Progresses in PET/CT radiomics for diagnosis and molecular typing of breast cancer

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Abstract. One of the top causes of cancer-related death in women is breast cancer (BC) , and the prevalence is increasing each year.The prevalence of BC has already surpassed lung cancer in 2020, making it the most prevalent cancer worldwide. Molecular typing of BC can affect the choice of diagnosis and treatment options, and the typing methods currently used in clinical practice are mainly through tissue biopsy. PET/CT, as a noninvasive test, has now been able to show BC progression at the molecular and cellular levels. Radiomics is an emerging imaging technique that describes the relationship between the intensity of pixels or voxels in a specific region and their location in this region in imaging data by mathematical methods, so as to provide objective quantitative indicators for clinical practice. Combining PET/CT with radiomics can greatly improve the precision of PET/CT in the diagnosis and typing of BC. This article reviews the progress in the application of PET/CT radiomics in the diagnosis, treatment and molecular typing of BC.

Keywords: breast cancer, PET/CT, molecular typing, radiomics.

1. Introduction

Among all female malignancies has the highest incidence. With the advancement and popularization of early screening methods, although the survival rate of women suffering from BC has increased, it is still cause massive death, accounting for about 15% of cancer-related deaths. In recent years, the incidence of BC has risen rapidly and shows a tendency to be younger. The gold standard to diagnose BC is biopsy. However, because BC is highly heterogeneous, the diagnostic results obtained by invasive procedures at present cannot well reflect the overall situation of the tumor, and invasive procedures have the disadvantages of low reproducibility and easy to lead to complications. So, establishing a dependable noninvasive diagnostic technique targeting early stage, molecular typing and precise treatment of BC is becoming more and more urgent.

PET/CT is a novel imaging equipment that organically complexes two superior imaging techniques. This technology is to inject trace amounts of positron nuclides tracers into the human body, and then use PET to detect the dispersion of these positron nuclides in organs. Meanwhile, CT is applied to accurately locate the distribution of these nuclides, so that this technology has the advantages of both PET and CT and exerts its greatest advantages. Compared with traditional invasive procedures, PET/CT has the advantages of reproducibility and less susceptibility to complications. On the basis of conventional imaging diagnosis, radiomics finds the connotation characteristics of the disease through deep mining data, thus reflecting the changes at the level of human tissues, cells and genes, which will have effective influences on clinical medicine. Radiomics has shown great advantages in BC typing, treatment options, and prognostic analysis by extracting high-throughput features from imaging to quantify BC. The combination of PET/CT and radiomics will greatly improve the accuracy of diagnosis and reduce the occurrence of complications, and this combination will be a hot issue in BC research.

2. Molecular typing of BC

According to molecular biology studies, BC is a heterogeneous disease.Therefore,BC has different molecular subtypes, and molecular typing is closely related to clinical prognosis. At present, four markers have been used for molecular typing of BC internationally, which are ER, HER-2, PR and

Ki-67 index. According to these 4 markers, BC can be divided into 4 types: ①Luminal A, ② Luminal B, ③HER-2 high expression, ④Triple negative BC (TNBC)[1]. Different molecular subtypes of BC have significantly different clinical manifestations, which will affect the clinical development of treatment options and the evaluation of their prognosis. At present, molecular typing of BC is mainly performed by needle biopsy, but the detection results obtained by needle biopsy of a single area cannot completely reflect the pathological characteristics of the entire BC lesion, and the molecular typing of the primary lesion and the metastasis may also be different, so simple needle biopsy may lead to inaccurate typing results and affect the diagnosis and treatment results and prognosis [2].

3. PET/CT radiomics for BC

3.1. PET/CT

Traditional imaging diagnostic methods mainly include ultrasound, CT and MRI, which have the advantage of high anatomical resolution and help to observe subtle morphological changes of the body, but they have some limitations in assessing molecular information changes such as the function and metabolism of the lesion. With the development of molecular imaging, ultrasound, MRI, nuclear medicine molecular imaging and optical molecular imaging can reflect the pathophysiological changes of the disease at micro levels, which has unique advantages to observe the receptor density and functional changes, gene expression, biochemical metabolism and cellular signal transduction in the diseased tissue cells[2]. Molecular imaging techniques can show gene or egg white abnormalities before tumor morphological changes and have unique advantages in early diagnosis of tumors and molecular typing. Among them, PET/CT combines PET with CT technology to provide molecular characteristics such as the metabolism status of the lesion by PET, meanwhine,CT supplies accurate anatomical localization of the lesion. Accurate localization and molecular information of the lesion can be obtained in one imaging session[3]. PET-CT has advantages in the early diagnosis of tumors, and because tumor cells are metabolically active and have a 2-10 times higher ability to take imaging agents than normal cells, lesions form significant "light spots" on images, and therefore, insidious tiny lesions can be found before anatomical changes have been produced in the early stage of tumors. In terms of safety, PET/CT is a noninvasive examination, and most of the nuclides used in the test are the same elements constituting human body,and have a short half-life.This feature also determines that the patient can repeat the examination in a short time, avoiding the disadvantages of low reproducibility of the original invasive examination.PET provides accurate molecular information of lesions,and CT provides accurate anatomical information of lesions.The combined examination results are more accurate than PET or CT alone, especially for the diagnosis of tiny lesions. In general, compared with other imaging examinations, which scan some specific sites selected.PET/CT is a one-time whole-body scan to obtain images of the multiple dimensions of the body,such as the coronal,cross-sectional and sagittal planes, which can comprehensively see the site of involvement and progression of the disease in the whole body. Because most cancers metastasize during disease progression, using PET/CT may reduce the likelihood of metastases being ignored.

3.1.1 ^{18}F-FDG

^{18}F-FDG PET/CT can detect hypermetabolic breast tumors and has been widely used for preliminary diagnosis of BC staging and assessment of efficacy.SUV_{max} can be used to evaluate the prognosis of BC patients. Generally, the lower this value means that the better the tumor differentiation and angiogenesis, the better the prognosis of patients[4].

JIA et al.[5] analyzed preoperative ^{18}F-FDG PET/CT examinations in 40 BC patients and showed that the course of tumor lesions was significantly correlated with SUV_{max} of ^{18}F-FDG , and more significant lesion uptake ^{18}F-FDG indicated more severe disease . TNBC accounts for about 15% ~ 20% of all BC and has some features such as high invasiveness, low age of onset, poor prognosis and

low patient survival. BC that are negative for both ER and PR tend to have higher SUVs, whereas TNBC patients tend to ingest more ^{18}F-FDG in their lesions.

KOO et al.[6]analyzed PET/CT in 103 cases of primary TNBC and positively correlated Ki-67 proliferation index and tumor size with SUV_{max} . In clinical diagnosis,due to the strong ability of tumor tissue to take up FDG,tumor lesions can be located and measured by analyzing the content and distribution of FDG in the lesions.In addition,lymph node metastasis and metastasis in other parts of body can also be efficiently determined for clinical staging to provide further clinical treatment.But ^{18}F- FDG is not a tumor-specific imaging agent, and a few false positives or false negatives may occur in clinical diagnosis .

In terms of BC histological classification, Moscoso et al.[7]used high-resolution PET/CT designed for breast disease for lesion scanning and showed that ^{18}F-FDG PET could not be utilized to distinguish invasive ductal carcinoma from invasive lobular carcinoma. Therefore, in order to increase the accuracy of diagnosis and histological classification of PET-CT in BC, the specificity and spatial resolution of imaging agents should be continuously improved .

3.1.2 ^{64}CuDOTA-trastuzumab

Several studies[8-11] have shown that ^{64}CuDOTA-trastuzumab PET/CT noninvasively detects HER-2 (+)BC lesions. HER-2 expression may change during the course of BC, and its expression status is usually assessed by obtaining tumor tissue by invasive modalities such as biopsy or surgery. When tumor recurrence or metastasis occurs, it may be difficult to obtain tumor lesions by invasive methods, so noninvasive detection of HER-2(+)BC lesions will be conducive to the diagnosis and treatment of BC.

SASADA et al.[8]injected ^{64}CuDOTA-trastuzumab into 38 patients with BC and performed PET/CT 48 hours later. The results showed that HER-2 specific primary BC lesions have higher sensitivity,accuracy and specificity, were 83.3%, 88.2% and 85.7% respectively.

MORTIMER et al.[11]injected ^{64}Cu-DOTA-trastuzumab into 11 HER-2(+)and 7 HER-2(-)patients with metastatic BC and performed PET/CT scans at 21-25 hours (first day) and 47-49 hours (second day) after injection to record SUV_{max} of radioactive lesions and found that ^{64}Cu-DOTA-trastuzumab uptake levels were closely related to HER-2 expression 1 day after injection.

TAMURA et al.[12]injected ^{64}Cu-DOTA-trastuzumab into 6 patients which have primary or metastatic HER-2 (+)BC and performed PET/CT 1, 24 and 48h later. The results reflected that the optimal time for tumor absorption of ^{64}Cu-DOTA-trastuzumab was 48h after injection, and ^{64}Cu-DOTA-trastuzumab PET/CT could be used to confirm HER-2(+) lesions in patients which have primary and metastatic BC(MBC).

Detection of HER-2 expression in BC by ^{64}Cu-DOTA-trastuzumab PET/CT imaging may become a common noninvasive test for the diagnosis of BC and its metastases and molecular typing[10-11], and can replace needle biopsy in specific cases to assess HER-2 expression levels and determine whether BC lesions are primary.

3.1.3 ^{18}F-fluoroestradiol (FES)

In the past, ER expression levels were usually assessed by immunohistochemical examination of tumor tissue biopsies. Because of the heterogeneity in ER expression, it has been difficult to make diagnostic and therapeutic strategies in MBC for long time. In recent years, it has been shown that ^{18}F-FES PET imaging can quantitatively assess ER expression levels and help to observe their heterogeneity[13] and provide a basis for clinical endocrine therapy.

XIE et al.[14]selected 51 BC patients who underwent ^{18}F-FES PET/CT and showed ER uncertainty and divided them into 3 groups, including 20 patients treated with chemotherapy (CT), 21 patients treated with endocrine therapy (ET), and 10 patients treated with combination therapy (CT + ET), and showed that ^{18}F-FES PET/CT could identify patients which have ER heterogeneity.Besides,patients with ER heterogeneity were more sensitive to CT than to ET.

YANG et al.[15]retrospectively reviewed 46 invasive BC patients who underwent ^{18}F-FES PET/CT and found that the extent of ^{18}F-FES uptake correlated with ER expression.

MAMMATAS et al.[16]performed ^{18}F-FES PET in 10 ER(+) metastatic BC patients and also showed a high pertinence between the extents of ^{18}F-FES uptake and ER expression levels.

3.1.4 ^{18}F-Dihydrotestosterone (FDHT)

MBC has a potential target,named Androgen receptor.[17-18]. During AR-targeted therapy, decreased uptake of ^{18}F-FDHT reflects AR occupancy and can be used to forecast reaction to therapy, and has been increasingly used to assess AR expression in BC in recent years.

VENEMA et al.[19]performed ^{18}F-FES and ^{18}FFDHT PET examinations in 13 ER(+) metastatic BC patients and showed that the degree of uptake correlated with AR and ER expression levels.

3.1.5 ^{68}Ga- prostate-specific membrane antigen (PSMA)

The current study[20]suggests that PSMA is associated with angiogenesis in many solid tumors, including BC .

MEDINA et al.[20]retrospectively analyzed 21 BC patients including all molecular subtypes and showed that among the three subtypes of triple-negative BC, LUM B HER-2 (+) and HER-2 high expression. The study concludes that ^{68}Ga-PSMA PET/CT imaging has significant DR in the staging of MBC, with a high incidence of TPN, LUM B(HER2+) and HER2-overexpressing patients.

3.1.6 ^{68}Ga- gastrin releasing peptide (GRP)

GRP mainly regulates gastrin release and gastrointestinal function, and recent studies[21]have shown that GRP receptor is overexpressed in ER(+) BC and associated metastatic lymph nodes. At present, ^{68}Ga-labeled GRP receptor antagonist (^{68}Ga-RM2) has been used for molecular imaging of BC.

MORGAT et al.[21]performed ^{68}Ga-RM2 and ^{18}F-FDG imaging in 14 BC samples and found that ^{68}Ga-RM2 uptake was higher in ER(+) and Ki-67 low-expressing tumors than ^{18}F-FDG, suggesting GRP receptor overexpression in ER(+) BC and its metastatic lymph nodes. Therefore, in some specific cases, GRP receptor-targeted imaging could replace ^{18}F-FDG imaging in ER(+) BC in the future. Since lutetium-177 can label GRP receptor antagonists, this offers new directions for patients with progressive metastatic disease receiving conventional therapy.

3.2. Radiomics

In 2012 , Dutch scholar Lambin et al.[22]first proposed and defined the concept of “radiomics”, that is, the application of a large number of automated algorithms to transform conventional medical images into high-dimensional feature spaces and further analyzed them. In the same year, Kumar et al.[23]further supplemented and improved the concept of radiomics, elaborated that feature information was extracted from medical images at high throughput, and used artificial intelligence analysis and deconstruction of such feature information. The actual "hidden" information in medical imaging is much more than that seen and obtained by physicians, and these "hidden" information theoretically provide more histopathological relevant data and is completely quantifiable[24]. Some scholars believe that the radiomics characteristics are the products affected by the genotype and phenotype of the tissue, so they can well reflect the biological characteristics of the tumor[25]. This technique has been applied in commonly used breast imaging methods such as X-ray, ultrasound and MRI, and has shown good prospects in the management of BC patients[26-28]. The application of radiomics in PET/CT has not been widely popularized, but a few application combining radiomics and PET/CT has significantly improved the function of PET/CT to diagnosis and classify BC. For example, ^{18}F-FDG PET has the disadvantage of low spatial resolution of images in supporting the diagnosis of tumors, prognostic evaluation, and monitoring the response of tumors to treatment, but it can better reflect the tumor after quantifying the uptake distribution in tumors through radiomics characteristics[29].Radiomics converts the omics characteristics of these medical images into quantifiable data in an effort to reveal the correlation between these quantitative data and clinical histology or biomarkers[30]. With the unprecedented improvement of computer computing ability and the continuous construction of large imaging data centers,radiomics has gradually integrated and

developed with AI, machine learning and deep learning, which has increasingly aroused more attention from clinicians, radiologists and computer scientists .

4. Summary

The application of PET/CT can reflect the progression of BC at a more micro level such as cellular and molecular, which is conductive to the diagnosis of BC and molecular typing.Different imaging probes have different sensitivities for different molecular subtypes and histological subtypes of BC, and the comprehensive use of multiple imaging probes is helpful for complementarity and fusion to comprehensively determine the molecular subtypes and histological subtypes of BC. At the same time, PET/CT also has the shortcomings of low spatial resolution of images. Combining PET/CT and radiomics technology can greatly improve the diagnosis and classification of BC and play a guiding role in the determination of treatment methods. By developing new imaging probes, the development prospects of PET/CT for BC will be further broadened in the future. In addition, strengthen the combination of PET/CT and radiomics technology and gradually integrate with AI, machine learning, deep learning etc.,will bring greater help to accurate diagnosis and treatment in the future.

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