Artificial Intelligence in PET/CT Oncologic Imaging

John A. Andreou
Paris A. Kosmidis
Athanasios D. Gouliamos
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Editors
John A. Andreou
Radiologic Imaging
Hygeia Hospital
Athens, Greece

Paris A. Kosmidis
Medical Oncology
Hygeia Hospital
Athens, Greece

Athanasios D. Gouliamos
Medical School
National and Kapodistrian University
of Athens
Athens, Greece

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This book is dedicated to all cancer patients and their families.
We are grateful to our teachers and thankful to our staff.

Foreword

Artificial Intelligence, aka AI, is a term that became very familiar to us in recent years. Indeed AI is part of our daily life, with a number of applications almost impossible to count, and now incorporated in most technological innovations. The relevance and impact of AI is hard to estimate, due to its incredibly rapid growth and diffusion, and this is true also for AI in medicine.

Proposal of using AI in medicine started in the 1950s, mainly as futuristic prediction, while a real boom occurred with the new millennium, and now counting thousands of papers and proposals every year, making difficult to stay updated, especially in areas where AI has been intensively studied, such as medical imaging.

For those reasons, it is very important to have reference reviews that make possible to understand the state of the art, and this is the scope of this book from J.Andreou, P. Kosmidis and A.Gouliamos, covering the applications of Artificial Intelligence in Oncological PET/CT.

The book is focused on the use of AI in the most advanced functional imaging method, and it covers all oncological clinical indications for PET/CT, being at the same time exhaustive and synthetic, while updated. Different perspectives are presented, as AI in PET/CT is clearly a very multidisciplinary field, bringing together the expertise of medical doctors, informatics, physics and many other professionals. The book is useful and recommended for all those specialists who will surely benefit from such a comprehensive text.

Diagnostic Imaging
University of Bologna,
Bologna, Italy
5 May 2022

Stefano Fanti

Preface

The content of this book is mainly updated chapters from the second edition of *Imaging in Clinical Oncology* (2017) with addition of an introductory chapter about AI systems for Oncology.

Originally positioned as a means for noninvasive molecular phenotyping and quantification in the 1970s, PET's technological improvements in the 2000s and PET/CT fusion imaging generated renewed interest in quantification, which has grown over the last 5 years for cancer treatment planning. With fusion imaging radiologists and oncologists can combine anatomical and metabolic information and estimate the response to therapy. This progress is parallel with the development of artificial intelligence (AI) systems for Oncology which is an AI system with the aim of providing the best possible treatment to patients suffering from lung, breast, brain, prostate, liver and other types of cancer.

Applications of AI systems in imaging modalities have the following trends:

1. Artificial intelligence applications may help in detection of disease, tissue characterisation (benign vs malignant), staging and correlation with molecular biomarkers.
2. Radiomic signatures may help in prediction of response to therapy, risk scores for recurrence and classification of patients based on prognosis.
3. Correlation of data sets with imaging findings and pathology findings.
4. AI is under intensive research for massive screening for early diagnosis of cancer. More specifically, radiological screening for lung and breast cancer is more advanced. Additionally, colorectal polyps screening is another attractive examination through colonoscopy for early diagnosis of cancer.

Considering how different things were 10 or 20 years ago can we imagine or foresee the advancements in medical technology in the next 10 years? We should be thankful to the many pioneers who have made PET/CT during the past 20 years what is today: a useful tool for depiction of anatomy and pathology for the benefit of millions of patients around the world.

Although technical difficulties were encountered at the beginning, limited applications of AI in PET/CT are already here and appear promising in the near future as have been in other imaging modalities. There is no doubt that

AI can help radiologists lessen their workload and oncologists develop novel tools.

Athens, Greece John A. Andreou
Athens, Greece Paris A. Kosmidis
Athens, Greece Athanasios D. Gouliamos
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The Editors.

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Introduction: Artificial Intelligence (AI) Systems for Oncology

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João Santinha, Ana Castro Verde, and Nikolaos Papanikolaou

1.1 Introduction

Artificial intelligence (AI) is a topic of growing interest in various fields, including finance, entertainment, transports, agriculture, and healthcare. The application of **machine learning (ML)** and **deep learning (DL)** algorithms in medicine was enabled by three essential aspects: the increase in data availability, the development of innovative software technologies, and the capacity improvement of the computing systems [1]. The former was most evident in radiology and nuclear medicine due to the accessibility of digitised images, but it also impacted dermatology, ophthalmology, histopathology, and clinical and genetic data. Although plenty of research was conducted several decades before, in the 2012 ImageNet Challenge—a natural image classification competition with more than 14 million images of more than 20,000 categories—a convolutional neural network (CNN) model named AlexNet was able to substantially reduce the classification error showing the potential of DL-based models in comparison with traditional computer vision approaches [2]. By this time, the limitation in transposing this work to medicine was the insufficient labelled data. Two facilitators for this were, in 2015/2016, the emergence of transfer learning algorithms [3]—where DL networks pre-trained on non-medical images are used and/or finetuned for medical imaging applications—and, in 2017/2018, the development of synthetic data augmentation—mainly, using Generative Adversarial Networks (GANs) to generate synthetic images that are visually mistaken with real medical images and, when fed into CNN, can increase the performance of these models in

João Santinha and Ana Castro Verde contributed equally with all other contributors.

J. Santinha
Computational Clinical Imaging Group, Champalimaud Experimental Clinical Research Programme, Champalimaud Foundation, Av. Brasília, Lisbon, Portugal

Instituto Superior Técnico, Universidade de Lisboa, Av. Rovisco Pais 1, Lisbon, Portugal
e-mail: joao.santinha@research.fchampalimaud.org

A. C. Verde
Computational Clinical Imaging Group, Champalimaud Experimental Clinical Research Programme, Champalimaud Foundation, Av. Brasília, Lisbon, Portugal
e-mail: ana.castroverde@research.fchampalimaud.org

N. Papanikolaou (✉)
Computational Clinical Imaging Group, Champalimaud Experimental Clinical Research Programme, Champalimaud Foundation, Av. Brasília, Lisbon, Portugal

Department of Radiology, Royal Marsden Hospital Downs Road, Sutton, UK
e-mail: nickolas.papanikolaou@research.fchampalimaud.org

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medical tasks. Besides those, additional contributions to the field were the UNet architecture for image segmentation in 2015 [4] and, in 2015/2016, the advent of multiple medical imaging DL challenges.

In parallel to the emergence of DL solutions for medical problems and as an extension of computer-aided diagnosis and detection (CAD) systems, **radiomics** (Fig. 1.1) was first coined in 2012 [5]. It is based on the principle that images contain unexplored information on the tumour phenotype and microenvironment that can only be identified through quantitative analysis [6]. Radiomics refers to the extraction of high-dimensional features reflecting intensity, shape, size or volume, and texture—from computer tomography (CT), magnetic resonance (MR), and positron emission tomography (PET) images. These features are to be combined with additional information from multiple data sources and used for hypothesis generation and testing. The number of radiomics publications (Fig. 1.2) has seen a drastic increase over the past 10 years, with more developments in oncology due to support from the National Cancer Institute (NCI) Quantitative Imaging Network (QIN). Although we verify this trend, further work is still necessary for tackling multiple challenges in the field (see Sect. 1.3 for a more detailed description) to achieve reproducible results with the end goal of clinical translation [7].

Overall, the establishment of validated imaging biomarkers is an opening opportunity to drive **precision medicine** forward by characterising a patient's tumoral heterogeneity across space and time [8].

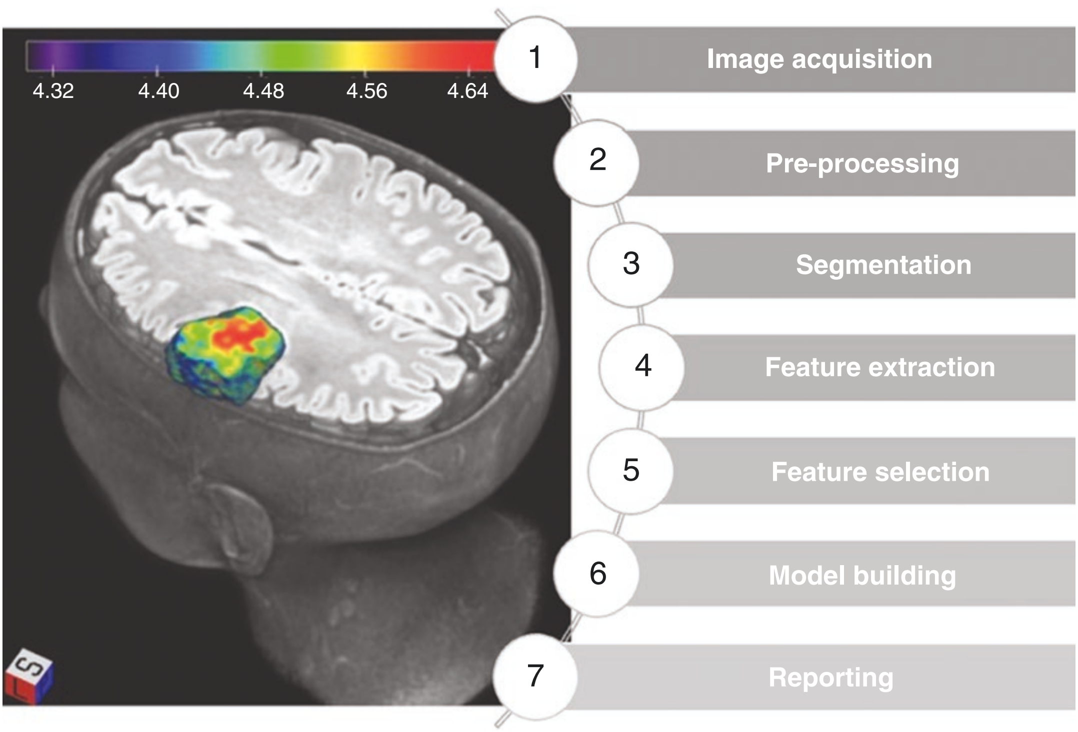

Fig. 1.1 The main steps of a Radiomics study, illustrated on the left by a 3D Radiomics map of the "'Entropy"' feature from a patient with a brain tumour

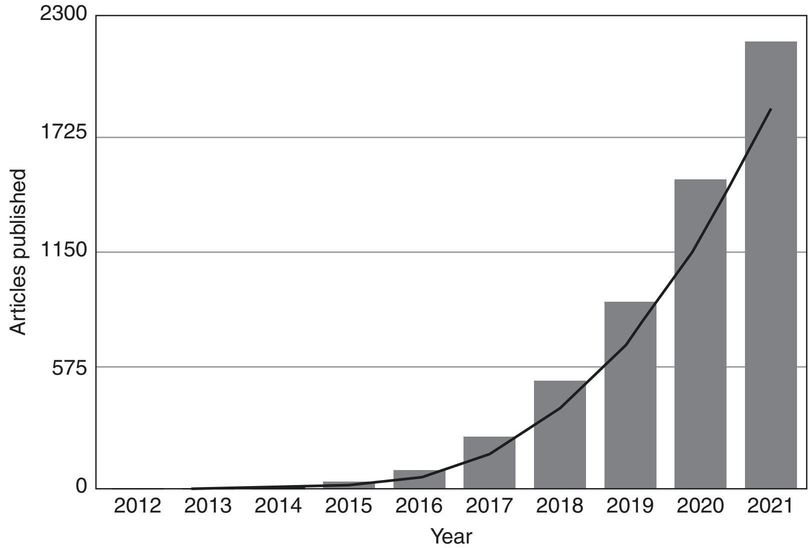

Fig. 1.2 Number of radiomics articles over time (in years) until 2021. (Data source: Pubmed)

1.2 Applications

Artificial intelligence (AI) has been applied to different fields with considerable success, and oncology is no exception. The utilisation of AI applications in oncology allows the optimisation of multiple tasks contributing to cancer detection, diagnosis, staging, treatment planning, and prognosis. Cancer imaging, encompassing digital pathology, radiographic imaging, and clinical photographs, is the area within AI in oncology where the most promising work has been done [1]. While in digital pathology and clinical pictures, the main focus has been to automate and improve image analysis and diagnostic performance, in radiology, the application of AI is also being widely applied to image reconstruction and enhancement, segmentation, and registration, and computer-aided detection (CADe) and computer-aided diagnosis (CADx) tasks with promising results. Improvements in image reconstruction and enhancement, segmentation, and registration may also improve results obtained in CADe and CADx tasks. Furthermore, these applications are expected to facilitate the radiologists' work by decreasing the variability inherent to interpretation and reducing human errors due to the short time to evaluate medical images and increased workload [9].

Regarding the use of AI in PET-CT images, several studies have already demonstrated that the use of AI in image reconstruction and enhancement allows faster acquisitions (low-count acquisitions) while providing better diagnostic images [10–14]. In the study performed by Arabiand Zaidi, a deep learning-based metal artefact reduction algorithm reduced the adverse effects of metal artefacts on PET images by improving the generation of accurate attenuation maps in the presence of CT images corrupted due to the presence of metallic implants [14]. Chaudhari and colleagues demonstrated that deep learning could reconstruct images from low-count whole-body PET acquisition (fourfold count reduction), restoring diagnostic image quality and maintaining SUV accuracy [11]. Furthermore, the authors showed that the method generalised on an external dataset comprised patients from multiple institutions and scanner types [11]. Gong et al. proposed an iterative reconstruction neural network that can improve PET image quality, outperforming denoising neural networks used as postprocessing tools and conventional penalised maximum likelihood methods [10]. More recently, Sanaat et al. and Feng et al. also investigated the use of deep learning methods to reconstruct PET images with 1/eighth of standard injected activity or acquisition time and within the limits of the current hardware, respectively [12, 13]. Some AI commercial applications like SubtlePET™ [15] and OncoFreeze AI [16] are already available for image reconstruction and enhancement.

In terms of AI-based segmentation, Edenbrandt and colleagues demonstrated the benefits of using convolutional neural networks to segment lesions in PSMAPET/CT images which reduced variability between readers [17]. In the studies by Zhao et al. and Moe et al., a multi-modality convolutional neural network with both PET and CT images as input showed significant improvements over methods that use only PET or CT [18, 19].

Several studies also investigated the use of AI for CADe and CADx in PET/CT images. Kawauchi and colleagues investigated the use of CNNs to classify patients into benign, malignant, or equivocal using FDG PET/CT examinations [20]. Peng et al. evaluated the prognostic value of DL PET/CT-based radiomics for individual induction chemotherapy in advanced nasopharyngeal carcinoma [21]. In another study by Polymeri et al., the authors assessed the association between DL-based quantification of PET/CT prostate gland uptake and overall survival [22], which was followed by a study by Borrelli and colleagues in which an AI method was developed to automatically detect lymph node metastasis that was shown to be associated with prostate cancer-specific survival [23]. Sibille and colleagues used DL to localise and classify uptake patterns into foci suspicious and non-suspicious in lymphoma and lung cancer [24]. An automatic method to detect abnormal lung lesions and calculate the total lesion glycolysis (TLG) on FDG PET-CT was developed by Borrelli and colleagues [25]. As for the use of texture-based analysis, the studies by Fan, Satoh, and Zheng assessed its performance for the differential diagnosis in spinal metastases, for comparing diagnosis of primary breast cancer using whole-body PET/CT and high-resolution dedicated breast PET, and to predict mediastinal node metastasis in non-small cell lung cancer patients, respectively [26–28].

1.3 Challenges

In combination with the growing number of applications of AI in oncology, some challenges need to be addressed for achieving the end goal of implementation into clinical practice. One can broadly divide these challenges into three topics: Data, AI Model, and AI Framework, as shown in Fig. 1.3. Firstly, challenges with Data come from the fact that the training data used to feed the algorithms can be **biased**, under-representing specific age, gender, and racial populations or perpetuating social biases, possibly leading to undertreatment of specific races and/or socioeconomic groups, known as under-served populations, by perpetuating systematic mistakes in inpatient care [29]. Potential solutions to this problem are, on the one hand, the utilisation of large *real-world* datasets that are representative across patient groups, time (historically vs. recently treated patients), and data sources (data obtained at different institutes, using different scanner models and manufacturers), and on the other hand, the development of methods to estimate and eliminate preexisting biases in the training data. However, the advent of larger datasets coming from multiple institutions is still hindered by the need to protect patient information, which may be overcome with federated learning. Furthermore, multiple institution datasets, acquired using different equipment, parameters, and/or reconstruction algorithms and settings, pose the challenge of data **heterogeneity**, leading to variability in algorithms' performance. Individual variations in the images can be observed in multi-centre studies, as shown in Fig. 1.4, resulting in a shift in data distribution across various settings. For the case of radiomics—mentioned previously in Sect. 1.1, different harmonisation methods can be applied to ensure repeatability and/or reproducibility of the radiomics features across diverse settings [30]. One possible scenario is to harmonise the image/intensities domain, whether by using guidelines for the acquisition and reconstruction parameters' standardisation or by utilising meth-