cm)	<0.01
SUVmax	8.44±4.49	13.21±4.29	0.018
MTV (median)	11.44 (ml)	87.51 (ml)	<0.01

The study included 40 patients. Average age was 61.3±9.5 years (range 38-81). Male/female ratio was 9.7/1. SUVmax and

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MTV measurement. The SUVmax ranged from 2.36 to 20.40 (mean 10.68±4.96). The median pretreatment MTV was 36.2 mL (range, 0.05-529.2 mL). Positron emission tomography–computed tomography scan results are listed in Table 1. A PET stage of IV was assigned to 46.9% of patients. The mean of tumor size, SUVmax and MTV in PET stage IV were significant higher than those in PET stage III respectively. The mean of survival time after first performing PET/CT was 12.6 months (95%CI: 9.5 – 15.5 months). Only one case survived up to 36 months (3.1%). Figure 1 shows survival stratified by PET stage. There was a statistically significantly correlation between PET stage and survival (p= 0.012), with survival decreasing as PET stage increased (Figure 2). Figures 3-6 are the PET-CT images of patient with SCLC at stage IV, according to the TNM classification. Our analysis conducted controlling for the MTV and other factors, the Multivariate Logistic Resession revealed a significant inverse relationship between MTV and affected survival rate. The detailed data are shown in Table 2.

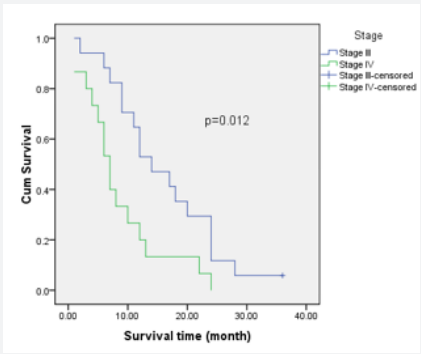

Figure 1: Positron emission tomography (PET) stage versus survival.

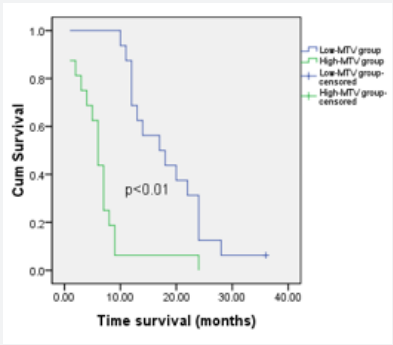

Figure 2: Pre-operative metabolic tumor volume (MTV) versus survival.

Table 2: Multivariate Logistic Resession.

Factor	P value
Sex	0.517
Age	0.162
Stage	0.429
Pretreatment SUVmax	0.001
Pretreatment MTV	0.001

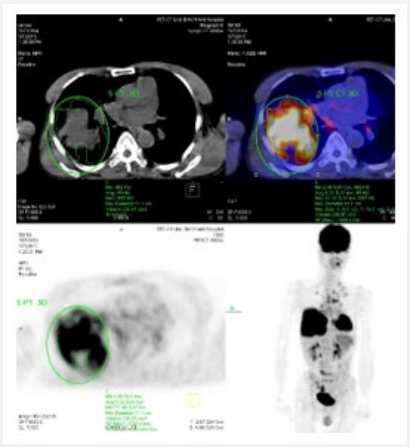

Figure 3: The primary tumor located at upper right lobe with tumor diameter was 11.1 cm and MTV was 236.97 ml.

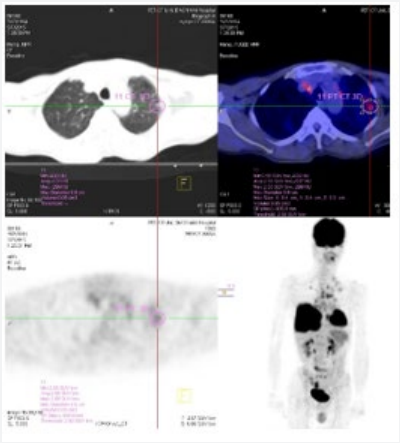

Figure 4: A leision located at upper left lobe was detected on PET/CT as lung metastasis with tumor diameter: 0.6 cm and MTV: 0.05 ml.

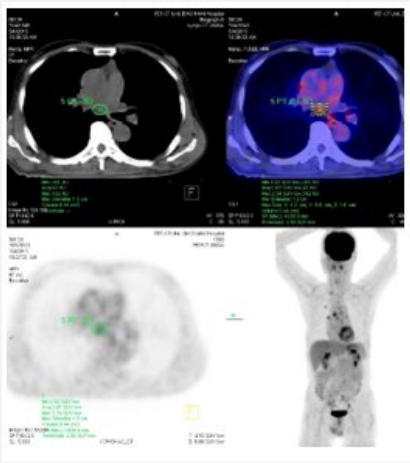

Figure 5: A mediastinal was detected by PET/CT as a metastasis leision with tumor diameter: 1.5 cm and MTV: 0.44 ml.

Discussion

Small cell lung cancer (SCLC) is a subtype of lung cancer with

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poor prognosis. It is estimated that nearly two million individuals are diagnosed as lung cancer every year, approximately 15% of which are SCLC [18]. SCLC is characterized by a rapid doubling time and the propensity for early dissemination. Chemotherapy remains the first line therapy for SCLC. Despite the initial response to chemotherapy, most tumors ultimately would develop drug resistance which is associated with the unsatisfied prognosis. Only 10–15% of patients with limited disease are still alive 2 years after diagnosis, while the overall survival (OS) of patients with extensive disease is even shorter [19,20]. All of patients in our study were at stage III and IV, so the survival time was within 36 months after first performing PET/CT. The mean of survival time was 12.6 months (95%CI: 9.5 – 15.5 months). Only one case survived up to 36 months (3.1%). Although CT or magnetic resonance imaging (MRI) provides precise anatomical and morphological information, the role of FDG-PET-CT has increased for diagnosis and staging of lung cancer [21]. Recently, FDG uptake has been reported to be a prognostic factor in patients with lung cancer [21-23]. Patz et al. [24] demonstrated that patients with positive FDG-PET-CT results, after treatment for lung cancer, had a significantly worse prognosis than patients with negative results.

The goal of our study was to understand the ability of PET-CT scan to predict overall outcome. Our results show that PET-CT scan can in fact act as a prognosticator for long-term survival. There are many different aspects of PET-CT scan that were reviewed in this study. Overall PET stage was seen to predict survival in our study. This finding has been seen previously [25] and is in part related to the poor overall outcome in patients identified with advanced disease, especially in patients with M1 disease [26].

Because patients with M1 disease have such guarded outcomes, we performed separate analyses of the role of MTV versus survival excluding these patients. Even after excluding patients with M1 disease, there was still a significant correlation between MTV and survival. Importantly, these analyses were performed adjusting for mass size to prevent potential confounding from a variable already known to be associated with worse survival. These findings are important in that they can perhaps guide treatment plan based on these values, as the MTV levels are known pretreatment. We also thought it was important to analyze the correlation of MTV with survival within each clinical stage. But it is not significant in this study because of small sample size.

Our study has shown that survival decreases as MTV of the primary tumor increases. An important point that remains to be discovered, however, is the mechanism of failure in these patients. One potential mechanism is that tumors with higher MTV values have a more advanced stage at surgery than predicted by the pretreatment PET stage, implying that as the MTV increases, accuracy decreases. Another potential mechanism is earlier local recurrence of disease, implying that tumors with higher MTV values are more locally aggressive. Yet another possible mechanism is an increased propensity for distant metastasis. Prospective studies are required to determine the absolute causes for decreased survival in patients with higher MTV values.

Although we believe that MTV should be used as a gradient, we attempted to find a cutoff value, above and below which there were significant differences in survival. We were able to achieve this for MTV, with values of 36.2 (ml). We believe that these cutoff points can be useful as a reference for clinicians, and may eventually be able to be incorporated into a staging system. Further prospective studies are required, however, before this goal can be achieved. This cutoff would be especially practical in patients with no evidence of mediastinal disease pretreatment. Better ability to stratify these patients would lead to more accurate prediction of long-term outcome and more appropriate treatment preoperatively. Our results argue that patients with a high MTV would potentially profit from a more aggressive treatment plan, including mediastinoscopy before resection of the primary tumor and adjuvant chemotherapy, regardless of final pathologic results.

Many studies were on prediction of survival or treatment outcome in patients with NSCLC but we did not find any report of those in SCLC using Primary tumor standardized uptake value on 18F-FDG PET/CT. SCLC is a subtype of lung cancer associated with dismal prognosis. The 7thTNM classification and VALSG staging system are the most widely used models to predict the clinical outcome of SCLC currently [27]. This study has some limitations because of the small sample size and all patients were at stage III and IV. Further studies with larger patient groups are needed to assess the relationship between primary tumor MTV and overall and disease-free survival in patients with SCLC.

Conclusion

In conclusion, a pretreatment MTV of ≥ 36.2 ml exhibited a worse OS compared with those with an MTV of < 36.2 in SCLC patients. These results indicate that pretreatment MTV is a prognostic marker that could be used to identify high-risk patients with SCLC. Additional studies are warranted to determine if pretreatment MTV is associated with long-term prognosis.

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