Editorial

Magnetic resonance imaging for staging of non-small-cell lung cancer—technical advances and unmet needs

Gregor Sommer, Bram Stieltjes

Clinic of Radiology and Nuclear Medicine, University of Basel Hospital, Basel, Switzerland

Correspondence to: Gregor Sommer, MD, MSc. Clinic of Radiology and Nuclear Medicine, University of Basel Hospital, Petersgraben 4, 4031 Basel, Switzerland. Email: gregor.sommer@usb.ch.

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Lung cancer has been and still is the most common cancer globally and with 1.8 million new cases in 2012 (1) makes up almost 13% of all newly diagnosed cancers. Despite substantial improvements in diagnosis, therapy, and prevention in the last decades and reduced mortality rates, lung cancer still is the most common cause of death from cancer with almost 1.6 million deaths in 2012 accounting for almost 20% of all cancer related deaths (1). With about 83%, non-small-cell lung cancer (NSCLC) is by far the most often-occurring tumor type within this group (2). Imaging has developed as an important factor for initial diagnosis, pre-interventional (i.e., non-invasive) staging and post interventional follow-up. In this editorial we will focus on the role of imaging in the context of staging of NSCLC, addressing in particular some of the most recently published data on magnetic resonance imaging (MRI) methods (3).

To be able to judge the current standing of MRI in this context, a comparative overview of the evolution of the current standard method, ^{18}F-fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) in NSCLC staging is mandatory. In the late 1990's, growing evidence supported that FDG-PET strongly improved staging accuracy, especially for N-staging, in comparison to computed tomography (CT) alone as reported in a large meta-analysis including a total of 43 studies encompassing almost 2,800 patients (4). Later, the combination of PET and CT in now commonly available PET/CT hybrid scanners enabled the quick integration of this modality into the clinical work-up of NSCLC staging, making it the current gold standard for imaging-based staging (5). However, it is not all gold that shines in this standard as outlined below. In the following, we will review current guidelines (6-8) for staging of NSCLC using FDG-PET/CT and compare the current status of MRI for staging of NSCLC with this body of reference.

^{18}F-fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT)

T-staging

Contrast enhanced chest-CT is considered the standard of care for initial staging but provides a low sensitivity (55%) and limited specificity (81%) (6). Furthermore, the reliability of predicting T3/T4 disease is poor (6). As shown in a meta-analysis of 40 studies encompassing 1,474 lesions, especially the sensitivity may be increased to 96% by adding FDG-PET without a clear increase in specificity (9). Final diagnosis using imaging is not recommended and invasive histopathological or cytological proof of malignancy is mandatory.

N-staging

N-staging is seen as the most important component of intrathoracic staging because it strongly affects both the extensiveness of therapy and the prognosis of the patient. In CT imaging, a size cut-off (commonly >1.0 cm) is used for differentiation of benign and malignant and yields an average sensitivity and specificity of 75% and 76% respectively (8). Adding FDG-PET provides clear improvements in both sensitivity (80-90%) and specificity (85-95%). Perhaps the most important strength of FDG-PET/CT is its high negative predictive value (NPV) of 95% (8). However, this does not hold for (6):

(I) Suspected N1 nodes: 30% FN for N 2-3;
(II) Primary tumor size >3 cm: NPV drops to 85-89%;
(III) Central tumors with negative FDG-PET/CT: FN in 21.6%.

As such, a negative nodal status in FDG-PET/CT in terms of morphology and metabolism is considered sufficient to avoid invasive preoperative staging if primary tumor size is ≤3 cm, but a positive FDG-PET/CT always requires additional histopathological verification (6).

M-staging

About 40% of the NSCLC patients do have a distant metastasis at the time of presentation and approximately 90% of these patients present with specific symptoms (8). The most common locations for extra-thoracic metastatic spread are the brain, bone, liver and adrenal glands. FDG-PET/CT is considered the superior imaging technology for detecting these metastases, except for those located in the brain, where sensitivity is limited by the high brain background FDG-uptake (7). Therefore, it is suggested that routine imaging of the brain with head MRI should be performed in patients with clinical stage III or IV NSCLC, even if they have a negative clinical evaluation (Grade 2C). CT is recommended only if MRI is not available (7).

In conclusion, based on extensive meta-analysis, combined FDG-PET/CT is currently the imaging modality of choice for TNM staging of NSCLC, complemented by MRI of the brain for clinical stages III-IV. However, both T-staging and N-staging, especially N-staging in FDG-PET positive lymph nodes clearly leaves room for improvement and shortcomings in this respect have spurred the development of alternative imaging approaches, mainly using MRI.

Magnetic resonance imaging (MRI)

Compared to the available studies on FDG-PET/CT, the current state of available data on MRI for staging of NSCLC leaves much to be desired. As a consequence, apart from screening for brain metastasis in high risk patients, MRI does not play a role in any of the current guidelines. Below we will review current approaches. We have divided the available methods into three groups, namely standard anatomical MRI, diffusion weighted-MRI (DW-MRI), and FDG-PET/MRI hybrid approaches. These three groups represent three distinct approaches with substantial literature reports.

Standard MRI sequences

The amount of existing data that directly compare MRI with CT or FDG-PET/CT for diagnostic assessment of NSCLC is limited. Using standard MRI sequences such as T2- and T1-weighted imaging, already papers from the early 1990's reported a comparable sensitivity and specificity of MRI (56% and 80%) and CT (63% and 84%) in distinguishing T3-T4 tumors from T0-T2 tumors (10). In the same data from 170 patients, MRI was found to be significantly more accurate than CT in diagnosis of mediastinal invasion, however, with no significant differences between the two techniques for diagnosis of bronchial involvement or chest wall invasion. A recent randomized study of 263 patients compared post-hoc co-registered whole-body FDG-PET/MRI and FDG-PET/CT with correct upstaging as the primary endpoint (11). In this study, co-registered whole-body FDG-PET/MRI performed better than FDG-PET/CT plus brain MRI in characterizing tumor extent, which was attributed by the authors to the superior capability of morphologic MRI to delineate the boundaries of the tumor against the mediastinum. However, with regard to the primary endpoint of the study, this did not result in a significant advantage for FDG-PET/MRI. Also, in an earlier study from the same group on 165 patients (12), no statistically significant difference between FDG-PET/CT and unenhanced whole-body MRI at 3T was seen in terms of overall staging accuracy. According to the current guidelines, MRI of the chest should not be performed routinely for staging of the mediastinum, but is considered useful when there is concern about involvement of the superior sulcus or the brachial plexus (7).

The additional benefit of morphologic MRI protocols over CT for nodal staging is generally limited, as these basically rely on the same imaging criteria as CT, which are size and shape of the node. Here, short TI inversion recovery (STIR) turbo spin-echo sequences may provide interesting additional options, as suggested repeatedly during the last decade by two research groups from Japan (3,13,14). In their most recent publication from June 2015 (3), Ohno *et al*. describe their method of using relaxation-time-dependent information from whole-body MRI with signal intensity (SI) assessment to be superior to FDG-PET/MR without SI assessment and FDG-PET/CT in terms of N-staging (91.4% accuracy for whole-body MRI and FDG-PET/MRI with SI assessment *vs*. 80.7% for FDG-PET/CT; P<0.001), assessment of distant metastatic spread (98.6% *vs*. 90.7% accuracy; P=0.003), overall

clinical stage (91.4% *vs*. 70.7% accuracy; P<0.001), and TNM-based assessment of operability (97.1% *vs*. 85.0% accuracy; P<0.001). For T-staging, no significant difference was found (94.3% *vs*. 91.4%). When judging these data, it must be said that notwithstanding the very promising results, this method requires further investigation: whole-body MRI with SI in this particular form, although initially developed and published over 10 years ago, has been applied until now—to the best of our knowledge—only by the two mentioned groups from Japan and has not been reproduced (and published) successfully anywhere else in the world. This could well be due to the complexity of the procedure that may pose a serious limitation for clinical acceptance. Simplification, standardization and further testing of the method within larger multi-center studies are mandatory steps toward a general acceptance of this promising technique in clinical practice.

Diffusion weighted MRI (DW-MRI)

DW-MRI is a meanwhile widely established MRI technique that is able to detect and identify hyper-cellular tissues such as metastases from cancer due to their dense microstructure that restricts diffusion of water molecules. The method, originally known from imaging of cerebrovascular infarction, has been adapted to whole-body oncologic imaging by Takahara and colleagues in 2004 (15). Since that time, several authors have investigated its potential use for staging of NSCLC. A meta-analysis performed by Wu and coauthors in 2012 (16) thoroughly analyzed all studies available at that time, that directly compared DW-MRI and FDG-PET/CT for N-staging of NSCLC. From a total of 19 studies that met the inclusion criteria and included a total of 2,845 pathologically confirmed patients, the pooled sensitivity of DW-MRI was 72% [95% confidence interval (CI): 63-80%], which was not significantly different from FDG-PET/CT [75% (68-81%); P=0.09]. However, the pooled specificity for DW-MRI of 95% (85-98%) was significantly higher than that of FDG-PET/CT [89% (85-91%); P=0.02]. In their conclusion, the authors state that despite their very positive results, a general recommendation for using DW-MRI in clinical practice cannot yet be made. Today, even though different groups have performed about half a dozen additional studies on this topic since that time, data from a large multi-center randomized trial confirming these promising results are still missing.

Hybrid FDG-PET/MRI

PET/MRI hybrid scanners are still quite novel to clinical radiology especially outside neuroradiology. As such, it is not surprising that the development of such scanners in the context of NSCLC is currently still in its infancy and suffers from intrinsic limitations. Due to ethical constraints, all below described studies performed an FDG-PET/MRI after an FDG-PET/CT using the same injected dose of FDG. This leads to biased comparisons since the PET component is favored in the PET/MRI machine due to longer latency after tracer injection. Furthermore, due to the lack of the CT component, the attenuation correction remains an issue in PET/MRI and further limits the comparability of quantitative PET results. Also, due to the long scan times inherent to the combination of FDG-PET/CT and FDG-PET/MRI, the MRI protocols are usually limited, thus not necessarily maximizing the diagnostic potential of the MRI-component.

The first feasibility study investigated a mixed group of ten patients with lung cancer and found a potential benefit of FDG-PET/MRI regarding infiltration of the chest wall (17). This potential benefit was not confirmed in the largest study so far focusing on NSCLC staging using FDG-PET/MRI on 22 patients (18). The same study showed a slight, non-significant improvement of FDG-PET/MRI for N-staging albeit on a very small number of LNs (n=22). Another study found, in a mixed group including staging-, follow-up-, and restaging patients (n=11), no significant differences in staging capability, but lower inter-observer variability for FDG-PET/CT compared to FDG-PET/MRI (19). Other studies have focused on N-staging, mainly comparing DW-MRI with standardized uptake value (SUV). In the largest study on this topic, 38 patients and approximately 100 LNs were evaluated showing a weak correlation between SUV_{max} and ADC_{mean} (20). However, the study was not designed to evaluate and compare the diagnostic performance in this respect. As a whole, the current literature on FDG-PET/MRI is hardly beyond the feasibility stage, as can be taken from the above mentioned summary. It seems candid to integrate promising methods from MRI as described in the previous two sections in larger studies that also provide a cross-over design on first method applied (PET/CT *vs*. PET/MRI) to obtain a fair and full evaluation of the true potential of FDG-PET/MRI.

Summary and conclusions

From looking at the past of MRI imaging for NSCLC, much can be learned about the future. First and foremost, compared to the amount and quality of data on FDG-PET/CT, there is a substantial lack of data on the added value of MRI apart from searching for brain metastases in high risk patients. Unfortunately, the current data at hand is scattered, often stemming from a single or few different sites, performed on limited numbers of patients, and with large variation of used methods. Furthermore, most applied quantitative methods described are painstaking and it is difficult to foresee a seamless integration of such methods in day-to-day clinical practice. The picture that emerges is somewhat saddening, especially bearing in mind the prevailing dismal prospects of patients with NSCLC, since some of the above discussed papers do indicate a potential of MRI and there are real challenges that if addressed may strongly improve patient management. These include the low positive predictive value of FDG-PET/CT positive LNs, the lack of accuracy in evaluation of mediastinal and chest wall infiltration for T-staging, and the decreased negative predictive value of FDG-PET/CT negative LNs in specific high risk sub groups. To address these issues, we need large, multi-center prospective interdisciplinary studies that have no favor towards a specific technology and bear clinical practicability in mind. We would like to use this editorial to spur a wave of enthusiasm considering such an approach. This is long due and in our opinion, extended feasibility studies in this context have little to add to the current state of the art in terms of patient benefit and science.

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Footnote

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