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Feasibility study of FDG PET/CT-derived primary tumour glycolysis as a prognostic indicator of survival in patients with non-small-cell lung cancer

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AIM: To assess the feasibility and prognostic value of measuring total lesion glycolysis of the primary tumour ($TLG_{primary}$) using combined 2-[18F]-fluoro-2-deoxy-D-glucose (FDG) positron-emission tomography/computed tomography (PET/CT) in patients with proven or suspected non-small-cell lung cancer (NSCLC) in the routine diagnostic setting.

MATERIALS AND METHODS: At the All wales Research and Diagnostic Positron Emission Tomography Centre in Cardiff (PETIC), in the calendar year 2011, 288 consecutive patients were identified with a single pulmonary mass in whom NSCLC was confirmed or clinically diagnosed following multidisciplinary team review. In a retrospective analysis, for each patient the PET-derived volume of the primary tumour and SUV_{MEAN} was calculated using adaptive thresholds of 40% and 50% of the SUV_{MAX} of the primary tumour. The $TLG_{primary}$ (calculated by volume x SUV_{MEAN}) was calculated at these two thresholds and was used to predict survival in a multivariate analysis with TNM (tumour, node, metastasis) stage, age, sex, and SUV_{MAX}. The primary endpoint was overall survival over a minimum follow-up of at least 7 months.

RESULTS: In virtually every case, the primary tumour could be measured using the automated software with minimal use of manual adjustments. In multivariate analysis, TNM clinical stage, log($TLG_{primary}$) and sex were independent predictors of overall survival.

CONCLUSION: Measurements of primary tumour total lesion glycolysis are simple to perform and provide additional prognostic information over and above that provided by TNM staging.

Introduction

Primary bronchogenic malignancy is the leading cause of cancer deaths worldwide.[1] The TNM staging classification is almost universally used for the rational selection of patients for surgery, radical oncological treatment, or palliative treatment.[2] The overall clinical stage, derived from the TNM descriptors has been shown to be a powerful predictive factor in non-small-cell lung cancer (NSCLC).[3] In many parts

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of the world, combined 2-[18F]-fluoro-2-deoxy-D-glucose (FDG) positron-emission tomography/computed tomography (PET/CT) is routinely used for the staging of patients with known or suspected NSNLC, and in particular, for the selection of these patients prior to radical therapy.

FDG PET/CT has been shown to improve the accuracy of tumour staging over and above that of conventional, contrast-enhanced CT.[4] There have been many reports regarding the additional prognostic information that PET/CT derived variables may contribute over and above that of the traditional TNM staging. Initially, many of these have focused on the maximum standardized uptake value (SUV_{MAX}) of the primary tumour. The SUV_{MAX} is calculated as:

$$SUV_{MAX} = \text{tissue activity (MBq/ml tissue)/injected dose (MBq/body weight in g)}$$

The SUV_{MAX} of the primary tumour in several retrospective studies has been shown to correlate with TNM stage, tumour size, and importantly subsequent prognosis, with more metabolically active tumours, yielding higher SUV_{MAX} measurements, being associated with worse prognosis.[5,6]

Because malignant tissue typically shows markedly increased metabolic activity compared to background tissue, it has proved relatively easy to define tumour volumes using automated and semi-automated software. A variety of mathematical approaches has been adopted using, for example, a fixed value of SUV to define the limits of the tumour or, more commonly, an adaptive threshold of a percentage of the SUV_{MAX} of the tumour.[7] Studies comparing PET-derived tumour volumes to histopathological volume have demonstrated that adaptive thresholds of around 41% of the maximum yield PET-derived volumes correlating best with histopathological volumes.[7,8]

The term metabolic tumour volume (MTV) has been coined to describe volumes derived from PET imaging studies. The term total lesion glycolysis (TLG) describes the product of the metabolic tumour volume multiplied by the mean SUV within that volume.[9]

Perhaps because of the relative simplicity of performing volume estimations in PET/CT, there have been a number of reports applying this methodology and assessing the relationship of PET derived volumes to those found at histopathology and correlating PET-derived volumes and related variables to clinical outcome. There are several retrospective studies that have found MTV and TLG to be independent prognostic indicators in a variety of malignancies. In a study of 151 patients, MTV of histologically proven oesophageal cancer was reported to be an independent predictor of survival, and gave good predictive performances for overall survival.[10] Both TLG and MTV have been found to be independent predictors of prognosis in groups of patients with malignant mesothelioma[11] and oropharyngeal squamous cell carcinoma.[12,13] In a group of 140 patients with diffuse large B cell lymphoma, TLG of multiple sites of disease was analysed with several margin thresholds. It was reported that a TLG with a 50% margin threshold was an independent predictor of survival.[14]

In a retrospective review of 92 patients with stage IV NSCLC, both primary lesion TLG ($TLG_{primary}$) and whole-body TLG (derived by a sum of the $TLG_{primary}$ and the TLG of each of the nodal and distant metastases) were calculated. Each of these variables was correlated with overall survival.[15] However, the authors of this paper did not evaluate the relative contribution of TLG to prognosis in a multivariate analysis in relation to the clinical stage derived from the TNM system.

In a series of 81 patients with advanced NSCLC and using univariate analysis only, a linear correlation was demonstrated between whole-body TLG and prognosis. This study again did not include multivariate analysis against the TNM system.[16]

In a series of 104 patients who were subsequently managed surgically, whole-body TLG was found to have a skewed distribution and a logarithmic transformation was applied to their data. The natural logarithm of the whole body MTV and TLG were correlated with overall survival in a multivariate analysis, which included the broad clinical stage, in which patients were assigned to either stage I and II or III and IV.[17]

In 169 patients managed without surgery, the square root of the primary tumour glycolysis was correlated with overall survival in a multivariate analysis that included tumour stage.[18,19]

Whole-body TLG estimations of primary tumour, nodal and distant metastases are relatively time consuming to calculate, involving the addition of all of the visible tumour elements. Therefore, straightforward measurements of the primary tumour only, based on simple thresholds of the SUV_{MAX} of the primary tumour might be easily and widely applied in the routine diagnostic clinical reporting setting. The present study attempted these measurements in a large cohort of patients being considered for radical therapy for NSCLC. The aims were to assess the ease and feasibility of routinely performing these measurements in clinical practice and to assess the prognostic significance of $TLG_{primary}$ against clinical stage, sex, and SUV_{MAX}.

Materials and methods

The study was based at the Wales Research and Diagnostic Positron Emission Tomography centre in Cardiff, South Wales which is a tertiary centre serving a catchment area of approximately 2.1 million patients. All patients attending the centre gave their informed written consent for the use of their images and clinical data for the purposes of research. The institutional review board confirmed that formal ethical review was not required for this retrospective observational study.

This was a retrospective study, reviewing patients undergoing FDG PET/CT imaging for the staging of histologically confirmed or radiologically suspected NSCLC. In Wales, central commissioners will only authorize funding for patients with NSCLC prior to proposed radical therapy (either radiotherapy or surgery). All patients referred for imaging were deemed to be potentially radically treatable based on CT and in terms of their performance status and other co-morbidities.

At PETIC, at the time of reporting PET/CT examinations, all patients were assigned a pathology code according to the