Chapter 22
Interactive Communication Between PET Specialists and Oncologists

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Abstract With an increasing number of positron emission tomography (PET) facilities while a growing shortage of PET specialists in mainland China, interactive communication between PET specialists and oncologists plays a crucial role in individualized management of cancer patients and survivors. It is essential that PET specialists should be well informed by oncologists of their patients' history, current problem, treatments, and particularly, the follow-up information. Vice versa, oncologists should be advised by PET specialists on their thorough interrogation, detailed observations, as well as potential false-positive or false-negative findings – some of which might be ignored in their reports. Improving communication and coordination between PET specialists and oncologists has been linked not only to greater understanding and cooperation but also better patient management. In addition, this interactive communication is an essential element of good collaboration for multicenter clinical trials, for instance, how to make PET as an imaging biomarker to evaluate efficacy more rapidly and to increase the probability of success in a clinical trial and how to move non-FDG radiopharmaceutical forward, etc. Here, our review focuses on the conceptual framework, key features, current problems, and future perspectives on this topic.

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22.1 Introduction

With an increasing number of positron emission tomography (PET) facilities while a growing shortage of PET specialists in China, interactive communication between PET specialists and oncologists plays a crucial role in individualized management of cancer patients and survivors [1]. In most of clinical settings, cancer patients receive direct or indirect care from a multidisciplinary medical team, including PET specialists and oncologists. The interactive communication regarding patient care is extremely important for diagnostic consistency and therapeutic efficiency [2]. Usually, oncologists select their therapeutic strategy largely on patient history, laboratory tests, and imaging studies including X-ray, ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI), single photon emission computed tomography (SPECT), or hybrid imaging modalities (i.e., SPECT/CT, PET/CT, or PET/MRI) [3]. PET specialists commonly use PET/CT with ^{18}F-FDG or other radiolabeled imaging agents to evaluate the accumulation or binding activity of a particular biological target or evaluate the functional or metabolic changes after a certain kind of therapy. Among all the current commercially available PET imaging agents, ^{18}F-FDG, the most commonly and widely used in the clinic, has the highest sensitivity, specificity, or accuracy in detecting many glucose-avid cancers compared to the other conventional anatomical imaging modalities. By visualized or semiquantitative analysis of the biochemical or biophysical information on whole-body PET images, PET specialists are being able to not only provide an accurate cancer stage (pinpoint the primary and/or metastatic lesions throughout the body) but also help to select particular targeted patients for the targeted therapy [4–7]. In addition, PET is helpful to assess a specific therapeutic efficacy and detect metastasis or recurrence much earlier than the other imaging modalities in many common cancers [8–11]. Obviously, in every process of patients' management, PET specialists could provide assistance to oncologists. Therefore, a strong cooperative relationship between them can offer efficient care to the cancer patients.

22.2 Oncologists

Defined in the American Society of Clinical Oncology (ASCO), an oncologist is a physician who is specialized in treating people with cancer [12]. There are three major types of oncologists: medical, surgical, and radiation. A medical oncologist is specialized in treating cancer with chemo-, immuno-, hormonal, or targeted therapy, while a surgical oncologist is specialized in the removal of the tumor and surrounding related tissues. And a radiation oncologist is specialized in radiation

therapy. Usually, these different types of oncologists need to work together in a relative late stage of cancer patient management.

22.3 PET Specialists and ^{18}F-FDG PET/CT

A PET specialist is a physician who is specialized in selecting the optimal imaging agent and acquisition protocol, interpreting PET or PET/CT images on the basis of physiological and biochemical information of the whole body and localized organs or tissues. In China, with an increasing number of PET facilities and lacking of PET specialists, most of the new PET specialists have been working as radiologists. From their point of view, PET may equal to the contrast CT or enhanced MRI. Nevertheless, they admit that PET is an important imaging approach in cancer patient management.

PET/CT technology is a novel combined method by which functional molecular information (PET) and anatomical information (CT) can be achieved simultaneously [4]. There are many radiotracers that can be used for PET/CT imaging, including ^{18}F-FDG, ^{18}F- or ^{11}C-acetate, ^{18}F- or ^{11}C-choline, etc. [13]. ^{18}F-FDG is the most widely used radiolabeled agent (or tracer) which is actively taken up and accumulated in cancer cells [4]. Since ^{18}F-FDG PET/CT can detect cancer cells at cellular and molecular levels, it is regarded as the most sensitive and specified method among current imaging modalities [14–16].

22.4 Important Roles of Oncologists and PET Specialists

Cancer is a group of disease, involving abnormal cell growth with the potential to invade or spread to other parts of the body [17]. In clinical practice, when a patient comes for unknown reasons like fever, weight loss, fatigue or elevated tumor markers, abnormal findings on US or X-ray, or in physical examinations, an experienced physician will consider “cancer” as one of her/his assumptions. If the patient has risk factors to cancer, oncologists will order specific laboratory tests and imaging examinations (including PET/CT, if available) for the patient. With patient’s medical history and PET/CT images, PET specialists can provide a valuable diagnosis for oncologists. If the patient is confirmed as having cancer, the oncologist will choose an appropriate treatment for him. After the treatment, PET specialists can evaluate its efficacy with PET or PET/CT. If the treatment is effective, the patient will be followed up for a certain period of time, otherwise, the oncologists will help the patient to choose another plan. Usually, during the post-therapeutic follow-up, PET specialists can use PET or PET/CT to detect the functional or metabolic change or recurrence much earlier than other imagining modalities (Fig. 22.1).

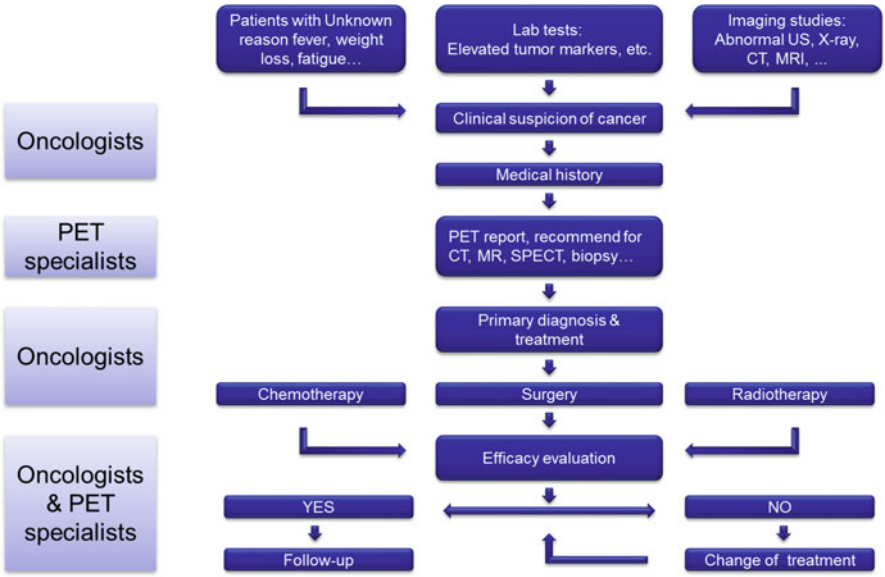

Fig. 22.1 Important roles of oncologists and PET specialists in cancer patient management

22.5 Communication Process

Communication is the process of passing information from a source to a receiver, which is classified into two models: linear and interactive. For the linear model, information is transmitted from sender to receiver via a channel without the sender receiving any feedback, i.e., PET specialist → report → oncologist → patient referring → PET specialist. While for the interactive model, it allows the sender to know that the message was received, i.e.: PET specialist ↔ oncologist. Interactive communication between PET specialists and oncologists allows these two groups to determine if the message was received and how accurately it was received.

Interactive communication is also considered as teamwork, which has the following characteristics:

1. Mutual respect and trust between team members
2. An equal voice for all members – different opinions valued
3. Resolution of conflict between team members
4. Encouragement of constructive discussion or debate
5. Ability to request and provide clarification if anything is unclear

22.6 What PET Specialists Can Do for Oncologists

PET specialists can effectively provide assistance for oncologists, such as (1) offering valuable diagnosis with important functional or metabolic information; (2) providing noninvasive overview of cancer stage; (3) monitoring therapeutic response, especially for the early stage of functional or metabolic changes after treatment; (4) follow-up and metastasis or recurrence detection; and (5) collaborating for clinical trials or other research projects.

22.6.1 Offering Valuable Diagnostic Information

A correct diagnosis is the key to suitable treatment. However, when a patient presenting nonspecific signs or symptoms (i.e., fever, tiredness, or weight loss) and when traditional imaging (i.e., X-ray, US, CT, or MRI) results are negative or controversial, PET or PET/CT could be used for an alternative diagnostic approach, and therefore, PET specialists can offer functional or metabolic diagnostic information to oncologists [18, 19].

Here is a case with unknown reason fever (Case 1):

A 71-year-old female patient who was admitted to the Department of Internal Medicine for fever with unknown reason. The fever lasted for 18 days and was treated with cefmetazole. The peak temperature reached 38.4 °C. In addition, she had a history of right hip pain 2 days prior to her fever. On her physical examination, she presented right hip tenderness without erythema, edema, or plump. On the laboratory results, tumor markers and other tests were in normal limits. She had performed Doppler ultrasound in the abdomen, lower limb arteries and deep veins, and cardiovascular and urinary systems with no remarkable findings. CT and enhanced MR in pelvic indicated a right iliac fossa abscess. In order to explore the cause to fever, she had a whole-body ^{18}F-FDG PET/CT scan. Surprisingly on PET/CT images, her ascending colon showed a hypermetabolic mass which was suspected for colon cancer (A). Therefore, she had colonoscopy that found a polypoid lesion (Is + IIc lesion) of 15-mm diameter in the ascending colon, with hyperemia and pedunculus (Fig. 22.2B). The patient and her family requested for an operation. After the operation, routine hematoxylin and eosin (HE) staining confirmed "moderately differentiated adenocarcinoma" with submucosal invasion (Fig. 22.2C).

For the suspected cancer patients with positive lab tests or imaging findings, the golden standard of diagnosis is pathological confirmation, which needs surgical resection or biopsy. Since these invasive operations might increase the risk of cancer spreading, and false-negative results may occur especially in a heterogeneous large lesion, noninvasive and sensitive imaging techniques are extremely

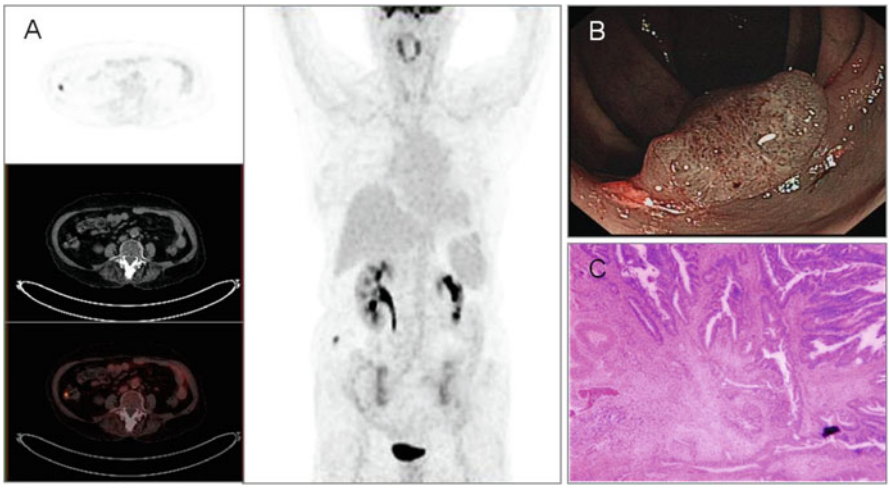

Fig. 22.2 (**a**) 18 F-FDG PET/CT images showed an area of intensive abnormal 18 F-FDG uptake in the ascending colon (*arrows*) with SUVmax = 6.00(1 h), 9.52(2 h). There was no increased ^{18}F-FDG uptake in the right lower limb. (**b**) Colonoscopy image. (**c**) Hematoxylin and eosin (HE) staining

needed. Since ^{18}F-FDG is actively accumulated in glucose-avid cancer cells, it could distinguish these cancer cells from the other noncancerous cells [4, 20]. Therefore, by using PET/CT imaging, PET specialists could offer valuable diagnostic information for oncologists.

22.6.2 Noninvasive Overview of Cancer Staging

Oncologists make treatment plan depending on various factors, for instance, a certain type of cancer, stage, gender, age, etc. Among these factors, cancer stage is the most crucial but most difficult to determine. Incorrect cancer stage will lead to poor prognosis of the patient. Underestimating the stage of the disease may lead to "positive resection margins" or unnecessary laparotomy, while overestimation of the stage may yield to ineffective treatment [21]. Although PET imaging studies are costly, it provides oncologists with important noninvasive overview of staging for making optimal choice of cancer patients.

For example, to determine the stage of non-small-cell lung cancer (NSCLC), multiple laboratory tests and imaging exams are required. Among all these examinations, high-resolution CT is currently the most frequently used in clinic. However, even if this imaging approach could provide accurate assessment of local tumor depth invasion (T), it lacks sensitivity and specificity in the assessment of

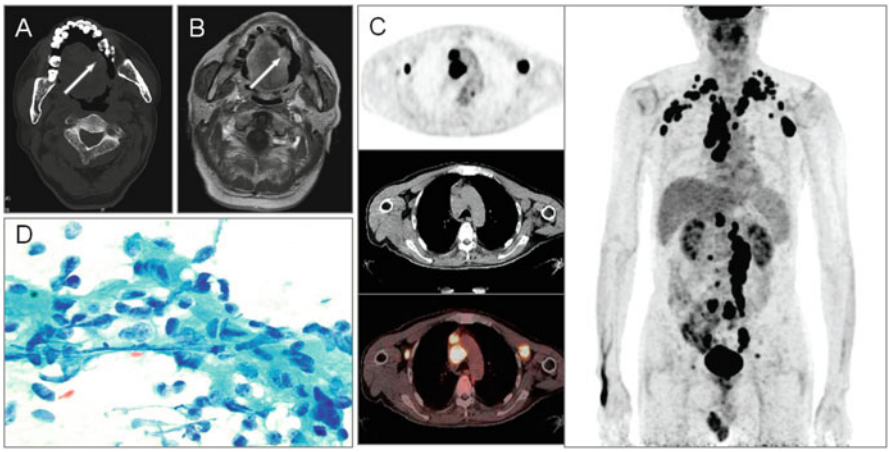

Fig. 22.3 (**a**) CT imaging detected a mass located in the left edge of the tongue (*arrow*). (**b**) MR imaging revealed a mass with long T1 and long T2 signals on the left edge of tongue, a size of 20-mm*10-mm, ill-defined margins (*arrow*). (**c**) ^{18}F-FDG PET/CT imaging showed intensive FDG uptake in the left tongue (SUVmax = 13.83), clavicle and axillary lymph nodes (SUVmax = 16.26), mediastinum (SUVmax = 17.35), ventral prostate (SUVmax = 14.40 at 1 h and SUVmax =20.46 at 2 h post ^{18}F-FDG injection), in retroperitoneum, bottom of mesentery, and left inguinal region's lymph nodes (SUVmax = 21.47). (**d**) Fine needle aspiration confirmed for squamous cell carcinoma

regional lymph node invasion (N) and distant metastasis (M). Although PET only is not so effective in assessing T, it has great superiority in assessing N and M. Recently, hybrid PET/CT has become one of the optimal imaging technologies for lung cancer staging, and significantly improved the detectability of local and distant metastases in patients with NSCLC, and reduced both the total number of thoracotomies and the number of futile thoracotomies [5, 22–24].

Here is a case of a tongue cancer patient with distant metastases (Case 2):

A 68-year-old male patient who was admitted to the Department of Oral and Maxillofacial Surgery. The patient presented left tongue ulcer for two months; incisional biopsy confirmed the diagnosis of squamous cell carcinoma in left ventral tongue at 1 week before PET/CT scan. On physical examination, his vital signs were normal, and he presented a size of 20-mm*18-mm, firm, ill-defined, and cauliflower-like neoplasm located in the left ventral tongue with obvious tenderness, but no palpable enlarged lymph nodes were found. On laboratory workup, PSA was 196.89 ng/ml and other tests were within the normal limits. After performing the head and neck CT and MR examinations (Fig. 22.3a and b), he was intended to have a surgical operation. However, the presurgical PET/CT indicated distant metastases (Fig. 22.3c). Therefore, he was performed a fine needle aspiration in the enlarged left inguinal lymph node and confirmed the diagnosis of metastasis from the left tongue (Case 2, Fig. 22.3d). Accordingly, he was treated with chemotherapy and radiotherapy.

Through the preoperative communication between the PET specialist and the oncologist, this patient avoided unnecessary surgery and administrated optimal care plan. Namely, with the noninvasive overview on ^{18}F-FDG PET/CT images, PET specialists are able to provide functional or metabolic information on T, but also more important information on N and M stages by the whole-body or total body images [25, 26].

22.6.3 Monitoring Efficacy of Treatments

The most common evaluation of a certain therapy to cancer is based on the initial diagnosis of TNM stage, which may reveal the current status and might predict the therapeutic outcome [27]. However, the morphologic and metabolic responses of cancer cells to a specific treatment are incongruent. For example, cetuximab and other targeted therapies inhibit cancer cell growth by inhibiting the proliferation, angiogenesis, and metastatic spread and by promoting apoptosis [28–30], which should be cytostatic rather than cytotoxic [27]. However, in many cases, especially in the early-phase post-therapy, the change of cellular or biochemical function may be significant, but a measurable reduction in tumor size may not occur. Therefore, tumor size can remain relatively unchanged while tumor metabolism can be markedly reduced immediately [31].

As a result, PET specialists play an important role in offering oncologists the real-time efficacy of a specific therapy and help oncologists to make adjustment to the current therapy or change to another option.

22.6.4 Detecting Metastasis or Recurrence in Follow-Up

The chance of survival depends on the type of cancer and extent of disease at the start of treatment. However, even with the rapid development of surgical, chemo-, radio-, hormonal, and gene therapy and targeted therapies, cancers cannot be completely cured in most cases [32]. Therefore, early detection of metastasis or recurrence is clinically important and helpful for improvement of the prognosis or survival of cancer patients [33].

Here is a case of non-Hodgkin's lymphoma with recurrence detected in the follow-up PET imaging (Case 3):

A 65-year-old Chinese female was admitted to the Department of Hematology for the right back pain which lasted for 2 weeks. She was diagnosed with non-Hodgkin's lymphoma 11 years ago and had an operation followed by six cycles of postoperative chemotherapy. Recurrence was detected 6 years ago and four cycles of chemotherapy was performed. One year prior to this admission, she had severe right back pain. ^{18}F-FDG PET/CT images found enlarged lymph

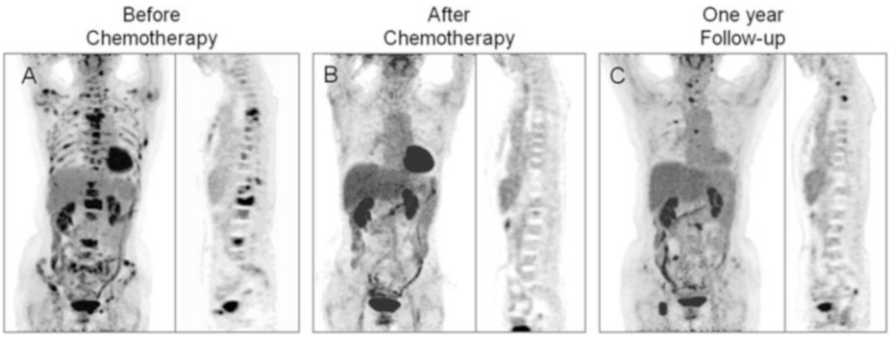

Fig. 22.4 (**a**) PET/CT showed increased FDG uptake in multiple bones, including sternum, vertebras, ribs, pelvis, etc. with maximum SUV of 6.65 in the left clavicle, 11.70 in the L1 vertebra, 5.18 in the ribs, and 5.40 in the right ilium. (**b**) PET/CT images showed normal FDG uptake in the whole body. (**c**) PET/CT images presented intensive FDG uptake in bowels with SUVmax of 5.69–10.22 in bones

nodes in the neck and multiple bones (Fig. 22.4a). After that, vertebral body biopsy confirmed diffuse large B-cell lymphoma and indicated recurrent with transformation. Therefore, the patient was performed eight cycles of chemotherapy. Immediately after the completion of chemotherapy, PET/CT showed negative FDG uptake in all lymph nodes (Fig. 22.4b). For this time, the patient felt backache again, PET/CT revealed intensive FDG uptake in bones, bowels, and cervical lymph nodes, which indicated the recurrence (Fig. 22.4c).

At present, multiple studies found that increased tumor marker level do not indicate localization of cancer. Although increasing of tumor marker levels may be the earliest indication of recurrent cancer, false-positive results may be found in some benign and physiologic conditions as well. Thus, follow-up PET/CT scans have an impact on patient management since it can provide the extended whole-body functional overview of recurrence or metastasis [11, 34, 35].

22.6.5 Research Collaborations

PET, including small-animal (or micro) PET and clinical PET, has become a requisite of cancer research in this century. The most significant advantage of PET method is that radiolabeled imaging agent (or radiotracer) could penetrate into the cell and thus make it possible to reveal the in vivo biodistribution and biochemical process of living cells [4]. Furthermore, not only limited to FDG, a glucose analogue, there are many other radiotracers, for instance, ^{11}C-choline used in prostate carcinoma [36], ^{11}C-acetate used in hepatocellular carcinoma [37],

^{13}N-ammonia used in pancreatic necrosis [38], etc. Hence, with the assistance of different PET imaging tracers, PET specialists could help oncologists to visualize different targets in the living body and test the efficacy of novel treatment [39, 40].

22.7 What Oncologists Can Do for PET Specialists?

Oncologists can also provide assistance to PET specialists, such as (1) referring appropriate patients, (2) provide patient education and (3) provide more detailed patient medical history, and (4) scientific research collaboration.

22.7.1 Referring Appropriate Patients

PET is a highly sensitive imaging method for the detection of early stage of cancer, occult recurrence, and metastasis since cancer-related metabolic abnormalities usually precede structural changes and are readily detected by PET [33]. However, if without clear clinical indication, excessive PET scanning is likely to identify harmless findings that lead to more tests, biopsy, or unnecessary surgery. Therefore, referring appropriate cancer or suspicious patients for PET imaging is the key to get better prognosis for patients.

22.7.2 Providing Detailed Medical History

FDG is not a cancer-specific agent, and false-positive findings in benign diseases may occur [41–43]. Infectious diseases (mycobacterial, fungal, bacterial infection), sarcoidosis, radiation pneumonitis, and postoperative surgical conditions have shown intense uptake, while tumors with low glycolytic activity such as adenomas, bronchoalveolar carcinomas, carcinoid tumors, low-grade lymphomas, and small-sized tumors have revealed false-negative findings on PET images.

Here is a false-positive case with tuberculosis (Case 4):

A 22-year-old Chinese male was admitted to the thoracic surgical department for right chest pain. It is a moderate and tolerable pain presented after taking a deep breath which lasted for about 1 year. He had no smoking and drinking history. On physical examination, his vital signs were normal, and he presented rough breath sounds without any other symptoms. On laboratory tests, his T-SPOT test was positive, and other tests were in normal limits, including tumor markers. He had performed X-ray and high-resolution CT in the chest. High-resolution CT indicated a 13-mm*6-mm nodule in the lateral segment of the right middle lung (Fig. 22.5b). In order to determine whether the nodule was of malignant

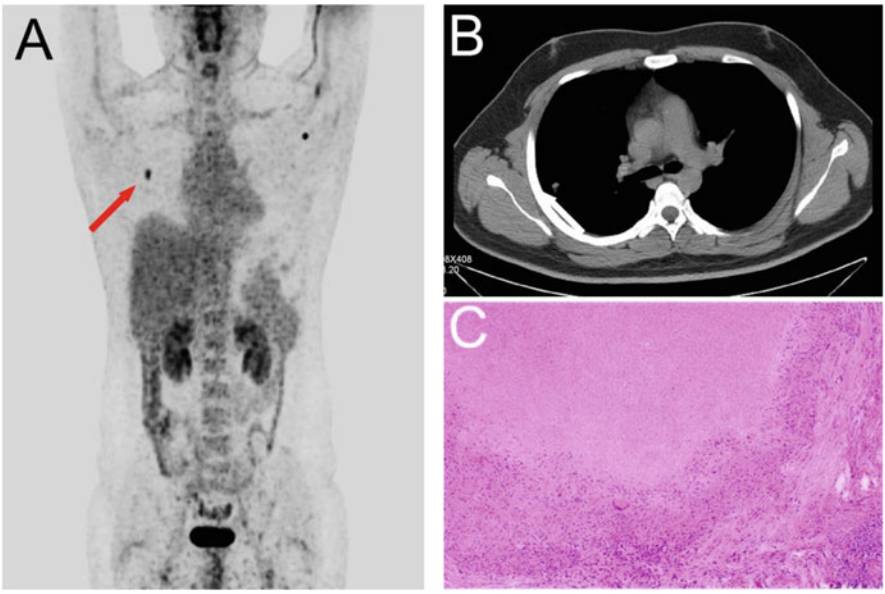

Fig. 22.5 (**a**) ^{18}F-FDG PET/CT images demonstrated a 12.9-mm*7.7-mm mass of intensive FDG uptake in the right middle lung (*red arrow*) with SUVmax = 5.33. (**b**) Diagnostic CT image showed a 13-mm*6-mm nodule in the lateral segment of the right middle lung. (**c**) Routine pathology of the mass revealed "chronic granulomatous inflammation"

etiology, the patient was referred for ^{18}F-FDG PET/CT imaging. On PET/CT images, a 12.9-mm*7.7-mm mass with intensive ^{18}F-FDG uptake was found in the lateral segment of the right middle lung (Fig. 22.5a). Based on the medical history (young man, nonsmoking, and moderate symptom), the PET specialist highly suspected for nonneoplastic diseases, such as tuberculosis or other inflammation despite the increased SUV value. However, the patient preferred to perform surgical resection. The pathological diagnosis verified it was inflammatory pseudotumor, tuberculosis (Fig. 22.5c).

22.7.3 Research Collaboration

PET is a functional molecular imaging technique which is based on radionuclide imaging of regional biochemistry in vivo. Biochemistry is considered the basis of diagnosis and of the planning and monitoring of treatment since the treatment of many diseases involves biochemical reactions. A number of radiolabeled PET tracers have been designed and developed to imaging the functional and biochemical process of tissues or cells which can be applied for experimental or clinical research, and can be initiated by either PET specialists or oncologists. The hybrid PET/CT not only can provide highly spatial resolution but also can reflect abnormal lesions, glucose, amino acid, nucleic acid, and gene. It is the only current imaging

method available from a physiological perspective and the molecular level for quantitative evaluation of biochemical changes. Oncologists pay more attention to the efficacy of different therapies, while PET specialists focus more on the applications of various radiotracers. Through collaborative research and interactive communication, PET specialists and oncologists may explore more on underlying mechanism of cancers.

22.8 Future Perspectives

Awareness of the impact of interactive communication between PET specialists and oncologists, particularly on patient referring, monitoring, and follow-up, is critical to the proper management of cancer patient. A PET specialist is different from a conventional radiologist, and proper interpretation of a PET image is different from a radiological film reading. PET specialists have to integrate the clinical, laboratory, pathophysiological, and even biochemical understandings on a specific disease and related disease progress. With the new development of molecular imaging agents and hybrid imaging modalities including PET/CT or PET/MRI, interactive multidisciplinary communications and international collaborations become more and more important [44, 45]. In the future, interactive communication methods include, but not limited to regular specialist attendance at team meetings, telephone discussions but also shared electric archives and massive open online course (MOOC). We assume that when cloud-based medical practice is applied for the future clinical practice, interactive communication will be even more important and more related to the better patient management.

22.9 Conclusions

Interactive communication is feedback and teamwork. Awareness of the impact of interactive communication between PET specialists and oncologists is critical to the proper management of cancer patient.

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