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Can CT measures of tumour heterogeneity stratify risk for nodal metastasis in patients with non-small cell lung cancer?

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AIM: To undertake a preliminary assessment of the potential for computed tomography (CT) measurement of tumour heterogeneity to stratify risk of nodal metastasis in patients with non-small cell lung cancer (NSCLC).

MATERIALS AND METHODS: Tumour heterogeneity in CT images from combined positron-emission tomography (PET)/CT examinations in 150 consecutive patients with NSCLC was assessed using CT texture analysis (CTTA). The short axis diameter of the largest mediastinal node was also measured. Forty-two patients without distant metastases subsequently had tumour nodal status confirmed at surgery (n=26) or endobronchial ultrasound (EBUS; n=16). CTTA parameters and largest nodal diameter were related to nodal status using the rank correlation and the risk ratio for each nodal stage (>N0, >N1, >N2) was compared between patients categorised as high and low risk by CTTA or nodal size. The most significant predictor of nodal status was related to overall survival using Kaplan–Meier analysis.

RESULTS: N-stage was more significantly correlated with CTTA than nodal diameter (Rs = -0.39, p=0.011, Rs = -0.45, p=0.0025, Rs = -0.40, p=0.0091 for normalised standard deviation (SD), normalised entropy and kurtosis respectively; Rs = -0.39, p=0.042 for nodal diameter). The presence of two or more high-risk CTTA values was the greatest risk factor for mediastinal metastasis (risk ratio: 11.0, 95% confidence interval: 1.56–77.8, p=0.0014) and was associated with significantly poorer overall survival (p=0.016).

CONCLUSION: CTTA in NSCLC is related to nodal status in patients without distant metastases and has the potential to inform selection of investigative strategies for the assessment of mediastinal malignancy.

Introduction

Non-small cell lung cancer (NSCLC) remains one of the leading causes of cancer in the Western World with a poor prognosis. Predictive factors of disease burden are required to help with decisions regarding options for clinical management. These circumstances are illustrated by the current clinical guidance for the management of NSCLC issued by the National Institute of Clinical Health and Excellence (NICE).[1] This guidance recommends different investigative strategies for the assessment of mediastinal disease according to the probability of mediastinal malignancy based

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on nodal size as depicted at computed tomography (CT). For patients with a low probability of mediastinal malignancy (15%; lymph nodes <10 mm maximum short axis on CT), the optimum strategy was determined to be staging with combined positron-emission tomography (PET)/CT alone. PET/CT, or endobronchial ultrasound (EBUS)-guided transbronchial needle aspiration (TBNA), or endoscopic ultrasound (EUS)-guided fine-needle aspiration, or non-ultrasound-guided TBNA are recommended for patients with an intermediate probability of mediastinal malignancy (50%; lymph nodes between 10 and 20 mm maximum short axis on CT) whereas neck ultrasound with sampling of visible lymph nodes, or non-ultrasound guided TBNA should be offered to patients with a high probability of mediastinal malignancy (85%; lymph nodes >20 mm maximum short axis on CT). New methods that can improve the risk stratification for mediastinal disease based on CT therefore have the potential to improve the selection of staging procedures for patients with NSCLC.

CT texture analysis (CTTA) is emerging as a technique for derivation of prognostic biomarkers for patients with NSCLC and other tumours.[2–5] CTTA evaluates quantitatively the distribution of CT attenuation values within a tumour to determine its heterogeneity. Tumour heterogeneity has been shown to relate to tumour aggression and treatment response, with hypoxia, mutations in epidermal growth factor receptor (EGFR) and Kirsten rat sarcoma viral oncogene homologue (KRAS) genes, and anaplastic lymphoma kinase (ALK) gene re-arrangements having been identified as potential biological correlates for CTTA values in NSCLC.[2] Given the prognostic significance of CTTA and its associated biological characteristics, it was hypothesised that CTTA can stratify risk for nodal metastatic disease in patients with NSCLC.

Materials and methods

Study design

A prospective observational study design was adopted, using patient data that were acquired as part of routine clinical care. The research was conducted in accordance with the requirements of the institutional ethics committee who waived the need for individual patient consent for this non-interventional study.

Patients

Imaging data were collected from 150 consecutive patients undergoing PET/CT for staging of NSCLC cancer. The study cohort of 42 patients comprised all those with no distant metastasis detected at PET/CT and subsequent confirmation of nodal status either at surgery (n=26) and or by EBUS with TBNA (n=16). Overall survival was determined from a median clinical follow-up period of 279 days (range: 59–437 days).

CT protocol and data analysis

Images were acquired using a Siemens mCT PET/CT system 120 kV, automated tube modulation (Care dose) with reference tube current set at 80 mAs, 5 mm sections and collimation 1.2 mm (Siemens, Erhlangen, Germany). Using TexRAD software (Feedback PLC, Cambridge, UK), CTTA was performed on the low-dose CT section that displayed the largest cross-sectional area of the tumour on soft-tissue windows as described previously.[2] Definition of the tumour boundary was assisted with reference to the PET-fused images and narrow CT windows (level 40 HU, width 150 HU). Automated segmentation tools were used to optimise consistency in the analysis between operators where possible, for example where the tumour was surrounded by aerated lung. Where the lung tumour was in contact with other tissues, such as the chest wall, mediastinum, or consolidated lung, manual selection of the region of interest (ROI) was required along that border and the automated segmentation tool could be used on those areas where the tumour bordered aerated lung. Segmentation tools excluded areas of tumour cavitation seen on CT but were not used to exclude areas of necrosis/photopaenia seen on the PET-fused images.

Based on the filtration-histogram CTTA approach utilised by the CTTA software, tumour heterogeneity at a scale of 4 mm was expressed as kurtosis, standard deviation (SD), and entropy. SD and entropy were both log-normalised to the tumour area determined by the number of pixels in the tumour ROI. Kurtosis is a measure of peakedness of the histogram and can be positive or negative (i.e., more peaked or flatter than a Gaussian (normal) distribution).[6] Kurtosis is inversely related to the number of objects by image filtration (whether bright or dark) and increased by intensity variations in highlighted objects.[6]

The short-axis diameter of the largest mediastinal node was also measured by a separate operator who was an accredited radiologist with more than 25 years of CT experience.

Statistics

The relationship between CTTA parameters and nodal status were determined using the rank correlation and compared to the correlation found between N-stage and mediastinal nodal size. If a significant correlation was found, patients were categorised as high or low risk for nodal metastases using the median texture value for the study cohort. The risk for each nodal stage (>N0, >N1, >N2) was compared between high- and low-risk patients and expressed as the risk ratio (with 95% confidence limits), with comparison against the risk ratios found for nodal size <10 mm versus ≥10 mm, using Fisher's exact test to assess statistical significance. The most significant predictor of nodal status was related to overall survival using Kaplan–Meier analysis. Kaplan–Meier analysis is a non-parametric statistic used to estimate survival function from lifetime data.

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