The potential contribution of artificial intelligence to dose reduction in diagnostic imaging of lung cancer

Alessandra Retico[1], Maria Evelina Fantacci[1,2]

[1]National Institute for Nuclear Physics (INFN), Pisa Division, Pisa, Italy; [2]Physics Department of University of Pisa, Pisa, Italy

Correspondence to: Alessandra Retico. National Institute for Nuclear Physics (INFN), Pisa Division, Pisa, Italy. Email: alessandra.retico@pi.infn.it; Maria Evelina Fantacci. Physics Department of University of Pisa, Pisa, Italy. Email: maria.evelina.fantacci@unipi.it.

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The efficient detection of lung nodules is an extremely important and challenging task, which has required in the recent years a joint effort by a wide community of scientists including chest doctors, radiologists, nuclear medicine physicians, and experts in medical instrumentation, image processing and artificial intelligence. The presence of lung nodules characterizes pathologies of great social impact, and their early detection, when they are still of limited size, can constitute the difference between a treatable and a mortal case. Lung nodules are the first radiological sign of lung cancer, which is one of the main health issues in developed countries, accounting for about 20% and 28% of cancer-related deaths in Europe (1) and in the United States, respectively, with a 5-year survival rate limited to 10–17% (2). Moreover, the lung is the second most common site of metastases from extra-thoracic malignancies after the liver, with approximately one third of patients with extra-thoracic cancer that develop lung metastases during the course of the disease (3). The National Lung Screening Trial (NLST) trial showed that three annual screening rounds of high-risk subjects using low-dose computed tomography (CT) reduced lung cancer mortality after 7 years by 20% in comparison to screening with chest radiography (4). Thus, lung cancer screening programs with low-dose CT are currently being implemented in the U.S. and will likely be followed by other countries (5). One of the major challenges of implementing CT-based screening programs is the enormous amount of CT images that radiologists have to analyze. Analogously, patients with lung metastases detected early after their onset have a higher chance of successfully undergoing to radical treatment (6), with a 5-year survival rates in case of surgery for lung metastases ranging in the 30–62% (7). Even in this case, CT is the state-of-the-art modality for the detection of pulmonary metastases. Unfortunately, the detection rate of lung metastases for single and double reading of CT exams is limited to 50% and 63%, respectively (8). The small size of most lung nodules, the location proximal to large vessels and the large number of CT slices to be reviewed have been suggested as possible causes of misidentifications by radiologists (9).

In this context, artificial-intelligence tools have been designed to support radiologists in the identification of lung nodules since when chest radiography was the diagnostic imaging modality of choice to detect lung cancer (10,11). With the advent of low-dose CT and in particular with its implementation in screening trials, many computer-aided detection (CAD) systems for lung nodule identification have been developed (12). The CAD potential in improving radiologists' performance has been deeply investigated, highlighting that the CAD can successfully be used as a second reader (13).

The research in lung cancer diagnosis is now advancing in two distinct fields: the improvement in the image acquisition instrumentation and reconstruction techniques based on iterative processes (14) is allowing to obtain high-quality CT images even at low and ultra-low dose (i.e., a dose amount very similar to that of a chest radiography), whereas the recent acceleration in the implementation of deep-learning methods in the medical imaging field is leading to an enhancement of the performance of CAD systems across different imaging modalities, in both detection and diagnosis tasks (15,16).

The dose reduction in CT acquisition can be achieved either fixing the X-ray tube voltage and lowering the tube current or reducing the scan duration. Lowering the tube voltage can also reduce the radiation dose.

The recent study conducted by Jin and colleagues (17) showed a direct comparison in lung nodule assessment on a cohort of 82 subjects that received both low-voltage (80 kV) and standard-voltage (120 kV) CT scans. Two different CAD systems for nodule size measurement and density evaluation were used in this study. The study suggests that images with high quality and optimal diagnostic value can be obtained with ultra-low-dose CT (ULD-CT) coupled with the iterative reconstruction algorithm as compared to standard dose CT, with significant discrepancies only in the mean CT values of larger nodules.

The dose reduction may also affect the performance of CAD systems for nodule detection. Je and colleagues studied this relationship on 25 asymptomatic volunteers (18). The dose reduction is achieved in this study by decreasing the X-ray tube current, i.e., using the following four different amperages: 32, 16, 8 and 4 mAs. Despite the CAD sensitivity to nodules is sensibly lowered passing from the dose levels corresponding to 32 to 4 mAs, a significant reduction of the performance is not observed at the intermediate dose levels, thus suggesting the possibility to reduce the exam dose up to certain extent.

The use of CAD systems can successfully overcome the additional difficulty in lung nodule detection due to dose reduction in ULD-CT. The two recent studies by Huber *et al.* (19) and by Messerli *et al.* (20) go in the same direction: ULD-CT, i.e., a CT scan acquired at the same dose rate of a chest radiography exam, when iterative reconstruction is implemented and when supported by the use of CAD, shows similar sensitivity to standard dose CT exam. The study of Huber *et al.* (19) is conducted on a lung phantom where 232 lung nodules of different sizes were randomly distributed. Standard-dose CT and ULD-CT scans were acquired and processed with the iterative reconstruction algorithm. Both CAD and maximum intensity projection (MIP) methods were used as support tools by radiologists. The use of CAD and MIP enhanced the radiologists' performance in nodule detection on ULD-CT, thus compensating the decrease in the detection performance due to dose reduction. Messerli and colleagues (20) demonstrated in an in-vivo investigation of 202 patients that a CAD system retains similar nodule detection performance on standard-dose CT (1/8 mSv) and on ULD-CT (0.13 mSv), with sensitivity of 70% and 68%, respectively. Additionally, CAD improves radiologists' performance in detecting nodules on ULD-CT scans.

CAD systems, mostly based on artificial intelligence approaches, are therefore acquiring a leading role in the possibility of reducing the dose in the screening CT examination, while maintaining the same diagnostic power.

A similar trend to that under way for the CT diagnostic modality is occurring in the field of nodule assessment, which is based on the evaluation of the patients' lesions with the positron emission tomography (PET), or with hybrid imaging obtained by PET combined with a morphological imaging modality. The advantage of acquiring both PET and CT images of a subject lies in the possibility of investigating both anatomical and functional information of organs. In a combined PET-CT system, the lower-resolution PET image, encoding the metabolic information, can be more precisely aligned with the higher-resolution CT image, encoding detailed anatomical information, and their overlay can be shown to the image reader. Similar considerations regarding functional *vs.* structural information and low *vs.* high resolution image characteristics hold for PET combined with magnetic resonance imaging (MRI) systems. Additionally, MRI can complement PET imaging with independent investigation of several functional and microstructural properties of tissues.

In PET imaging, the amount of radiotracer dose correlates with the level of image quality. The role of artificial intelligence in reconstructing good quality images in hybrid imaging at a small percentage of radiotracer with respect to standard acquisition has been already investigated and validated with promising results in neuroimaging applications, such as on FDG (^{18}F-fluorodeoxyglucose) images of patients with recurrent glioblastoma and on ^{18}F-florbetaben PET-MRI images of patients who underwent simultaneous PET-MRI amyloid examinations (21). The current role of PET-CT using FDG also in pulmonary nodule staging has been recently reviewed by Groheux and colleagues (22). PET investigation is recommended for solid nodules with diameter of 8–10 mm or larger.

We can affirm that in hybrid imaging systems the availability of two sets of images carrying out independent information represents an intriguing challenge for CAD system developers. Combining complementary approaches for nodule detection and characterization opens up a wide range of strategies to implement. An example of CAD system developed to assist clinicians in PET-CT image reviewing has already been reported by Teramoto and colleagues (23). In their approach, two independent analysis pipelines were executed on CT and PET scans, based on handcrafted feature selection and a Support Vector Machine (SVM) classification. As a result, in the analysis of 50 PET-CT exams, the authors obtained a nodule sensitivity of 67% at 5.6 false positive detection per scan (FP/scan) and 38% at 1.0 FP/scan, respectively. The two pipelines were then integrated by merging the outputs of the two analyses, i.e., all findings detected either on CT or on PET were retained, leading to an improvement of the detection performance up to 80% sensitivity at 6.6 FP/scan. Another approach in lung nodule detection and characterization with PET-CT has been reported by Zhao *et al.* (24). The authors implemented a method which integrates PET and CT data since the beginning. After the lung segmentation was defined on the CT images, the suspicious areas were first identified on PET images and then marked on CT images accordingly. Textural features were extracted from CT data and metabolic information from PET data for each suspicious area; the features were finally analyzed by a SVM. This approach, developed and validated on a dataset of 219 scans, reached a sensitivity of 95.6% at 2.9 FP/scan.

Let us recap the evolution described above for nodule detection in screening CT: (I) demonstration of the efficacy of low-dose CT in nodule identification in lung cancer screening; (II) demonstration of the CAD capability to enhance radiologists' performance; (III) investigation of the possibly to move to ULD-CT in lung cancer screening maintaining high diagnostic power thanks to artificial intelligence approaches, e.g., CAD systems.

That paradigm can be rephrased as follows for nodule staging by PET-CT: (I) demonstration of the efficacy of PET-CT in staging pulmonary nodules; (II) demonstration of the CAD capability to enhance radiologists' performance; (III) investigation of the possibly to move to ULD PET while maintaining similar diagnostic/staging performance.

It seems that for lung cancer staging with PET-CT the research has already gone through points 1 and 2 and is now working on the issue described in point 3. In this regard, the work by Schwyzer and colleagues (25) constitutes an initial implementation of a deep residual neural network to detect lung cancer and places the basis of such investigation, by evaluating the efficacy of machine-learning approaches on PET data with reduced dose. The authors simulated a dose reduction in PET data, i.e., beside the standard full-dose reconstructions (PET100%) two additional reconstructions were generated: PET10% (simulating a tenfold reduced dose) and PET3.3% (simulating a thirtyfold reduced dose). The authors analyzed 3,936 PET slices including images where the lung tumor was visually present and images of patients with no lung cancer. They implemented a transfer-learning approach to perform a binary classification of the PET slices where the lung tumor was visible versus slices of patients with no lung cancer using a pre-trained deep residual neural network and partitioning the image sample into 10 subsets for train and testing in a ten-fold cross-validation scheme. The study was carried out on a sample of one hundred patients, including 50 patients with histologically proven lung cancer (30 with adenocarcinoma, 11 with squamous cell carcinoma, 3 with mixed adeno-squamous carcinoma, 2 with small cell lung cancer, and 4 with other subtypes) and 50 patients without any lung lesion. By comparing the results obtained in the three dose amounts in terms of area under the receiver operating characteristic (ROC) curve (AUC), sensitivity and specificity, and by singly evaluating the lesions leading to false classification, they concluded that a combination of advanced PET detector technology and image analysis with machine-learning algorithms may allow fully automated detection of lung cancer at very low effective radiation doses of 0.11 mSv (i.e., 3.3% of current clinical routine). Despite an independent validation of the proposed approach is advisable on PET data natively acquired at different dose levels, since the dose-reduction simulation procedure can be affected by a different noise distribution with respect to real data, the evidence provided by Schwyzer *et al.* that the use of deep-learning procedure is in favor of the possibility of reducing the dose in PET exam is certainly exciting.

Since the advent of the use of digital formats in biomedical imaging (initially by the digitization of radiographic films) researchers have developed numerical systems for image processing and analysis. Starting from the implementation of the first image filters in the late 1970s, passing from the development of supervised techniques for disease classification in the 1990s, the fields of application of image processing and analysis strategies have largely increased, covering a wide range of image modalities and many diverse detection/diagnosis/staging objectives. Nowadays, software tools for image classification, lesion detection, object segmentation and registration are more and more often integrated in commercial medical imaging devices. The new frontiers of research in this field rely on the emerging deep-learning based techniques, whose continuous progress and applicability is strictly related to the increasing availability of powerful computing resources. Already established deep-learning contributions in various areas of application in medical imaging have recently been reviewed by Litjens *et al.* (16), spanning almost all image modalities (MRI, CT, ultrasound, X-ray, microscopy, etc.), targeting most body regions and covering many different tasks, e.g., detection, segmentation, registration, classification of organs, structures and lesions. The community of researchers working in this field is very active, with many new results appearing in the literature every day.

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