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Positron Emission Tomography derived Parameters as Predictive Factors and Survival in Non-small Cell Lung Cancer Patients

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Abstract

Background: CT-PET (Computed Tomography-Positron Emission Tomography) provides additional information regarding tumour characteristics, aggressive tumour behaviour and serves as a prognostic indicator.

Methods: Thirty one patients with NSCLC were retrospectively reviewed. PET parameters were calculated including maximum and mean Standardised Uptake Value (SUV), Metabolic Tumour Volume (MTV) and Total Lesion Glycolysis (TLG=MTV× SUV_{mean}). The correlation between each parameter was investigated using Pearson's correlation tests. The tumour doubling time (DT) was calculated from pre-treatment and treatment planning CT scans. The DT was divided into 2 groups: A-rapid (DT<180 d) and B-slow (DT>180 d) for survival calculation.

Results: The mean age at diagnosis was 75 (55-87) years, 22 (66.7%) were male and 9 (27.3%) were female. The majority of patients had stage I and II (93.5%) disease. The correlation between DT to TLG and SUV_{mean} was significant with Pearson's correlation of -0.363 (p-value of 0.045 on 2 tailed) and -0.399 (p-value of 0.024 on 2 tailed) respectively. DT correlation to SUV_{max} and MTV was not significant on Pearson's correlation of -0.337 (p- value of 0.064 on 2 tailed test) and -0.309 (p-value of 0.091 on 2 tailed) respectively. The 2 year overall survival was 45.2% and median survival was 503 days for the whole group. The median survival was 468 days in group A-rapid and 503 days in B-slow group patients. There was no statistically significant difference between the groups (Log Rank Mantle Cox with p-value=0.681).

Conclusions: This study compares the relationship of PET parameters (SUV, MTV and TLG) and DT and prediction of prognostication. Although the clinical significance can be far reaching at this stage, TLG and SUV_{max} are promising predictive factors for doubling time in NSCLC. Larger studies are needed to support the findings.

Keywords: Positron emission tomography; Non-small cell lung cancer; Tumour; Glycolysis

Introduction

Lung cancer affects one million people worldwide [1]. The treatment of stage I to IIIA Non-Small Cell Lung Cancer (NSCLC) in patients without any major risk factors is surgical resection. In recent years with the advancement in staging techniques and use of metabolic imaging, many lung cancers are being diagnosed that are small or constitute primarily ground-glass opacities. The standard treatments of these cancers are surgery such as sub lobar resection while nonsurgical approaches such as Stereotactic Body Radio Therapy (SBRT) are becoming more common. With the advent of new minimally invasive options, the criteria to classify a patient as unfit for radical treatment i.e., co morbidities to undergo lung resection are being redefined.

PET (Positron Emission Tomography) is a metabolic scan that provides information regarding the physiological and biological behaviour of tumour tissue [2]. Integrated CT-PET (Computed Tomography-Positron Emission Tomography) is a precious investigation tool in staging of non-small cell lung cancer (NSCLC). PET scan is now considered as a core investigation in diagnosis of lung cancer which aids in more accurate staging for lung cancer and has been confirmed in the meta-analysis [3-6]. In addition to its superiority to CT in the staging, it provides additional information regarding tumour characteristics, aggressive tumour behaviour and serves as a prognostic indicator. The information provided by the CT-PET scan is then fused with the treatment planning scan for defining the Gross Tumour Volume (GTV), location of the metabolic active part of the tumour and monitoring response during chemotherapy [7].

The aim of this study is to evaluate F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET) derived parameters, such as standardized uptake value SUV_{max}, SUV_{mean}, Metabolic Tumour Volume (MTV) and Total Lesion Glycolysis (TLG), as predictive factors for Doubling time in early stage inoperable non-small cell lung cancer and survival in patients treated with radical radiotherapy.

Methods and Statistics

Patient and treatment characteristic

From 1st January 2012 to 30th December 2013, all patients referred for CT-PET for evaluation of known NSCLC or suspected lung cancer and who were being considered for potentially curative therapies were

retrospectively reviewed. Patients were identified from the Queen Elizabeth Hospital NHS Trust cancer centre. Stage I to IIIA non-small cell lung cancer patients who had CT-PET and staging CT scans within 90 days and treated radically with radiotherapy were included in the study. Patients were excluded if they have synchronous second cancer or have a history of cancers other than basal cell and squamous cell carcinoma of skin, performance status 3 or above, unable to tolerate radiotherapy.

This study is from single centre and patients who were eligible with Non-small cell lung cancer diagnosed between January 2012 and December 2013 were identified and analysed. Patients with Inoperable NSCLC, which were referred for radical radiotherapy from multidisciplinary meeting, were included. The clinical characteristics, histologic type, stage of disease, demographic details and methods of treatment were noted. Patients underwent a routine workup, including a clinical examination, contrast-enhanced CT of the chest and CT-PET scan to define the stage. The clinical stage was retrospectively defined according to the 2009 Union for International Cancer Control classification [8]. All the patients were discussed in the multidisciplinary meeting which consisted of clinical and medical oncologists, thoracic surgeons, histopathologists, radiologists and specialist nurses. The patients included in the study were not suitable for curative surgery and have significant co-morbidities. In addition to that 3 patients were diagnosed with metastatic disease based on FDG-CT-PET and went on to receive palliative chemotherapy.

Patients with stage I to IIIA with disease which can be encompassed in a single radical radiotherapy field and were able to receive radical dose of radiotherapy were included. While the advanced disease such as stage IIIB was excluded because of the spread of the disease which is not possible to treat radically and might have required multimodality treatment.

Patients with stage IV disease were excluded because the aim of treatment in advanced disease is not curable. Furthermore, we wanted to study the relationship between the doubling times from the diagnosis without any major interference of confounding factors, so people who received chemotherapy were excluded. Patients who had wide spread disease would be difficult to delineate accurately and Region of Interest (ROI) would also be variable and can be susceptible to a partial volume effect with increase chance of inclusion of uninvolved surrounding tissue. Systemic treatment can also have significant effect on the tumour biology which can potentially change the PET signals.

The Standardized Uptake Value (SUV) is often used in PET imaging for a simple semi-quantitative analysis. The SUV is calculated either pixel-wise yielding a parametric image, or over a Region of Interest (ROI). It is described in two either as SUV_{max} or mean. It has been mentioned in studies that SUV_{max} may be associated in predicting prognosis [9]. Metabolic tumour volume (MTV) is defined as the volume of tumour tissues with increased FDG uptake. This novel index in PET-FDG target volume is calculated mostly by visual delineation of tumour edge or side-by-side analysis with contrast-enhanced CT scan. Doubling Time is the longest and shortest diameters of the tumour were measured on the Scans at same level. Growth rate was expressed as volume doubling time (D_t), which was calculated from the volume at t_1 (V_1) and at t_2 (V_2). CT-PET scan provides high-impact and powerful prognostic stratification in staging newly diagnosed non-small cell lung cancer [10]. Few studies have shown that metabolic scans and its derived parameters in patients with early-stage non-small-cell lung cancer (NSCLC) are associated with tumour doubling time and survival [11-13]. The most studies associated with PET scan and prognoses are with surgery here, I have discussed CT-PET parameters such as Doubling Time, Metabolic Tumour Volume, SUV_{max}, SUV_{mean} and Total Lesion Glycolysis in correlation to radical radiotherapy in inoperable early stage lung cancer. This study has approached this aspect of CT-PET guided functional imaging and its derived parameter to explore the correlation between the doubling time and survival.

Estimation of the SUV of the primary lesion in Regions of Interest (ROIs) were done by the radiologist and cross checked by another member of the team. FDG uptake in these regions was quantified by calculating the SUV in each pixel according to the following formula: SUV=activity concentration/(injected dose/body weight) [14]. The maximum and mean SUV were calculated to minimize the partial volume effects. All patients received radical radiotherapy conformal planned radiotherapy receiving 55 Gys in 20 fractions. The tumour doubling time was calculated from Pre-treatment and treatment planning CT scans. The doubling time (DT) was divided into 2 groups: rapid (DT<180 d) and slow (DT>180 d) [15] for survival calculation.

Standardized uptake value (SUV)

In CT-PET Imaging the Standardized Uptake Value (SUV) is used for a simple semi-quantitative analysis [16]. The calculation of SUV is performed by pixel wise acquiescent a parametric image, or over a Region of Interest (ROI). The SUV is defined as the ratio of the tissue radioactivity concentration 'c' (e.g. in MBq/kg=kBq/g) at time point't', and the injected activity (e.g., in MBq, extrapolated to the same time t) divided by the body weight 'w' (e.g., in kg)→SUV (t)=c (t)/{(injected activity) (t)/body weight (w)}.

Metabolic tumour volume (MTV)

Defined is the volume of tumour tissues with increased FDG uptake and it is a novel index in FDG-PET. Metabolic tumour volume is calculated mostly by visual delineation of tumour edge or side-by-side analysis with contrast-enhanced CT scan.

Doubling time

The longest and shortest diameters of the tumour were measured on the Scans at same level at t_1 and t_2 in each case. The volume (V) of the tumour was calculated with the help of contouring programme. The volume (V) of the tumour can also be calculated as follows: $V=4/3\ \pi ab^2$, where a = longest diameter and b = shortest diameter. Growth rate was expressed as volume doubling time (D_t), which was calculated from the volume at t_1 (V_1) and at t_2 (V_2) by the following formula

$\rightarrow V_2=V_1\ 2^{\ t/Dt} \rightarrow Dt=t \log 2/(\log V_2/V_1)$ (where t=interval between t_1 and t_2) [17,18].

Correlation was noted and significance was calculated using spearman's correlation coefficient, for bivariate correlation of tumour Doubling time with MTV, SUV_{max}, and TLG. The survival calculation was done using Kaplan Meier's method according to the groups.

The diagnosis of lung cancer and determination of histological type were made from histological or cytological specimens in all cases except one where PET scan was significant and further biopsy was not possible.

18F-FDG PET acquisitions

All CT-PET studies were conducted before the radical radiotherapy treatment. Patients were advised to stop any strenuous exercise such as long walks, gym sessions swimming or carrying heavy weights 24 hours prior to the appointment and fasting of 6 hours before the 18 F-FDG administration. Images were acquired of whole body after 60 minutes of 18-FDG administration. Optimized reconstruction parameters were used on the standard optimized clinical protocol. The CT-PET images were corrected for attenuation using CT based attenuation correction.

PET image analysis

All considered parameters were extracted from the baseline PET images. For each individual, the primary tumour was acknowledged on the baseline pre-treatment PET images by a radiologist. Three independently SUV measurements and three parameters related to the tumour functional dimensions, namely the Metabolic Tumour Volume (MTV) and Total Lesion Glycolysis (TLG) [19] were extracted for each primary lesion. SUV measurements considered were SUV_{max} which is maximum uptake and SUV_{mean} as the average uptake within the delineated tumour. SUV_{max} and SUV_{mean} are clearly independent of the tumour delineation strategy used, while MTV depends upon the delineation by the operator such as radiologist and oncologist. The derived TLG values depend on the SUV_{mean} and delineation process.

	%	Number
Age, years		
Mean	75	
Range	55-87	
Sex		
Male	70.96	22
Female	29.04	9
Stage		
T1 and N0 Stage I	19.32	6
T2 and N0 Stage 1 and 2A	45.08	14
T3 and N0 Stage 2B	9.66	3
T1 and N1 Stage 2A	9.66	3
T2 and N1 Stage 2A	9.66	3
T3 and N1 Stage 3A	6.44	2
Histology		
Non Squamous cell Carcinoma	38.7	12
Squamous cell Carcinoma	61.3	19

Table 1: summarises the Clinical characteristics, histologic type, stage, demographic details and method of treatment.

Results

179 patients with non-small cell lung cancer diagnosed between 1st January 2012 and 30th December 2013 were reviewed. Out of these 31 patients had stage I to IIIA non-small cell lung cancer, have follow-up data available for analysis, who had CT-PET and staging CT scans within 90 days. All patients were treated with radical dose of 55 Gy in 20 fractions.

The mean age at diagnosis was 75 years with range from 55 to 87 years. 22 (70.96%) were males and 9 (29.04%) were females. The majority of patients included were of stage I and II (93.5%) diseases except 2 (6. 5%) patients who had stage 3A disease. T1 and T2 comprises majority of the study population (64.4%) and 25.76% present had lymph nodes involvement. The most common subtype was squamous cell carcinoma comprising of 19 (61.30)% of the patients in the study. All patients received radical conformal planned radiotherapy receiving 55 Gy in 20 fractions. All patients completed the radiotherapy as planned in 4 weeks.

The pathological lesion was measured on the pre-treatment CT planning scan and initial volume of tumour was taken from the CT scan done at the time of PET Scan. The mean volume doubling time for all 31 cases was 240.45 days. Males showed a mean doubling time of 201.54 (19 to 1055 days) and females have the mean doubling time of 335(23 to 1139 days), which was shorter when compared to doubling time of males.

Differences in mean doubling time were observed between histological types which was 186 (range 19 to 1055) days for squamous cell carcinoma, Adenocarcinoma had a doubling time of 200 (95 to 421) days and 389 (44 to 1139) days for others. The tumour doubling time calculated from Pre-treatment and treatment planning CT scans. The doubling time (DT) was divided into 2 groups: rapid (DT<180 d) and slow (DT>180 d) [20] for survival calculation.

Doubling time relationships between SUV_{mean}, SUV_{max}, MTV and TLG were observed. Doubling time relationships between SUV_{mean}, SUV_{max}, MTV and TLG were observed. The correlation between Doubling time to TLG and SUV_{mean} was statistically significant with Pearson's correlation of -0.363 (p value of 0.045 on 2 tailed) and -0.399 (p-value of 0.024 on 2 tailed) respectively. Doubling time correlation to SUV_{max} and MTV was statistically not significant on Pearson's correlation of -0.337 (p- value of 0.064 on 2 tailed test) and -0.309 (p-value of 0.091 on 2 tailed) respectively.

The primary lung cancers were classified into two groups by growth rate. Group A (rapid growing) comprised tumours with a doubling time =<180 days, group B (slow growing) comprised tumours with a doubling time>180 days.

There were 22 cases in group A and 9 in group B. The distribution by group and histological type is shown in Table 1. The cumulative survival curves of the patients in each group of tumour growth were compared to analyse whether or not tumour growth rate influenced the prognosis of the patients. The survival curves for the 31 lung cancer patients after the initiation of treatment according to growth rate groups are shown in Figures 1-3. The 2 year overall survival was 45.2% and median survival was 503 days for the whole group, 468 days in group A patients (rapid) and 503days for the patients in group B. The

median survival rate for the patients in group A and B was statistically not significant (Log Rank Mantle Cox with p-value=0.681).

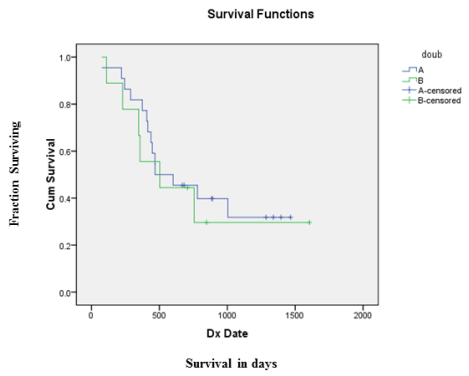

Figure 1: Survival based on doubling time A-rapid (DT<180 d) and B-slow (Dt>180 d).

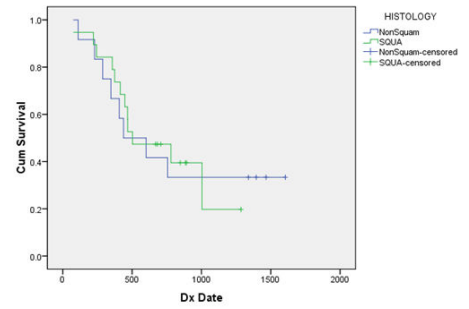

Figure 2: Survival Functions.

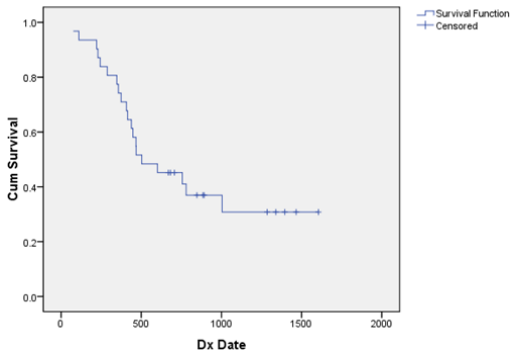

Figure 3: Survival Function.

Discussion

The growth rate of malignant tumours depends on both rate of proliferation and rate of loss of tumour cells. It has been pointed out that tumours with rapid growth rates showed poorer prognoses [21]. In this study, the FDG-PET parameters, including SUV_{mean}, SUV_{max}, and TLG, could be useful for predicting doubling time and overall survival in NSCLC patients receiving radical radiotherapy [22]. SUV_{max} is a measurement of metabolic activity per body weight and reflects only the point of maximum metabolic activity in a tumour whereas SUV_{mean} gives the average value from the region of interest. In contrast, TLG, which is defined as the product of SUV_{mean} and Metabolic Tumor Volume, has been suggested to better reflect metabolic activity in whole tumours and have prognostic implications [23]. In the past, it has been demonstrated that PET scan has valuable role in predicting stage, recurrence, and survival [24]. It has been mentioned in studies that SUV_{max} may be associated in predicting prognosis [25] in NSCLC patients who underwent surgery [26]. In 2008 a meta-analysis reported that lower SUV_{max} is correlated with favourable outcomes in patients with advanced NSCLC [27]. Bivariate analysis which showed that the doubling time is correlated significantly with TLG and SUV_{mean}. The other variables like SUV_{max} and MTV was not statistically significant but the correlation was negative. The doubling time is also important in standard linear-quadratic survival model especially with regards to radiotherapy fractionation. It can be used to investigate different schedules of radiation treatment and to study further to see how these may affect the different tumours with different repopulation kinetics [28]. There are studies which have shown that the repopulation during radiotherapy is a major concern of treatment failure [29]. Various fractionated radiotherapy schedule stated in the literature over the past few decades, it is only within the last decade that the biological factors and its effect on proliferation have been studied in detail with respect to tumour repopulation. This vital awareness is still far from fully understood in radiotherapy community with respect to the PET scan and its volumetric derived parameters. Several studies have indicated that the degree of 18F-2-deoxy-2-fluoro-D-glucose (FDG) uptake in cancer can be used as a prognostic marker but this is yet to be proven in lung cancer [30,31].

This result suggests that TLG and SUV_{mean} may be more useful than the other FDG-PET defined parameters for calculation of doubling time in patients with NSCLC. It has been mentioned that doubling time has prognostic [32] value and metabolic tumour volume being related to stage and survival in patients with non small cell lung cancer [33]. Few studies have demonstrated the association of TLG with recurrence in patients with epithelial ovarian cancer [34], prognostic value with malignant pleural mesothelioma [35], breast cancer, osteosarcoma [36], oesophageal cancer [37] and colorectal cancer [38]. In conjunction with our result, the available data suggest that TLG can be one of the useful FDG-PET parameters for prognostication. In our study, the patient population is homogeneous and all the patients received standard radical radiotherapy without concurrent chemotherapy as a first-line treatment. In addition to above more detailed clinical information such as PS, histology, and responses to treatments, was available from the medical records in all cases, we included these important variables that may be strongly associated with patient survival, in the multivariate analysis to clearly show the clinical significance of TLG. Therefore, these results could provide noteworthy evidence to supplement the idea. In light of such findings, the TLG measurement on FDG-PET imaging could be routinely suggested to advanced and inoperable NSCLC patients who are scheduled to receive radical treatment [39]. Currently, pathological and molecular examinations, such as immunohistochemical analyses and/or PCR assays, are extensively employed for prognostication of NSCLC patients. In lung cancer, paraffin embedded specimens are obtained by transbronchial or radiologically guided needle biopsy are the usual practice for tumour categorization, these samples are difficult

to obtain and often too small to allow detection of pathological and molecular signatures in heterogeneous cancer tissues. Our present findings suggest that FDG-PET may be useful as a non-invasive imaging tool for prediction doubling time in NSCLC patients, whose tumour tissues are difficult to obtain for detailed pathological and molecular characterization.

The cradle of the radiobiological representation and doubling time depends upon the assumption that SUVs are correlated with tumour burden. This postulation has been a topic of investigation in a number of the studies with mixed results. In one of the extensive reviews [40], 18F-FDG-PET parameters has shown to be prognostic factors for survival in univariate analysis, only couple of studies showed such uptake to be a predictor of survival in multivariate analysis [41]. In one of the breast cancer study PET alongside The tumour marker has been implicated in calculation of doubling time of tumour in predicting the recurrence. Chung et al. [39] has demonstrated that the TLG and MTV correlation with the prognosis in advance lung cancer. Zhang et al. [40] have dwelled into new PET/CT volumetric prognostic index for non-small cell lung cancer.

The major limitations of this study are its small size and its retrospective nature. The next step would be to review prospectively the PET as a part of bigger trial and evaluate the PET based parameters. In this way exceptional source of data for an MTV analysis would be available, not only to validate this study but also evaluate the response of treatment to different histological types of lung cancers. If a relationship between PET based parameters and survival is established in a much reasonable sized study, these parameters will be a precious machination to stratify patients for risk-adapted treatment in potentially curable inoperable non-small cell lung cancer.

Conclusion

Integrated CT-PET is a valuable investigation tool in preoperative staging of NSCLC. In addition to its superiority to CT in the preoperative staging, it provides additional information regarding tumour characteristics, aggressive tumour behaviour and serves as a prognostic indicator. This study has shown significant correlation between TLG and SUV_{mean} to doubling time which not only helps in prognostication but also provides an avenue for further research. In this study we investigated the correlation between SUV_{mean}, SUV_{max} and TLG in lung cancer patients treated radically with radiotherapy. Such information may be helpful in selecting patients preoperatively into receiving neoadjuvant chemotherapy or not. Prospective, randomised and multi centre trials are warranted.

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