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Original research

PROGNOSTIC ROLE OF PRIMARY TUMOR STANDARDIZED UPTAKE VALUE ON 18F-FDG PET/CT IN ADVANCED SMALL CELL LUNG CANCER

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ABSTRACT

Objectives: *To evaluate 18FDG PET-CT for the prediction of overall survival in patients with small cell lung cancer after concurrent chemoradiotherapy.*

Methods: *Forty patients with pathologically proven stage III and III SCLC had FDG PET-CT scans before concurrent chemoradiotherapy. The maximum standardized uptake value (SUVmax) of the primary lung lesion was calculated. The relationship between the SUVmax and the long-term survival was studied after concurrent chemoradiotherapy.*

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 mean SUVmax of primary tumors was 10.68 ± 4.96, and patients were divided into higher (≥ 9.16) and lower (<9.16) SUVmax groups. The higher SUVmax group exhibited a significantly worse OS compared with the lower SUVmax group. Resession revealed a significant inverse relationship between SUVmax and affected survival rate.*

Conclusion: *The prognosis of patients with SCLC who are diagnosed at advanced stage remains poor. 18FDG PET-CT is an effective method to predict the treatment outcomes of SCLC.*

Keywords: *Small cell lung cancer, prognosis, FDG-PET, survival.*

I. 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. 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. However, patients with SCLC may experience a worse outcome than expected. Increased FDG uptake by lung cancer cells, measured as the maximum standardized uptake value (SUVmax), has been reported to predict the biologic aggressiveness of both early and advanced NSCLC [7]; however, we do not find any prognostic studies for SCLC.

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The aim of this study was to to evaluate the correlation between the maximum standardized uptake value (SUVmax) and overall survival (OS) in patients with small cell lung cancer after concurrent chemoradiotherapy (CCRT).

II. MATERIAL AND METHODS

2.1. Clinical data

We prospectively analyzed the 18F-FDG PET-CT findings of 40 newly diagnosed SCLC patients. 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 was 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. 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 under estimation of SUV. Exclusion criteria were as follows: (a) poor performance status; (b) diabetes (due to poor uptake of FDG); (c) pregnancy.

2.2. 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/m^2) given on days 1, 8, paclitaxel (150 mg/m^2 d) given on days 1, 8, or docetaxel (75 mg/m^2 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.

2.3. 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, and the SUVmax of lesions was obtained from transaxial images.

2.4. Standardized uptake values

The maximum SUV [SUVmax, the activity from the maximum - valued pixel within the tumour volume of interest (VOI); hereafter referred to as SUV] normalized to injected activity and patient body weight was calculated at approximately 60 min after tracer injection for each primary lesion and the chosen metastatic lesion with use of the following equation: SUV = maximum activity concentration in the VOI [kBq/ml]/ (injected dose [MBq/ml]/patient body weight [kg]). In patients with multiple metastatic lesions, the lesion with the largest diameter was chosen to prevent partial volume effects (Figure 1).

Tumors were classified into 2 groups by SUVmax base on the median of SUVmax: low-SUVmax < median and high - SUVmax ≥ median.

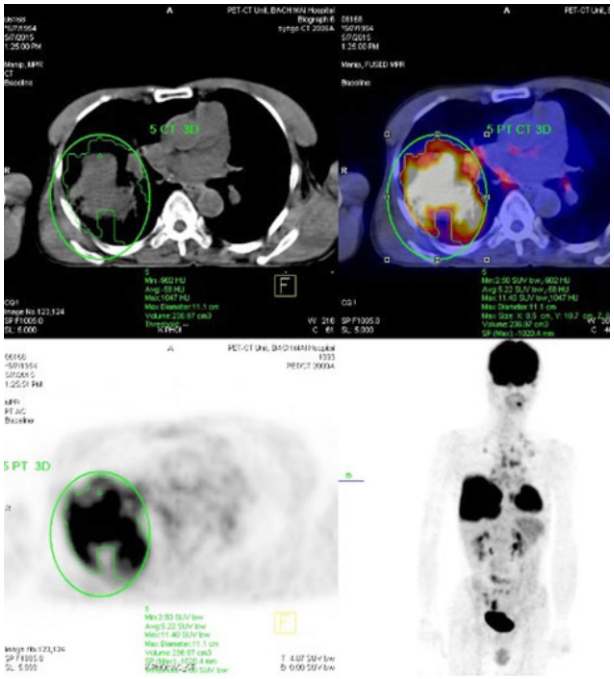

Figure 1: The primary tumor located at upper right lobe with tumor diameter was 11.1 cm and SUVmax was 11.40.

2.5. 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).

III. RESULTS

The study included 40 patients. Average age was 61.3 ± 9.5 years (range 38 - 81). Male/female ratio was 9.7/1. The SUVmax ranged from 2.36 to 20.40 (mean 10.68 ± 4.96). The median SUVmax was 9.16, the low SUVmax group ranged from 2.36 to 9.13 (mean of 6.58 ± 2.19), and the high SUVmax group ranged from 9.20 to 20.40 (mean of 14.78 ± 3.18).

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 and SUVmax 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%).

Table 1: Positron emission tomography - computed tomography s can results.

Variables	Stage III	Stage IV	p-value
N	17	15	
PET tumor size, mean (cm)	2.61±0.88	7.88±1.96	< 0.01
SUVmax	8.44±4.49	13.21±4.29	0.018

Figure 2 shows survival stratified by PET stage. There was a significantly correlation between PET stage and survival (p = 0.012), with survival decreasing as PET stage increased.

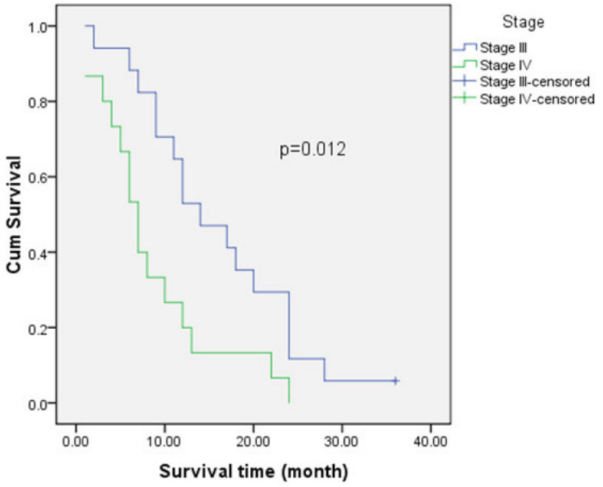

Figure 2: Positron emission tomography (PET) stage versus survival

Although SUV is a continuous variable, we thought that estabishing "high-risk" and "low-risk" groups, based on SUV values, would act as a useful reference for clinicians. Dichotoization of SUV values was based on the median values. Patients who had an SUVmax higher than 9.16 had worse survival than patients with an SUVmax less than 9.16 (p < 0.01; Figures 3 and Figure 4).

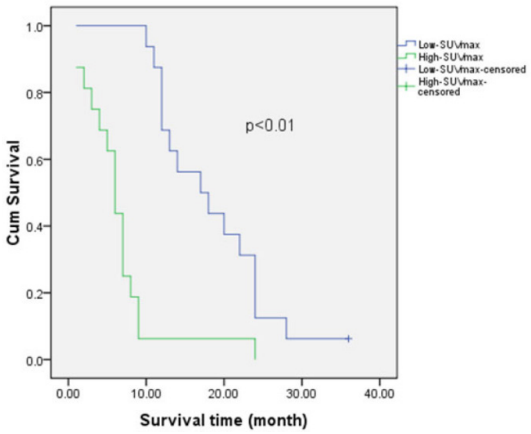

Figure 3: Standardized uptake value of the primary mass (SUVmax) versus survival

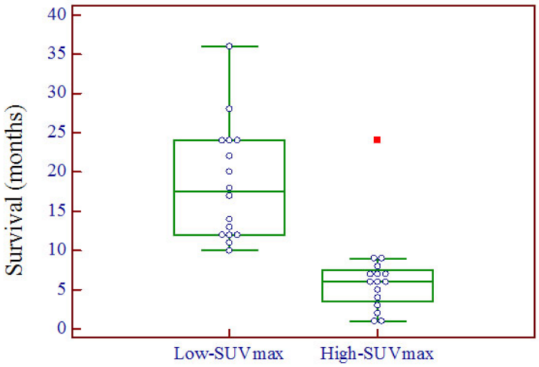

Figure 4: Association between primary mass (SUVmax) and survival

Our analysis conducted controlling for the SUVmax and other factors, the Multivariate Logistic Resession revealed a significant inverse relationship between SUVmax and affected survival rate. The detailed data is shown in Table 2

Table 2: Multivariate logistic resession

Factors	p-value
Sex	0.517
Age	0.162
Stage	0.429
Pretreatment SUV max	0.001

IV. DISCUSSION

Small cell lung cancer (SCLC) is a subtype of lung cancer with poor prognosis. It is estimated that nearly two million individuals are diagnosed as lung cancer every year, approximately 15% of which are SCLC [8]. 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 poor 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 [9]. 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. Recently, FDG uptake has been reported to be a prognostic factor in patients with lung cancer. Patz et al. demonstrated that patients with positive FDG-PET-CT results, after treatment for lung cancer, had a significantly worse prognosis than patients with negative results [10].

The goal of our study was to understand the ability of PET-CT scan to predict overall outcomes. 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 [11] and is in part related to the poor overall outcome in patients identified with advanced disease, especially in patients with M1 disease.

Because patients with M1 disease have such guarded outcomes, we performed separate analyses of the role of SUV versus survival excluding these patients. Even after excluding patients with M1 disease, there was still a significant correlation between SUV 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 SUV levels are known pretreatment.

We also thought it was important to analyze the correlation of SUV 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 SUV 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 SUV values have a more advanced stage at surgery than predicted by the pretreatment PET stage, implying that as the SUV increases, accuracy decreases. Another potential mechanism is earlier local recurrence of disease, implying that tumors with higher SUV 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 SUV values.

Although we believe that SUV 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 SUVmax, with values of 9.16. 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 SUV 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,while we found one report of those in SCLC using quantitative18F-FDG PET/CT [12]. According this report, 51 patients were progressive or recurrent with the median 6.9 months of progression free survival (PFS); and 50 patients were died with the median 11.7 months of overall survival (OS). Univariate analysis showed that MTVsum, TLGsum, number of lesions, live metastasis, bone metastasis, the cycle of chemotherapy and thoracic radiation therapy were all associated with PFS and OS (all $P < 0.05$). Multivariate analysis demonstrated that live metastasis, the cycle of chemotherapy, MTVsum, TLGsum were the independent predictors of PFS (all $P < 0.05$); and TLG sum were the independent predictors of OS (all $P < 0.05$). 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 [13].

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 and/ or early stage SCLC (stage I and II) included as controlsare needed to assess the relationship between primary tumor SUVmax and overall and disease-free survival in patients with SCLC.

V. CONCLUSION

In conclusion, the prediction of patients with stage III and IV SCLC is very poor. A pretreatment SUVmax of ≥ 9.16 exhibited a worse OS compared with those with an SUVmax of < 9.16 in SCLC patients. These results indicate that pretreatment SUVmax is a prognostic marker that could be used to identify high-risk patients with SCLC. Additional studies are warranted to determine if pretreatment SUVmax is associated with long-term prognosis.

Ethics approval

This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of HCMC Oncology Hospital.

Competing interests

The authors declare that they have no competing interests.

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