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Original article

Performance of automatic image segmentation algorithms for calculating total lesion glycolysis for early response monitoring in non-small cell lung cancer patients during concomitant chemoradiotherapy

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ABSTRACT

Background and purpose: This study evaluated the use of total lesion glycolysis (TLG) determined by different automatic segmentation algorithms, for early response monitoring in non-small cell lung cancer (NSCLC) patients during concomitant chemoradiotherapy.

Materials and methods: Twenty-seven patients with locally advanced NSCLC treated with concomitant chemoradiotherapy underwent ^{18}F-fluorodeoxyglucose (FDG) PET/CT imaging before and in the second week of treatment. Segmentation of the primary tumours and lymph nodes was performed using fixed threshold segmentation at (i) 40% SUV_{max} (T40), (ii) 50% SUV_{max} (T50), (iii) relative-threshold-level (RTL), (iv) signal-to-background ratio (SBR), and (v) fuzzy locally adaptive Bayesian (FLAB) segmentation. Association of primary tumour TLG (TLG_T), lymph node TLG (TLG_{LN}), summed TLG ($TLG_S = TLG_T + TLG_{LN}$), and relative TLG decrease (ΔTLG) with overall-survival (OS) and progression-free survival (PFS) was determined using univariate Cox regression models.

Results: Pretreatment TLG_T was predictive for PFS and OS, irrespective of the segmentation method used. Inclusion of TLG_{LN} improved disease and early response assessment, with pretreatment TLG_S more strongly associated with PFS and OS than TLG_T for all segmentation algorithms. This was also the case for ΔTLG_S, which was significantly associated with PFS and OS, with the exception of RTL and T40.

Conclusions: ΔTLG_S was significantly associated with PFS and OS, except for RTL and T40. Inclusion of TLG_{LN} improves early treatment response monitoring during concomitant chemoradiotherapy with FDG-PET.

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Non-small cell lung (NSCLC) cancer remains a disease with a generally poor prognosis [1]. At the time of diagnosis, one third of patients with NSCLC presents with locally advanced non-metastatic disease [1]. For these patients, radiotherapy in combination with chemotherapy is the accepted standard of care. With the aim of improving patient outcome, combined and intensified treatment approaches are increasingly being investigated. However, not all patients equally benefit from these treatment approaches and rational selection of available treatment options in a personalized medicine framework is required [2].

Positron emission tomography (PET) in combination with X-ray computed tomography (CT) with the glucose analogue ^{18}F-fluorodeoxyglucose (FDG) has proven to be a valuable tool to personalize treatment for this patient group [2]. Firstly, incorporation of FDG-PET images into the radiotherapy planning algorithm improves definition of gross tumour volume (GTV) [3–5] and might facilitate the concept of selective nodal irradiation [6]. Secondly, it has been shown that FDG-PET can identify areas that are at risk of local relapse [7,8], permitting to use the concept of molecular imaging-based dose painting [9]. Thirdly, several studies emphasize the ability of FDG-PET to monitor therapy response at an early treatment stage using quantitative PET indices [10–14]. Early

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response monitoring during treatment can facilitate clinical decision-making and improve patient management through early treatment adaptation and thereby avoidance of unnecessary side effects and costs of ineffective treatment.

However, employing the concept of FDG-PET-guided treatment decisions requires robust and standardized methods to derive these quantitative indices from PET images. Particularly, the strong dependence of most image-derived response indices on quantification of lesion volume emphasizes the need for standardized and consistent determination of these volumes in PET images. In this regard, there has been a widespread interest in the development of automated segmentation algorithms for PET. Over the years, there has been a rapid growth of segmentation algorithms for PET reported in the literature [15], an event which is also referred to as '*yapetism*' (''yet another PET segmentation method'') [16]. Difficulties encountered by these algorithms for automatic lesion segmentation in PET images are local contrast variations due to heterogeneous FDG uptake in the lesion, adjacent FDG-avid anatomy and lymph nodes, and relatively high noise content of PET images, often rendering the task of automatic lesion delineation challenging [15]. This becomes even more difficult when automatic segmentation has to be performed on low contrast interim and end-of-treatment PET images, where radiotracer uptake can be considerably reduced due to therapy effects. However, up until this day there is no standardized method for automatically determining lesion volume on PET images and many studies consider different segmentation algorithms for this purpose [17,18]. The purpose of this study was to evaluate this clinical applicability and performance of several established segmentation algorithms for generating plausible segmentation volumes that can be applied specifically to predict therapy response during treatment for patients with locally advanced stage IIIA or IIIB NSCLC treated with concomitant chemoradiotherapy. The predictive value of total lesion glycolysis (TLG), as determined by these different algorithms, for progression free survival (PFS) and overall survival (OS) was evaluated.

Materials and methods

Patients

A total of 27 patients with newly diagnosed stage IIIA or stage IIIB NSCLC were prospectively included in this study, as described before [10]. Patients were treated with concomitant radiotherapy and chemotherapy. This study was approved by the institutional review board (IRB) of the Radboud university medical centre. Written informed consent was obtained from every patient. Patient characteristics are summarized in Table 1.

Table 1
Patients characteristics.

Characteristics of patient population	
Male (Female)	18 (9)
Median age (range) [y]	58 (42–77)
Histological type	
Non-small cell lung cancer (NSCLC)	
Squamous cell carcinoma	10
Adenocarcinoma	14
NSCLC not otherwise specified	3
Disease stage	
IIIA	20
IIIB	7
Performance-score (ECOG)	
0	20
1	7
Smoking status	
Current smoker	11
Former smoker	16
Lesion location	
Right upper lobe	10
Right middle lobe	4
Right lower lobe	2
Left upper lobe	7
Left lower lobe	2
Pretreatment PET acquisition	
Number of bed positions	7–8
Administered FDG activity [MBq]	267 ± 48
Incubation time [min]	75 ± 7.5
Acquisition time per bed position [min]	4
Interim PET acquisition	
Number of bed positions	3–4
Administered FDG activity [MBq]	269 ± 49
Incubation time [min]	78 ± 8.0
Acquisition time per bed position [min]	4

Data are reported as mean ± standard deviation. PET = positron emission tomography, FDG = ^{18}F-fluorodeoxyglycose.

Treatment and follow-up

Intensity modulated radiotherapy (IMRT) was performed (10 MV photons), consisting of 33 fractions of 2 Gy (5 fractions a week for 6 week and 3 days) resulting in a total dose of 66 Gy on the primary tumour and affected lymph nodes (i.e. pathologically proven or FDG-avid lymph nodes). Chemotherapy consisted of two cycles of cisplatin 50 mg/m^2 intravenously (day 1, 8, 22, and 29) and etoposide 100 mg/m^2 intravenously (day 1–3, and day 22–24). Median overall treatment time was 45 days (range 43–48 days). Patients with progressive disease during follow-up received palliative treatment. Follow-up during and after treatment consisted of clinical examination at regular intervals. When residual or recurrent disease was suspected, chest X-ray and chest CT-scans were performed. For each patient, sequential FDG-PET/CT imaging was performed before and during treatment. The pretreatment scan was obtained before treatment (median 11 days, range 1–28 days) whilst interim FDG-PET imaging was performed in the second week during concomitant treatment (median 14 days, range 13–16 days), always before the second cycle of chemotherapy after 20 Gy radiotherapy. According to the treatment protocol all patients started with radiotherapy at the first day of the first cycle of chemotherapy, i.e. no neo-adjuvant treatment was applied.

Patient preparation and FDG PET imaging

Imaging was performed using a hybrid Biograph Duo PET/CT scanner (Siemens Medical Solution, Knoxville, TN, USA). The PET scanner was accredited by the Research 4 Life (EARL) initiative for quantitative FDG-PET/CT studies [19]. Before image acquisition, patients fasted for at least six hours and blood glucose levels were lower than 8.2 mmol L^{-1} in all patients. The amount of activity administered to the patient was adjusted to the patient's weight and was 3.45 MBq kg^{-1}. Details regarding the PET acquisition protocol are summarized in Table 1. No respiratory gating was performed. For the purpose of attenuation correction and anatomical reference, a low dose (LD) CT scan was acquired with a reference tube current time product of 40 mA s. LDCT scans were acquired during timed unforced expiration breath-hold. Modulation of X-ray tube current was performed using CARE Dose 4D. Reconstruction of PET images was performed with a 2D ordered subset expectation maximization (2DOSEM) algorithm using a matrix size of 128 × 128, 4 iterations and 16 subsets. Post reconstruction filtering was performed using a three-dimensional Gaussian filter kernel with a full width at half maximum of 5 mm.

Image segmentation

The primary tumour and FDG positive lymph nodes were delineated on the pretreatment and interim PET images. Firstly,

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