AI/ML Imaging Applications in Body Oncology

10

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Contents

10.1 General Principles

In the following, the structure of the chapter is outlined and general principles as well as issues of artificial intelligence (AI) in nuclear medicine are discussed. There is no clear definition of AI in medical imaging nor a clear demarcation to conventional analysis techniques. Thus, other advanced image analysis methods like radiomics are summarized in this chapter as well.

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P. Veit-Haibach, K. Herrmann (eds.), *Artificial Intelligence/Machine Learning in Nuclear Medicine and Hybrid Imaging*, https://doi.org/10.1007/978-3-031-00119-2_10

The utilization of AI for detecting diseases in medical image data is rapidly emerging [1]. Consequently, AI in nuclear medicine has been widely employed for image data, and also for electronic health record data [2]. When applied to image data, AI may be used to determine the stage according to an existing staging system (like the bone scan index), to improve an existing staging system (e.g. by simplification of TIRADS), to generate new staging systems that are to complex or too time-consuming to be performed by medical experts (e.g. whole-body tumor volume quantification in PET-CTs) or to directly predict a clinically relevant endpoint (e.g. estimate grading of tumor, predict overall survival time). When applied to electronic health record data, AI may be used to predict endpoints as well. Additional approaches seem promising, like the utilization of artificial intelligence to form real-world control groups for image centric trial, as has been demonstrated for therapeutic trials [3].

An organ-wise structure is chosen to organize this chapter, as it focuses on the application of AI to oncological imaging. However, as AI is emerging in the field of nuclear medicine, two underlying trends can be observed: whole-body tumor volume quantification and individual lesion delineation. Quantification of the molecular whole-body tumor volume (e.g. ^{18}F-FDG or PSMA avid tumor parts in contrast to morphological tumor volume) is feasible using semi-automated approaches that facilitate the quantification by AI methods. Yet, medial expert interaction is still needed to obtain valid results. Such quantification approaches are clinically needed, as the whole-body tumor volume might be a more precise parameter to assess the extent of an oncological disease [4]. Moreover, quantifying of the whole-body tumor volume might enable more precise therapy response monitoring. The second trend is to automatically delineate and grade malignancy suspicious lesions in nuclear medicine imaging by employing AI. This is a more complex and error prone task, compared to just providing assistance to medical experts. However, several studies that are presented here could demonstrate extremely promising results (e.g. fully automatic delineation of all malignancy suspicious lesions). Therefore, both the tumor volume quantification trend and individual lesion delineation trend will ultimately merge when lesion-wise classification becomes even better and is thus suited for tumor volume quantification.

There are some unsolved issues regarding the application of AI in the field of nuclear medicine and especially in oncological settings. As outlined, the quantification of the tumor volume comes into focus of many software tools that analyze PET-CT data. Yet, there is no consensus how to determine a reference standard for tumor volume quantification. It may be evident, that morphological information (e.g. obtained from the CT component) is not ideal as reference to assess the molecular volume. However, there are several strategies for the segmentation of PET volume as well, like applying a fixed threshold (e.g. every voxel >6 SUV is tumor), applying relative thresholding (e.g. 50% of local SUV_{max}), or others. Future studies have to evaluate which tumor segmentation method is closest to the actual tumor volume and should therefore be used as reference standard for AI algorithms. To this end, it might be warranted to employ the concept of probabilistic segmentations that addresses issues arising from inter- and intra-rater variance in tumor segmentations [5]. Finally, one has to bear in mind that it is at least as difficult to develop AI for a specific task as proving its incremental benefit for the patient and implementing it in the clinical routine [6, 7].

10.2 Brain

10.2.1 Glioma

The characterization of cerebral gliomas has moved from a morphological-based classification to molecular profiling, comprising of markers like IDH1 mutation status [8]. This is due to the heterogeneity of gliomas, which cannot sufficiently be differentiated by conventional imaging. Therefore, molecular imaging approaches together with machine learning methods have

been proposed to enable an improved noninvasive glioma profiling. Kebir et al. could show that ^{11}C-MET PET and machine learning enabled the noninvasive diagnosis of the IDH1 status of gliomas; an area under the curve (AUC) of 0.79 was reached [9]. However, the analyzed patient collective was relatively small (n = 39) and future corroborating studies are needed.

Haubold et al. employed multiparametric ^{18}F-FET PET-MR to noninvasively estimate grading and molecular profiles of gliomas [10]. Interestingly, the integration of ^{18}F-FET features (like SUV_{max}) into the multiparametric MRI features has improved the estimation neither of grading nor of molecular profiling. For example, the estimation of IDH1 status had an AUC of 88% (excluding PET features). Yet again, the patient collective was relatively small (n = 42), especially given the large number of 19.284 features that were extracted for each patient.

10.3 Neck

10.3.1 Head and Neck Cancer

^{18}F-FDG PET-CT is a reference standard examination for the detection of cervical lymph node metastases of patients with head and neck cancer; especially, if subsequent radiotherapy is planned [11]. However, the differentiation between physiological lymph nodes and suspicious lymph node metastases in ^{18}F-FDG PET-CT might be challenging. To this end, Chen et al. have proposed a tool which combines both radiomics and 3D convolutional neuronal networks for the characterization of cervical lymph node metastases using PET-CT [12]. Unfortunately, the patient collective was small (n = 59) and the reference standard for nodal involvement was an expert rating.

Huang et al. proposed a method for the automated delineation of head and neck cancer using PET-CT data and demonstrated its feasibility [13]. Yet, despite the use of bicentric data, the generalizability of the presented approach still needs to be proven. Zhao et al. have followed a similar approach and aimed at the automated delineation of nasopharyngeal carcinoma on PET-CT data [14]. The authors adopted the U-Net design which used both PET and CT images as input and achieved a dice score (which is a measure of segmentation accuracy) of 87.5%.

10.3.2 Thyroid Cancer

Thyroid nodules are frequently seen on ultrasound examinations; however, only a small fraction of thyroid nodules is caused by thyroid cancer [15]. To facilitate the characterization of thyroid nodules as either malignancy suspicious or benign, the ACR TI-RADS system has been proposed [16]. ACR TI-RADS comprises five categories (like echogenicity or shape) and allocates a score for the degree of each category. The sum of all five category scores stratifies the likelihood of the presence of thyroid cancer. The likelihood of cancer is in turn graded in five categories (1-benign to 5-highly suspicious). Despite good reason for the individual categories, no study could corroborate a given score (e.g. in the echogenicity category, the hyperechoic criterium has a score of 1, whereas hyoechoic has a score of 2). Therefore, Wildman-Tobriner et al. used AI to evaluate, if the individual scores of ultrasound features were appropriate or if ACR TI-RADS could be simplified. Interestingly, the scores of their revised ACR TI-RADS called AI TI-RADS were indeed simplified (e.g. hyperechoic criterium got a score of 0 and was therefore neglectable, whereas hypoechoic remained with score of 2). Moreover, the authors could corroborate that the sensitivity of AI TI-RADS remained high compared to conventional ACR TI-RADS (93%), whereas the specificity of AI TI-RADS increased compared to ACR TI-RADS (65% vs. 47%). This interesting work could facilitate the use of this manual classification system and might be expanded to other classifications as well.

Instead of training a neuronal network to estimate an ACT TI-RADS score (or a similar classification), some groups directly used the histological classification as ground truth for training and evaluation. Ko et al. could show that a convolutional neuronal network obtained high AUC results (0.835–0.850) and was not

statistically differed form radiologists (AUC: 0.805–0.860) [17]. Importantly, histological ground truth was present for all patients. There have also been reports on optimized network architectures dedicated to ultrasound images of thyroid cancer [18]. Li et al. presented a retrospective multicenter study evaluating the performance of a neuronal network in detecting thyroid cancer by ultrasound images, which comprised 45.644 patients [19]. Importantly, external validation cohorts were present as well. For the internal validation cohort, both sensitivity (93.4%) and specificity (86.1%) were remarkably high. The authors concluded that sensitivity was similar to a group of skilled radiologists, but the specificity was statistically significantly improved.

10.4 Thorax

10.4.1 Lung Cancer

Fluorodeoxyglucose (^{18}F-FDG) PET-CT is the standard diagnostic tool for the staging of patients with lung cancer [20]. Sibille et al. developed a software for the automated segmentation of suspicious FDG foci using acquisitions of 302 lung cancer patients amongst other patients [21]. The proposed software runs fully automatically and estimates not only the classification of each ^{18}F-FDG hot spot (suspicious i.e. metastasis vs. not suspicious i.e. physiologic) but also the anatomical location of each hot spot (e.g. lymph node level). The accuracies both of classification (AUC = 0.98) and of anatomical location (accuracy = 97% for body part, 84% for organ or tissue) were remarkably high. Interestingly, the proposed neuronal network did not segment the ^{18}F-FDG foci in the PET acquisition, but in contrast analyzed hotspots found by conventional thresholding. This procedure might lead to inaccuracies, as confluent lesions or confluence between a metastasis and an organ with physiological ^{18}F-FDG accumulation might not be separated properly by conventional thresholding. The neuronal networks used by this software require the input of coronal reformatted image data. Each tracer accumulation is analyzed separately and only its immediate vicinity is present to the network. Because of that, the input of the entire PET as maximum intensity projection (MIP) significantly improved the accuracy. Similar to the human perception, the MIP and other reformations may facilitate the recognition of global uptake patterns, e.g. caused by brown adipose tissue activation. Additionally, CT information was used in conjunction with the PET as input for the neuronal network and significantly improved the accuracy compared to PET only inputs. Future studies have to evaluate the predictive potential of the automatically determined ^{18}F-FDG tumor volume.

10.5 Abdomen

10.5.1 Esophageal Cancer

Beukinga et al. used ^{18}F-FDG PET examinations before and after neoadjuvant radio chemotherapy to predict the outcome of patients suffering from esophageal cancer [22]. The authors extracted radiomic features, which combined with the T-stage could predict complete pathologic response with high accuracy (AUC = 0.81). However, only 73 patients were included in this study, which might limit the transferability to larger or inhomogeneous patient collectives.

10.5.2 Liver Tumor

Radioembolization with ^{90}Y spheres is a therapeutic option for patients with liver metastases or primary hepatic tumor and also known as selective internal radioembolization (SIRT). Due to impairment of uninvolved liver tissue and generally end stage disease, the prediction of overall survival prior to SIRT is clinically needed. Therefore, Ingirsch et al. had retrospectively analyzed electronic health records (e.g. blood level of bilirubin, age) of 366 patients that received ^{90}Y radioembolization by using machine learning methods [23]. The authors identified baseline cholinesterase and bilirubin levels as predictor for overall survival after SIRT.

10.5.3 Prostate Cancer

Prostate cancer is the leading cause of cancer-related death in men and has a remarkably early tendency to form metastases; already at time of prostatectomy, approximately 70% of men show prostate cancer cell in the bone marrow [24]. The sensitive detection of metastases as well as monitoring of the whole-body tumor load is of great clinical importance. To this end, prostate-specific membrane antigen (PSMA) targeting PET-CT has been widely employed and could demonstrate superior performance both in primary and recurrent prostate cancer [25, 26]. Several AI-based approaches have tried to analyze PSMA-PET examinations with regard to individual lesion classification and whole-body tumor volume.

Zhao et al. have developed a neuronal network for the delineation of PSMA avid metastases in the pelvic area [27]. The authors had adopted the U-Net architecture to include both PET and CT slices as input and aimed at a voxel wise segmentation of prostate cancer metastases [28]. The network employs axial, coronal and sagittal reformations as input to mimic the reading of a human expert. For training and evaluation, metastases were manually delineated by nuclear medicine experts in 193 PSMA PET acquisitions; their delineations were used as ground truth data. The limitation to the pelvic region was necessary due to proof of concept nature of the publication; however, extension to the whole body seems also feasible. The work of Zhao et al. is of great relevance, as it enables the fully automated segmentation of prostate cancer metastases with great precision (99%) and recall (99%). However, because of point spread artifacts, it could prove disadvantageous that the proposed neuronal network outputs the tumor segmentation.

Gafita et al. proposed an open source software (qPSMA) for the semi-automated quantification of the whole-body tumor burden in PSMA-PET CTs [29]. Despite the name prostate-specific membrane antigen, PSMA shows physiological accumulation in many organs, like in liver, spleen, bowel, kidneys, salivary glands and others. The qPSMA software assists the reading physician in segmenting all prostate cancer metastases by excluding some organs with physiological update from the analysis. To this end, a random forest-based algorithm is used by qPSMA to segment organs with physiological PSMA accumulation employing the CT component [30]. The qPSMA software not only masks out physiological PSMA uptake, but likewise segments PSMA foci with a patient specific SUV threshold. Each voxel exceeding this threshold is regarded as metastases, if it is not manually or automatically excluded. In addition, qPSMA enables the adjustment of predefined organ exclusion masks and facilitates the exclusion or inclusion of missed PSMA foci using brush tools. For example, liver metastases had to be added manually due to the heuristic logic that the liver uptake is physiologic, and the entire liver therefore be removed from the analysis. The inter-rater and intra-rater correlation of qPSMA is high for the segmentation of individual metastasis.

An approach similar to qPSMA was proposed by Seifert et al. [31]. Likewise, it facilitates the semiautomated quantification of the whole-body tumor volume by excluding physiologic PSMA foci from the analysis. Moreover, it automatically assigns the anatomical location to each PSMA focus. In contrast to qPSMA, the software employs a two-step approach for delineation of foci: first, voxels exceeding a patient-specific threshold are selected as candidate lesions. Second, these candidate lesions were segmented by thresholding with 50% of the local SUV_{max}. Thereby, no brush tools are needed for refinement; physiological candidate lesions can be deleted easily. The author could show that this procedure achieves a high inter-rater agreement. Interestingly, the authors also reported that semi-automatically quantified whole-body tumor volume stratified end-stage prostate cancer patients according to the overall survival.

10.6 Skeleton

10.6.1 Bone Metastases

Bone scans are primarily used for the detection and monitoring of bone metastases and one of the high throughput examinations of nuclear medicine. Especially for therapy monitoring of prostate cancer patients, bone scans are an established imaging method [32]. However, the interpretation of bone scans to calculate a quantitative biomarker, which is called bone scan index (BSI), is time-consuming [33, 34]. To calculate the BSI, at first, the fraction of metastatic involvement of each bone has to be calculated. Second, this fraction is multiplied with the fraction that the bone constitutes to the entire skeleton. By summation of all values, the BSI is obtained. Thereby, BSI represents the fraction of metastatically affected bone, i.e. a BSI of 3 means that 3% of the entire skeletal mass is affected by metastases.

Several solutions have been proposed to automatically quantify the BSI. Among them is the work of Ulmert et al., who proposed a method which uses neuronal networks for the automated segmentation and classification of hotspots in bone scans [35]. Interestingly, the development of the first prototype dates back to 2006, where AI was not the now established buzzword, which might be the reason why the authors called their work "computer-based decision support system" [36]. The automatically derived BSI could statistically significant stratify prostate cancer patients according to overall survival [37].

As mentioned above, PSMA-PET-CT has emerged as reference standard examination for patients with prostate cancer. Therefore, the quantification of the osseous tumor volume from PSMA-PET-CT, similar to the BSI, is of importance. To this end, Bieth et al. have proposed a software for the quantification of the osseous tumor burden using PSMA-PET-CT acquisitions [38]. Hammes et al. followed a similar approach (EBONI) and provided the source code of their software [39].

10.7 Hematopoietic System

10.7.1 Lymphoma

^{18}F-FDG -PET-CT is a standard diagnostic for staging and therapy monitoring of lymphoma patients. However, due to highly variable physiological ^{18}F-FDG uptake, the interpretation of ^{18}F-FDG PET acquisitions is challenging, especially for neuronal networks. The software proposed by Sibille et al. that was already presented above was not only trained using lung cancer patients, but with ^{18}F-FDG PET-CTs of lymphoma patients (n = 327) as well [21]. Therefore, the software obtained high accuracy in the classification (AUC = 0.95) and the determination of the anatomical location (Accuracy = 97% for body part and 84% for organ or tissue). Thereby, the automatic quantification of a whole-body tumor volume is feasible. Future studies have to elucidate if the automatically determined tumor volume can stratify patients according to their overall survival or other clinically relevant end points.

10.7.2 Multiple Myeloma

Multiple myeloma (MM) is a clonal plasma cell neoplasia and detection of bone lesions is crucial during diagnostic work-up. MM lesions not only display an important criterion for the initiation of treatment but moreover discriminate MM from pre-malignant diseases such as monoclonal gammopathy of undetermined significance. Whole body low-dose CT is the gold standard in MM, but MRI is attributed with a higher sensitivity in the detection of small MM lesions. CXCR4-directed PET imaging with ^{68}Ga-Pentixafor represents another imaging modality for the detection of active MM lesions.

Martínez-Martínez et al. have developed a fully automated method that identifies bone marrow infiltration in low-dose CT of MM patients [40]. Their method was validated on a dataset of

127 subjects where it was able to discriminate bone marrow infiltration in patients with MM from healthy controls with an AUC of 0.996. The limitation of their study is that their method is only validated for the bone marrow infiltration in the femur. However, lesion distribution in MM patients ranges from a single lesion to multiple lesions with a disseminated pattern and those lesions do not necessarily have to affect the femur.

An automated approach to determine whole-body bone lesions in MM patients was conducted by Xu et al. [41]. The combination of ^{68}Ga-Pentixafor PET that registers elevated CXCR4-expression within MM lesions with anatomical features from the CT-scan was used in this study. Two CNNs (V-Net and W-Net) were used for the segmentation and detection of MM lesions. Their study that was first verified in digital phantoms (n = 120) and further validated in a small patient cohort (n = 12) revealed that the W-Net architecture with the combination of PET and CT data was most accurate in lesion detection and achieved a dice-score of 73%. However, this study was mainly conducted on digital phantoms and further validation in a bigger patient cohort and correlation to clinical parameters such as treatment response or overall survival has to be evaluated.

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