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What you see is (not) what you get: tools for a non-radiologist to evaluate image quality in lung cancer

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ABSTRACT

Medical images are an integral part of oncological patient records and they are reviewed by many different specialists. Therefore, it is important that besides imaging experts, other clinicians are also aware that the diagnostic value of a scan is influenced by the applied imaging protocol.

Based on two clinical lung cancer trials, we experienced that, even within a study protocol, there is a large variability in imaging parameters, which has direct impact on the interpretation of the image. These two trials were: 1) the NTR3628 in which the added value of gadolinium magnetic resonance imaging (Gd-MRI) to dedicated contrast enhanced computed tomography (CE-CT) for detecting asymptomatic brain metastases in stage III non-small cell lung cancer (NSCLC) was investigated and 2) a sub-study of the NVALT 12 trial (NCT01171170) in which repeated 18 F-fludeoxyglucose positron emission tomography (^{18}F-FDG-PET) imaging for early response assessment was investigated.

Based on the problems encountered in the two trials, we provide recommendations for non-radiology clinicians, which can be used in daily interpretation of imaging. Variations in image parameters cannot only influence trial results, but sub-optimal imaging can also influence treatment decisions in daily lung cancer care, when a physician is not aware of the scanning details.

1. Introduction

Medical imaging is an essential component of the diagnostic procedures performed in lung cancer. Next to that, it is also used for response assessment. The imaging modalities used in oncology have evolved from simple X-rays to computed tomography (CT)- and magnetic resonance imaging (MRI) scans. Nuclear imaging has innovated by the introduction of positron-emission tomography (PET) with several tracers being ^{18}F-fludeoxyglucose (^{18}F-FDG) most frequently used. An ^{18}F-FDG-PET-scan using an integrated PET-CT scanner combined with a contrast enhanced CT (CE-CT) is nowadays a standard staging technique in thoracic oncology. Due to ongoing technological innovations, the sensitivity and specificity of these modalities have significantly improved. However, many factors, as patient preparation, image acquisition and reconstruction parameters affect the quality and accuracy of all these exams [1].

Images are nowadays an integral part of electronic patient records and can be reviewed directly by many different health care specialists. Consequently, it is important that besides the imaging experts (i.e. radiologists and nuclear medicine physicians), other reviewing clinicians are aware that the diagnostic value of a scan is influenced by the applied imaging protocol and can recognize common artifacts (e.g. breathing artifacts). More knowledge on this topic will provide clinicians tools to communicate with their imaging colleagues to prevent

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image misinterpretation and to select the appropriate image acquisition protocol.

In two recently performed clinical trials (NTR3628 and NCT01171170) studying patients with non-small cell lung cancer (NSCLC) we experienced that, even though specific imaging guidelines were mandated by the trial protocol, there was a large variability in imaging parameters. This influenced not only the outcome of the trial but could also have impact on treatment by their clinical physician (medical oncologist/pulmonologist). In this manuscript, we describe the imaging problems encountered in these two trials. Furthermore, we will provide recommendations to guide clinicians in the interpretation of medical imaging based on our experience. Our goal is that this will result in improved clinical care as well as imaging standardization, not only in future multicenter studies, but also in daily clinical care.

2. Methods

2.1. NVALT12 ^{18}F-FDG PET/CT imaging sub-study

In all lung cancer patients eligible for therapy with curative intent, not only a CE- chest-CT, but also a whole body ^{18}F-FDG-PET is recommended [2,3]. The ^{18}F-FDG-PET, performed with a non-diagnostic low dose CT (LD-CT) for attenuation correction can be extended by an additional diagnostic CE-CT of the chest (with or without the upper abdomen and brain).

In the multicenter randomized phase II NVALT12 trial (NCT01171170) chemo-naïve patients with stage IV non-squamous NSCLC were treated with paclitaxel-carboplatin-bevacizumab with or without nitroglycerin patches. For patients in whom an ^{18}F-FDG-PET at baseline was performed as part of standard work-up, a second study ^{18}F-FDG-PET was performed within three weeks after start of treatment. The two ^{18}F-FDG-PETs were used for response assessment, and results have been reported [4]. It was assumed that image acquisition was per the European Association of Nuclear Medicine (EANM) guidelines for tumor imaging version 1 as introduced in 2009, therefore no PET guidelines were added to the protocol [1].

2.2. Study NTR3628: brain imaging

Although patients with brain metastases often have neurological complaints, 3–21% of neurologically asymptomatic patients with otherwise stage I–III lung cancer are diagnosed with brain metastases on MRI [5]. This diagnosis is especially important in patients that are potentially eligible for therapy with curative intent. A post-gadolinium-MRI (post-Gd-MRI) is the imaging modality of choice, but when MRI is contra-indicated or too difficult to arrange within a reasonable time scale, a diagnostic CE-CT is an acceptable alternative [2,3]. Except for the recommendation to include Gd-contrast series, no recommendations are given in the ESMO and NCCN lung cancer guidelines regarding the minimal requirements for this brain MRI (e.g. applied MRI sequences (e.g. T1, T2 FLAIR, diffusion weighted imaging) and minimum contrast amount) [2,3]. For brain CTs, intravenous administration of iodine-containing contrast is advised but otherwise no recommendations are made (e.g. minimum number of mAs and minimum contrast dose) [2,3].

In the multicenter NTR3628 study, the additional value of a post-contrast brain MRI was evaluated in stage III (based on ^{18}F-FDG-PET/CE-CT) NSCLC patients. All patients underwent a dedicated brain CE-CT as part of the staging whole body ^{18}F-FDG-PET as standard of care [6]. Imaging requirements were: a standard ^{18}F-FDG-PET/CE-CT protocol that included a diagnostic CE-CT brain, and a 1.5T Gd-MRI brain (1 mm slices, 0.1 mmol/kg gadolinium), with a magnetization transfer contrast (MTC) pre-pulse to increase sensitivity and an additional post-contrast FLAIR sequence. MRI parameters were as recommended by an experienced neuro-radiologist (PH) and followed the American College of Radiology Appropriateness Criteria (ACR AC) [7]. After inclusion of all patients, CE-CTs and MRIs were per protocol centrally reviewed by PH for protocol adherence and presence of brain metastases.

3. Results

3.1. NVALT12 ^{18}F-FDG PET/CT imaging sub-study

In the imaging analysis sub-study of the NVALT12, 167 baseline scans and 118 follow-up PET scans for response evaluation were present. Only 97 (34%) of the 285 ^{18}F-FDG-PETs performed in this study had an ^{18}F-FDG uptake time as recommended by the EANM. Fifty-four (19%) scans had both uptake times in agreement with the uniform protocols for imaging in clinical trials (UPICT) guidelines. Supplementary material S1 shows the uptake times of the baseline- and the response scans ranked in ascending order for the baseline scan, only the uptake times between the red lines can be used for response assessment. The other investigated parameters in this imaging sub-study, correction factors (attenuation, randoms, scatter) and reconstruction

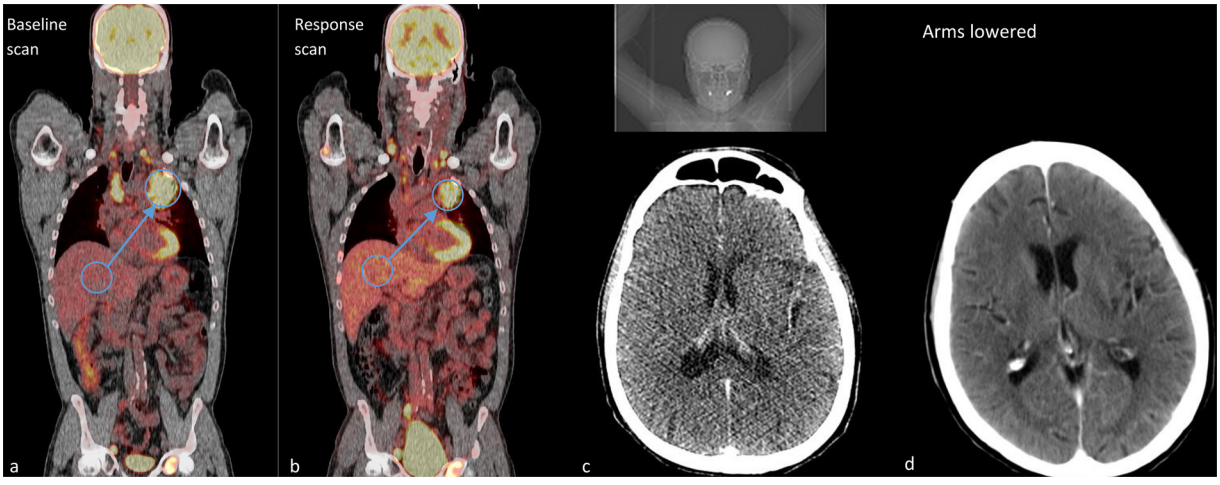

Fig. 1. a) Baseline ^{18}F-FDG-PET/CT scan of the NCT01171170 trial; b) Response ^{18}F-FDG-PET/CT scan of the same patient, showing that a different SUV_{mean} of the liver can lead to a visually underestimation of response in the tumor; c) Axial CT image of the brain of the NTR3628 after contrast administration, reconstructed with a field of view of 500 × 500 mm with raised arms (note the high level of noise and the streak artifacts due to beam hardening); d) Axial CT image of the brain of the same patient at approximate the same level, also after contrast administration, reconstructed with a FOV of 200 × 200 mm with the arms lowered. The window and level setting are identical as well as other acquisition parameters for all imaging, note the difference in image quality.