Applications of FDG PET in Oncology

Best Clinical Practice

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Preface

Although cancer is still the leading cause of death in many countries, recent epoch-making advance in molecular biology facilitates to reveal the nature of cancer at the level of gene and the era of "precision medicine" has come. New therapeutic strategies for cancer are established based on these genomic information. In response to this progress in cancer treatment, the concept of molecular imaging has also been introduced in the field of diagnostic imaging sciences. Nuclear medicine tests that can evaluate the functional features of lesions would be clinical molecular imaging tests. Among them, F-18 FDG PET tests that can provide metabolic activity of glucose in tissues including cancer lesions are attracting a strong attention in oncology.

Many research works in the field of nuclear medicine have demonstrated the usefulness of FDG PET tests in clinical oncology. However, FDG PET tests have not been so familiar in routine clinical practice in many countries maybe due to its very high cost.

In Japan, more than 50 years have passed since the universal public health insurance system was established. According to this unique system, every people can rather easily receive advanced health care when it is covered by public health insurance. Fortunately, FDG PET test is now covered by public health insurance for a wide variety of cancer except for early stage of gastric cancer in Japan and is a popular imaging tests for many clinicians in the field of oncology.

This book introduces the current situation of FDG PET tests under unique healthcare system in Japan from the viewpoints of experts of clinical oncology, and this book will contribute to the global spread of FDG PET test.

An introduction to the subject of the book should not be confused with a preface. A preface concerns the book itself (e.g., why it is important, why it was written), while an introduction presents the subject matter of the book.

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Contents

Chapter 1
Overview of FDG PET in Oncology in Japan

Takahiro Morita and Hirofumi Fujii

1.1 Introduction

Currently, the quality of life is important in the treatment of cancer patients and minimally invasive and individualized therapy is required. Accurate evaluation of the characteristics of a tumor is very important for optimized cancer therapy and imaging tests play an important role in the management of cancer. Computed tomography (CT) and magnetic resonance imaging (MRI) are popular imaging tests and they can provide minute morphological information about tumor lesions. However, recently nonsurgical treatments such as chemotherapy and radiotherapy are often used and the evaluation of functional aspects of tumors is very important to successfully perform these kinds of therapies. For example, tumors do not always decrease in size after successful chemotherapy using molecular targeted agents such as imatinib mesylate [1]. Under such situations, F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET) is commonly performed to evaluate metabolic activity of tumors and this imaging test is getting popular in Japan as in other developed countries.

Japanese greatly contributed to clinical introduction of this useful PET agent. FDG was first synthesized by Ido, a Japanese researcher [2]. The clinical usefulness of this PET agent in the field of oncology was also first reported by a Japanese nuclear medicine physician. Yonekura reported increased accumulation of FDG in metastatic liver tumors of colon cancer patients [3]. That is why we Japanese are closely linked with the application of FDG to clinical oncology. In this chapter, we review the current situation of FDG PET tests in Japan.

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1.2 Clinical Application of FDG PET Tests in the Field of Oncology

FDG accumulates in tissues according to their metabolic activity of glucose. Although FDG is phosphorylated inside cells as glucose, phosphorylated FDG is metabolized no more unlike glucose. Phosphorylated FDG is dephosphorylated in normal cells while this phosphorylated compound cannot be dephosphorylated in most tumor cells due to their weak dephosphorylase activity. As a result, FDG stays in tumor tissues according to their metabolic activity. This accumulation mechanism of FDG is called metabolic trapping.

As PET can quantitatively evaluate the accumulation of probes in lesions, FDG PET can objectively examine the metabolic activity of glucose using indices. Standardized uptake value (SUV) is the most common index.

The main roles of FDG PET are as follows: (1) differential diagnosis of already-known lesions, (2) staging of malignant tumors, (3) evaluation of therapeutic effects of nonsurgical treatment, and (4) surveillance of recurrent tumors.

The second and fourth roles are to detect malignant lesions and the first and third ones are to evaluate the functional aspect of already-known lesions. Although these four roles of FDG PET are all important in the field of oncology, the second and fourth roles are covered by public health insurance in Japan. However, the remaining first and third roles are not clearly covered by public health insurance although these roles are undoubtfully important in clinical practice. This situation should be improved. More detailed information about the coverage of FDG PET by public health insurance is described later.

Currently, FDG PET test is usually performed combined with morphological imaging tests such as CT and MRI. These kinds of hybrid imaging can provide both anatomical and functional information about tumor lesions at the same time and fusion of both kinds of images is very useful to understand the features of tumors.

Recently, combined scanners such as PET/CT scanners and PET/MRI are getting popular and we can get clear superimposed images using these hybrid scanners.

After this, four major roles of FDG PET in clinical oncology are concretely explained showing fusion images obtained by combined scanners.

1.2.1 Differential Diagnosis of Already-Known Lesions

FDG PET can evaluate the metabolic activity of glucose in a lesion. Generally speaking, malignant tumors are avid of glucose due to increased glycolysis called Warburg effects [4]. Therefore, malignant tumors are likely to show higher uptake of FDG than benign lesions (Fig. 1.1). However, some inflammatory and benign diseases such as sarcoidosis, uterine leiomyoma, and neurogenic tumor show rather high activity in FDG PET tests and it is not easy to distinguish malignant tumor from nonmalignant disease only by FDG PET test.

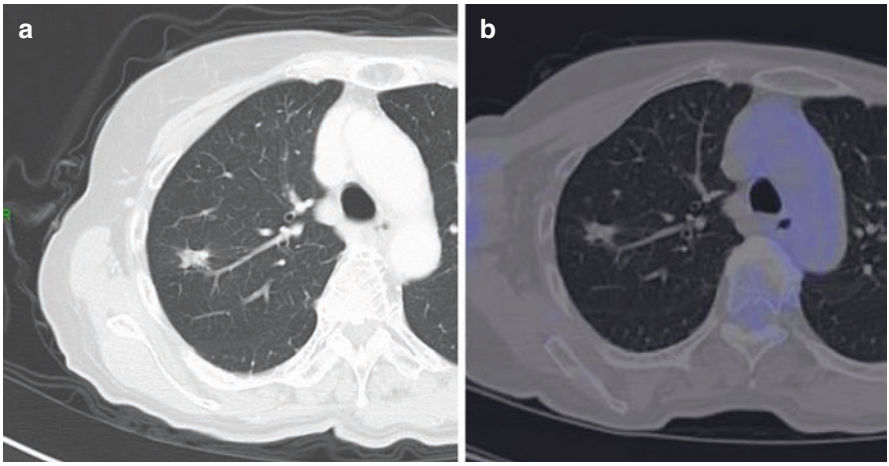


Fig. 1.1 A 60s' female with nonmalignant pulmonary lesion. (**a**) A high-resolution CT image shows an irregular shaped lesion in the upper lobe of the right lung. Lung cancer cannot be ruled out. (**b**) An FDG/PET fusion image shows faint uptake in this irregular-shaped lesion, suggesting its low metabolic activity. Surgical resection confirmed the diagnosis of no malignancy 2 years later

FDG PET is also useful to judge the grade of malignancy of neoplasms. Neuroendocrine tumor (NET) is a unique neoplasm showing a variety of malignancy and the evaluation of its grade of malignancy is important to receive the optimal therapy. Kubota reported that FDG PET and somatostatin receptor scintigraphy (SRS) play different roles in the evaluation of NET [5]. FDG PET can reflect the grade of malignancy, while SRS can reflect the degree of differentiation. He demonstrated the inverse correlation between SRS uptake and FDG uptake in metastatic NET lesions. (Figs. 1.2 and 1.3)

1.2.2 Staging of Malignant Tumors

Accurate staging is essential to optimized cancer therapy. Tumor stages are often judged using TNM classification determined by International Union Against Cancer [6]. T factor is the extent of the primary tumor. N factor is the extent of regional lymph node metastasis and M factor is the absence or presence of distant metastasis. FDG PET is often useful to determine the N factor and M factor. FDG PET can detect metastatic lesions in regional lymph nodes whose size are within normal limits and those located in unusual areas such as abdominal metastases from lung cancer (Fig. 1.4).

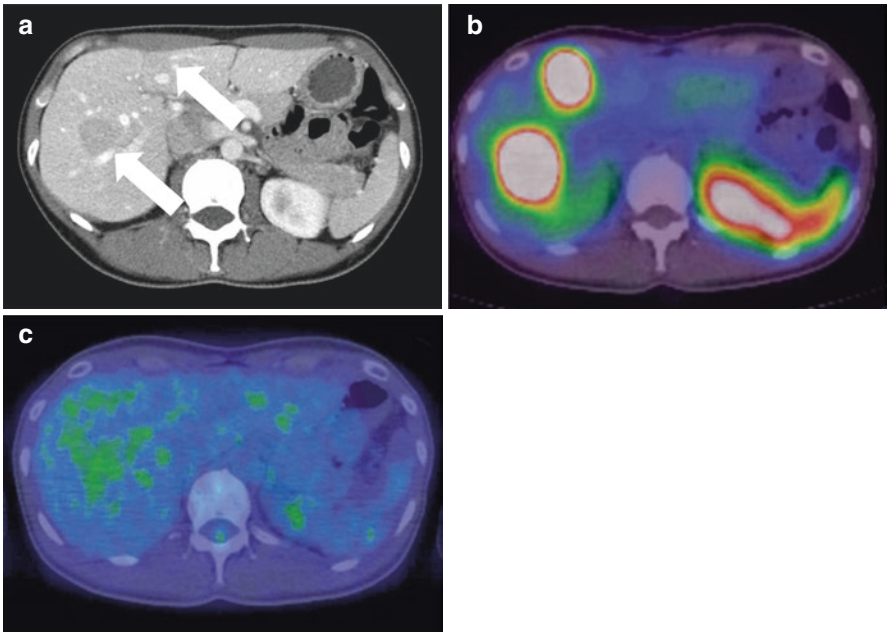


Fig. 1.2 A 30s' female with multiple liver metastases from G2 NET originated in the small intestine. (**a**) A contrast-enhanced CT image depicts poorly enhanced lesions in the right hepatic lobe (arrows). (**b**) Somatostatin receptor scintigraphy (SRS) (24 h after the injection) reveals strong expression of receptors on these lesions, indicating that lesions are well-differentiated. (**c**) An FDG/PET fusion image shows faint uptake in these lesions, suggesting their low metabolic activity

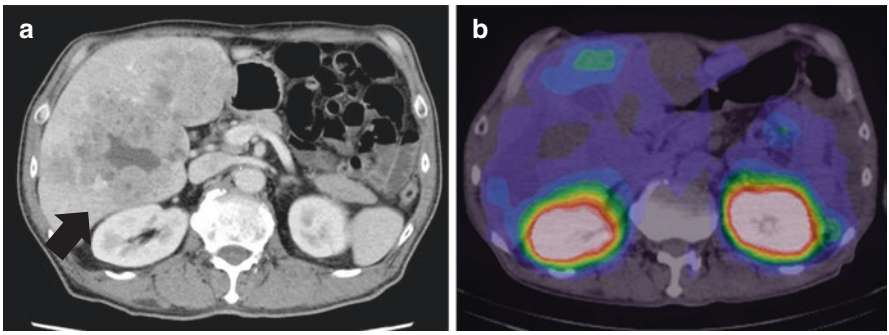
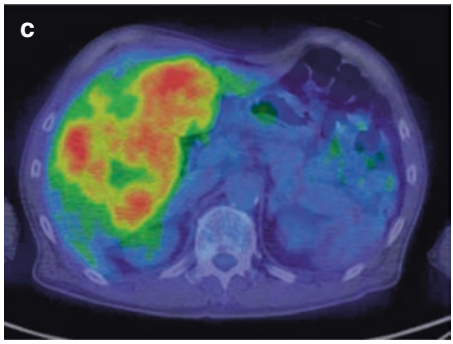


Fig. 1.3 A 60s' male with multiple liver metastases from primary unknown G3 NET. (**a**) A contrast-enhanced CT image depicts poorly enhanced irregular-shaped lesions in the right hepatic lobe (arrow). (**b**) Somatostatin receptor scintigraphy (SRS) (24 h after the injection) reveals weak expression of receptors on these lesions, indicating that lesions are poorly differentiated. (**c**) An FDG/PET fusion image shows strong uptake in these lesions, suggesting their high metabolic activity

Fig. 1.3 (continued)



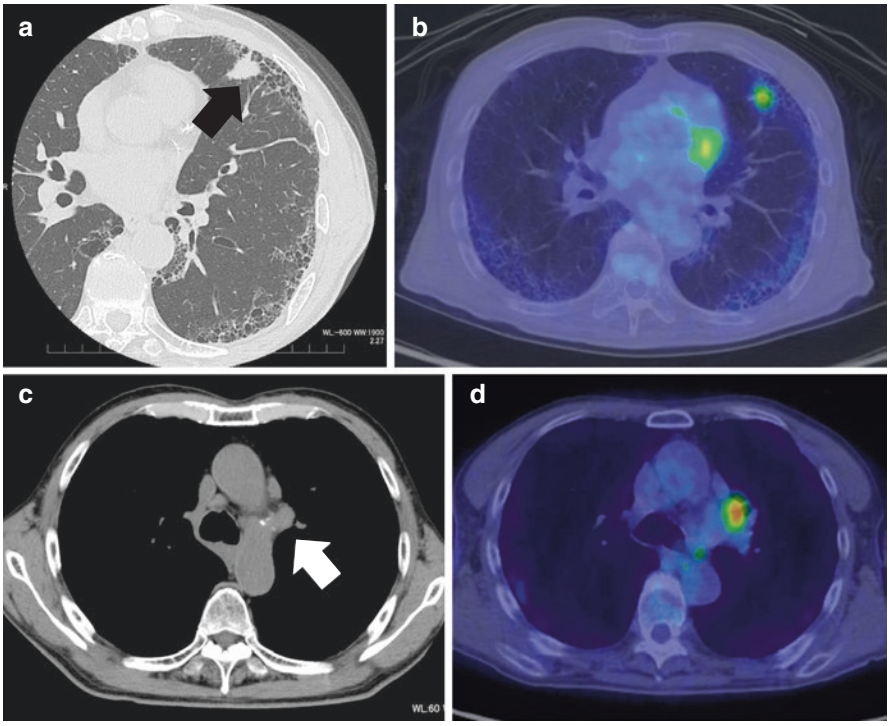


Fig. 1.4 A 70s' male with lung cancer. (**a**) A high-resolution CT image depicts an irregular-shaped lesion in the left upper lobe (S4b) (arrow). Interstitial pneumonitis is shown in the peripheral regions of both lungs. (**b**) An FDG/PET fusion image shows increased uptake in this lesion indicating malignant tumor. (**c**) A CT image detects multiple swollen lymph nodes in the mediastinum. (**d**) An FDG/PET fusion image shows strong activity only in some ipsilateral mediastinal lymph nodes, suggesting that hot nodes are metastatic (arrow in (**c**)) and others are reactive. These findings were confirmed by histopathological diagnosis after the surgery. The histological type was poorly differentiated adenocarcinoma and the pathological stage was pT1b, pN2, cM0, p-Stage IIIA according to UICC 8th

1.2.3 Evaluation of Therapeutic Effects of Nonsurgical Treatment

When tumors are treated by chemotherapy and/or radiotherapy, lesions do not rapidly disappear unlike surgical resection. Tumors usually decrease in size after successful nonsurgical treatment. Under such situations, therapeutic effects are usually assessed using some criteria. The most popular one is the Response Evaluation Criteria in Solid Tumors (RECIST) (version 1.1) [7]. The longitudinal change of tumor size is an important parameter in this criterion. However, new therapeutic drugs such as molecular targeted agents do not always shrink lesions even after successful therapy. In such cases, the evaluation of the metabolic activity of tumors is useful and FDG PET can provide useful information about the glucose metabolism of lesions [8]. Recently, Wahl proposed the PET Response Criteria in Solid Tumors (PERCIST). The PERCIST can help clinicians with valuable information of therapeutic response at an earlier stage because FDG PET can correctly evaluate the therapeutic effects before morphological changes appear [9] (Fig. 1.5).

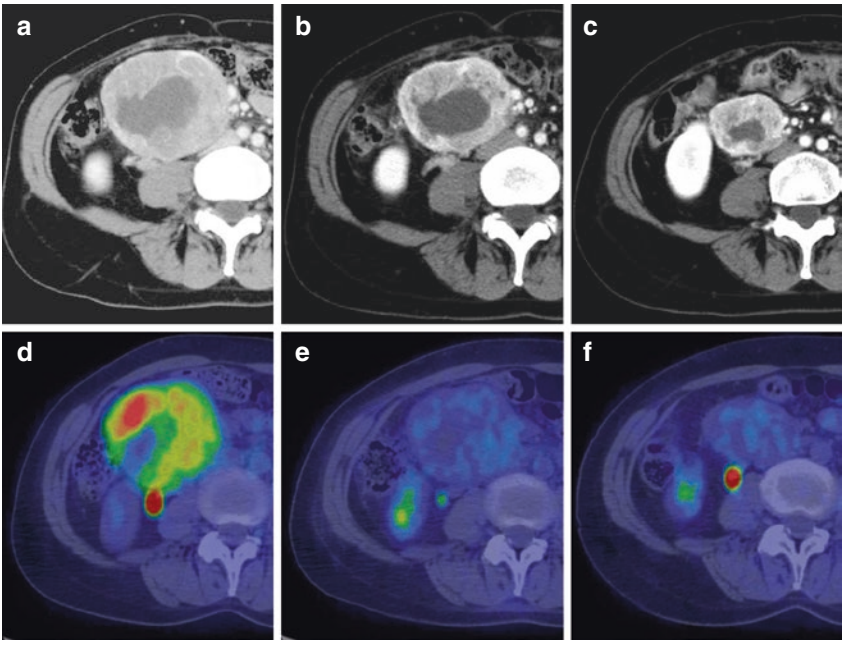


Fig. 1.5 A 40s' female with primary gastrointestinal stromal tumors of duodenum. (**a**) A pretreatment contrast-enhanced CT image depicts a lesion with heterogeneous density as large as 90 mm. (**b**) A contrast-enhanced CT image obtained at 2 weeks after the initiation of the treatment using imatinib mesylate shows a mildly shrunken tumor. (**c**) A contrast-enhanced CT image obtained at 8 months later shows a shrunken tumor as small as 50 mm. (**d**) A pretreatment FDG/PET fusion image shows strong activity in the tumor (SUVmax = 8.13). (**e**) An FDG/PET fusion image obtained at 2 weeks larger shows dramatically decreased activity in the tumor (SUVmax = 2.99). (**f**) An FDG/PET fusion image obtained at 8 months larger indicates low activity in the tumor (SUVmax = 1.70). These images demonstrate that FDG PET can predict the therapeutic effects earlier than morphological imaging tests

1.2.4 Surveillance of Recurrent Tumors

Malignant tumors can recur even when the initial treatment was quite successful. Patients must have regular checkups. The regular checkup schedules depend on the type and stage of cancer and so on. Metastatic lesions can appear in unexpected areas. When recurrence was suspected by tumor marker tests and CT tests failed to identify recurrence, survey of whole body using FDG PET might be useful to detect recurrent tumors with unusual locations (Figs. 1.6 and 1.7).

1.3 The Role of FDG PET Tests Appeared in Japanese Clinical Guidelines for Major Cancer

Currently, clinical guidelines for various kinds of diseases are published in many countries. These guidelines explain standard management methods at that time to

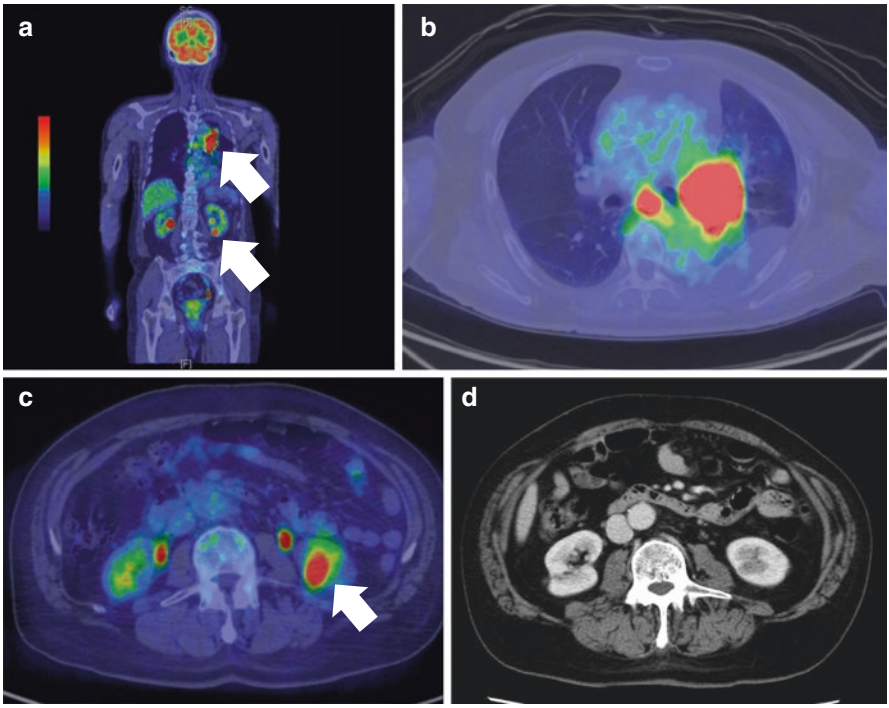


Fig. 1.6 A 70s' male with surgically treated left lung cancer. (**a**) A postoperative FDG/PET fusion coronal section image indicates strong uptake in the chest and left kidney (arrows), suggesting recurrent tumors. (**b**) A chest FDG/PET fusion image shows strong uptake in the remaining left lung and mediastinum, compatible with recurrence. (**c**) An abdominal FDG/PET fusion image shows strong activity in the left kidney (arrow), indicating malignant tumor. (**d**) However, an abdominal contrast-enhanced CT image fails to clearly depict recurrence in the left kidney

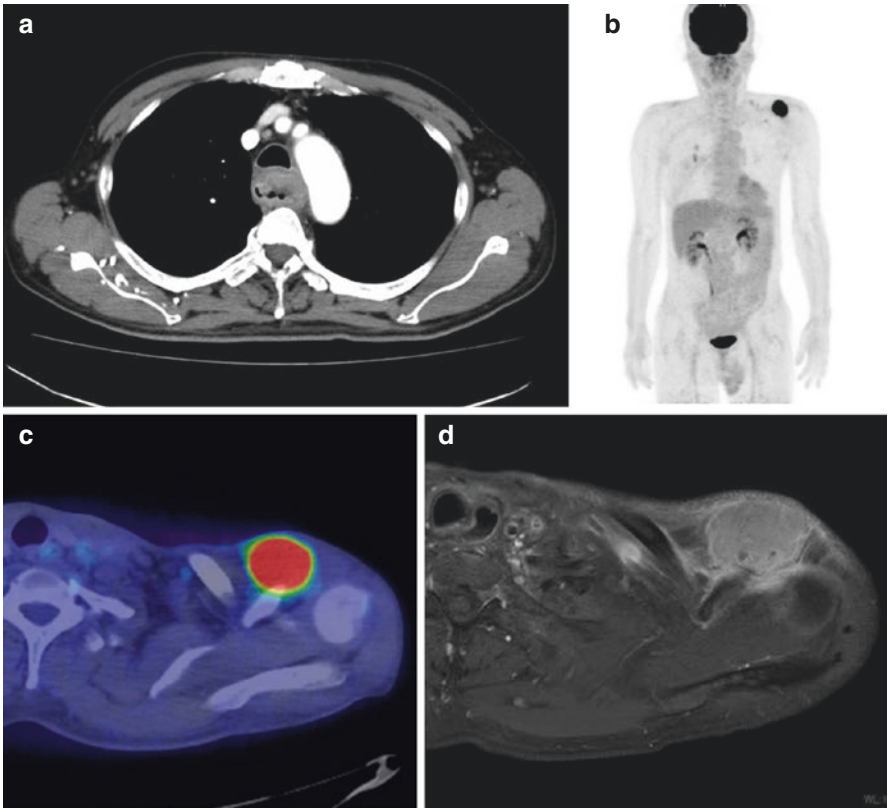


Fig. 1.7 A 50s' male with surgically treated esophageal cancer. (**a**) A preoperative contrast-enhanced CT depicts a tumor in the upper third of the thoracic esophagus. (**b**) The postoperative follow-up FDG maximum intensity projection image detects abnormal strong uptake around the left shoulder. (**c**) A FDG/PET fusion image depicts strong uptake in the muscle around the left shoulder joint. (**d**) A MRI gadolinium-enhanced T1-weighted image shows a heterogeneously enhanced mass in the muscle around the left shoulder joint. The subsequent biopsy confirmed the diagnosis of intramuscular metastasis from esophageal carcinoma

provide appropriate medical procedures for every cancer patient. In the field of oncology, one of the most famous ones is NCCN guidelines published by the National Comprehensive Cancer Network (NCCN) in the USA. NCCN provides clinical guidelines for more than 50 kinds of malignancy and they are open for the public (https://www.nccn.org/). Although their contents are well organized, these guidelines are published based on the clinical evidence obtained mainly in the USA and the contents are not always fit for Japanese cancer patients.

After this, we explain how FDG PET test is recommended in Japanese clinical guidelines for major cancer.

1.3.1 Lung Cancer

The following five clinical questions (CQs) appear in Guidelines for Diagnosis and Treatment of Lung Cancer 2019 issued by the Japan Lung Cancer Society [10].

CQ 2. Is PET/CT useful to detect lung cancer?

Recommendations: It is recommended not to perform PET/CT test to detect lung cancer.

(Recommendation grade 2, evidence level C, agreement rate 94%)

CQ 4. When it is difficult to diagnose a nodule as lung cancer by high resolution CT test, are contrast-enhanced CT, MRI and/or FDG-PET/CT useful?

Recommendations: FDG-PET/CT is recommended.

(Recommendation grade 1, evidence level C, agreement rate 67%)

CQ 19. Which tests are required to diagnose T factor?

Recommendations: FDG-PET/CT is recommended when invasion to mediastinum, chest wall and/or atelectasis surrounding lung tissues must be judged.

(Recommendation grade 1, evidence level C, agreement rate 100%)

CQ 20. Which tests are required to diagnose N factor?

Recommendations: Contrast-enhanced chest CT and FDG-PET/CT are recommended.

(Recommendation grade 1, evidence level A, agreement rate 100%)

CQ 21. Which tests are required to diagnose M factor?

(a) FDG-PET/CT and contrast-enhanced brain MRI are recommended.
(Recommendation grade 1, evidence level A, agreement rate 100%)

(b) When a solitary metastatic lesion is suspected by FDG PET/CT, it is recommended to confirm the diagnosis by other imaging tests and/or pathological tests as far as possible.
(Recommendation grade 2, evidence level B, agreement rate 100%)

1.3.2 Breast Cancer

The following contents appear in The Japanese Breast Cancer Society Clinical Practice Guidelines for Breast Cancer issued by the Japanese Breast Cancer Society. These guidelines appear on the following website described by Japanese: http://jbcs.gr.jp/guidline/2018/

In the section of "Overview 6: Follow-up after the initial treatment", the usefulness of FDG-PET is described as follows:

There is no prospective study about the usefulness of FDG-PET after the initial treatment. FDG-PET shows higher sensitivity and specificity in the detection of recurrent breast cancer, compared to conventional imaging (CI) such as mammography, ultrasonography, CT, MRI, X-ray test and bone scintigraphy. However, various sensitivity and specificity of FDG-PET were reported. Although the combination

of FDG-PET and CI is useful, CI should not be replaced by FDG-PET. There are no reports that demonstrate the benefit of FDG PET in the light of survival rate, quality of life and medical economics.

The usefulness of FDG PET is also described in the following questions.

CQ 7. Is preoperative whole-body screening using CT, PET, PET-CT is recommended for patients with stage I and II breast cancer?

Recommendation: It is mildly recommended not to do preoperative whole-body screening using CT, PET, PET-CT.

(Recommendation grade 3, evidence level very weak, agreement rate 92% 11/12)

Future research question (FQ) 3. Is mammoPET recommended to dense breast cases as additional screening test for breast cancer?

Statement: When an examinee agreed after sufficient explanation about risk and benefit, screening test using mammoPET would be acceptable.

FQ 7. Is mammoPET recommended for the prediction of pathological CR and the early evaluation of therapeutic effects to preoperative chemotherapy?

Statement: There is some evidence that demonstrates the usefulness of mammoPET in the prediction of pathological CR and the early evaluation of therapeutic effects to preoperative chemotherapy.

1.3.3 Head and Neck Cancer

The following contents appear in Japanese Clinical Practice Guidelines for Head and Neck Cancer 2018 issued by the Japan Society for Head and Neck Cancer [11].

In the section of overview, the usefulness of FDG PET and PET/CT in the diagnosis of lymph node metastases and distant metastases is described. FDG PET and PET/CT are useful for metastatic cervical lymph nodes with unknown primary tumors.

The usefulness of FDG PET is also described in following clinical questions.

CQ 1–1 Is CT useful in the diagnosis of N factor of head and neck cancer?

Recommendation: CT is useful in the diagnosis of N factor of head and neck cancer. (Recommendation grade B)

In the explanation of this clinical question, the additional role of PET and PET/CT is described.

CQ 1–6 Is FDG-PET useful in the staging of head and neck cancer?

Recommendation: PET is useful in the diagnosis of N factor and M factor in the staging as well as the diagnosis of recurrent tumor. (Recommendation grade B)

CQ 1–7 Are imaging tests useful in the follow-up after the treatment?

Recommendation: It is reported that PET-CT is useful in the evaluation of therapeutic effects of chemotherapy. (Recommendation grade B)

1.3.4 Colorectal Cancer

The following description appears in guidelines 2019 for the treatment of colorectal cancer issued by the Japanese Society for Cancer of the Colon and Rectum [12].

PET/CT test is useful to detect and diagnose the recurrence in case with suspicious findings. But, this test is not recommended for the surveillance.

1.3.5 Malignant Soft Tissue Tumor

The following two CQs appear in the draft version of Clinical Practice Guidelines on the Management of Soft Tissue Tumors 2020 issued by the Japanese Orthopaedic Association [13].

CQ 4 Is preoperative PET recommended for patients with malignant soft tissue sarcoma?

Recommendation: Preoperative PET is recommended for patients with malignant soft tissue sarcoma.

(Recommendation grade 2, evidence level C, agreement rate 100%)

CQ 5 Is postoperative PET recommended for patients with malignant soft tissue sarcoma?

Recommendation: Postoperative PET is recommended for patients with malignant soft tissue sarcoma.

(Recommendation grade 2, evidence level C, agreement rate 92%)

1.3.6 Skin Cancer

The following two CQs appear in Skin Cancer Clinical Guidelines (version 2) issued by the Japanese Dermatological Association and Japan Skin Cancer Society [14].

CQ 8 Is preoperative imaging tests recommended to detect metastatic lesions of malignant melanoma?

Recommendation: For clinical stage (CS) 0, it is not recommended to perform chest X-ray, ultrasonography, CT and PET. (Recommendation grade C2)

For CS I to IIB, it can be considered to perform chest X-ray, ultrasonography, CT and PET. However, it cannot be recommended for all cases. (Recommendation grade C1)

For CS IIc to III, it is recommended to perform some of chest X-ray, ultrasonography, CT and PET depending on the location of metastatic lymph nodes and potential risk of metastatic lesions. (Recommendation grade B)

CQ 20 Are routine whole-body imaging tests recommended to patients who received complete resection of tumors?

Recommendation: For CS 0, routine whole-body imaging tests cannot be recommended. (Recommendation grade C2)

For CS I to IIB, it can be considered to perform routine whole-body imaging tests. However, it cannot be recommended for all cases. The types of imaging tests and their intervals depend on the condition of each patient. (Recommendation grade C1).

For CS IIc to III, it is recommended to perform routine whole-body imaging tests to detect occult lymph node metastases and unexpected distant metastases. The types of imaging tests and their intervals depend on the condition of each patient. (Recommendation grade B)

1.3.7 Malignant Lymphoma

The following contents concerning malignant lymphoma appear in JSH practical guidelines for hematological malignancies, 2018 issued by the Japanese Society of Hematology [15].

In the section of "Overview" of malignant lymphoma, the usefulness of FDG PET for staging and evaluation of therapeutic effects are described.

Although gallium scintigraphy was previously used for staging of malignant lymphoma, PET-CT is currently used for staging due to its excellent sensitivity and specificity. Since FDG uptake in lymphoma lesions depends on their histological type, FDG PET or, if possible, PET-CT should be performed before treatment when FDG PET or PET-CT will be used for the evaluation of therapeutic effects.

As for the evaluation of therapeutic effects of lymphoma, "Report of an International Workshop to standardize response criteria for non-Hodgkin's lymphomas" was issued in 1999 and this criterion has been widely used. CT plays an important role in this criterion. But, recently, FDG PET is getting popular and its usefulness has been reported. In 2007, "Revised response criteria for malignant lymphoma" using FDG PET was issued for the evaluation of therapeutic effects of diffuse large B cell lymphoma and non-Hodgkin lymphoma. Five-point scale is recommended when FDG PET is used for the evaluation of therapeutic effects. Although this criterion was published for international clinical trials, it can be applied to clinical practice.

The usefulness of FDG PET for routine follow-up is not recommended due to no established evidence.

The following two CQs concerning FDG PET appear in JSH practical guidelines for hematological malignancies, 2018.

One is for diffuse large B cell lymphoma (DLBCL) and not otherwise specified (NOS).

CQ 11 Is interim PET, which is PET performed during the initial treatment, useful to predict the prognosis of DLBCL?

Answer: Although negative interim PET suggests a good prognosis, positive interim PET does not always mean a poor prognosis. Therefore, prognostic value of

interim PET is limited. There are insufficient data to recommend interim PET to clinical practice. Further clinical trial is required. (Recommendation grade 2B)

Another clinical question is for Hodgkin lymphoma (HL).

CQ 9 Is interim PET useful to predict the prognosis of advanced-stage classical HL?

Answer: Interim PET has prognostic value in patients with advanced-stage classical HL. (Recommendation grade 2A)

1.4 Nationwide Survey of FDG PET Tests

In Japan, a nationwide survey of in vivo nuclear medicine practice has been performed by Japan Radioisotope Association (JRIA) every 5 years since 1982 and the data concerning PET tests have been collected since 1987.

In this survey, a set of questionnaire sheets are sent to all medical institutes and hospitals with nuclear medicine facilities by JRIA and each institute or hospital answered the types and numbers of PET tests that were performed in the previous year.

Since more than 90% of questionnaire sheets are sent back to JRIA, the obtained data are considered reliable to overview the situation of nuclear medicine practice in Japan at that time.

The most recent survey was the eigth one, which was performed in 2017 [16, 17]. The questionnaire sheets were sent to 1249 nuclear medicine facilities in Japan and 1132 responded. Since the response rate exceeded 90%, we think that the obtained results rather accurately reflect the current situation of FDG PET in Japan.

This newest survey revealed that the number of clinical PET facilities was 389 and that of F-18 tests was 56,686 per month.

This survey also indicated a dramatic increase of the number of facilities with PET cameras and that of FDG PET tests in these 30 years as shown in Figs. 1.8, 1.9 and 1.10.

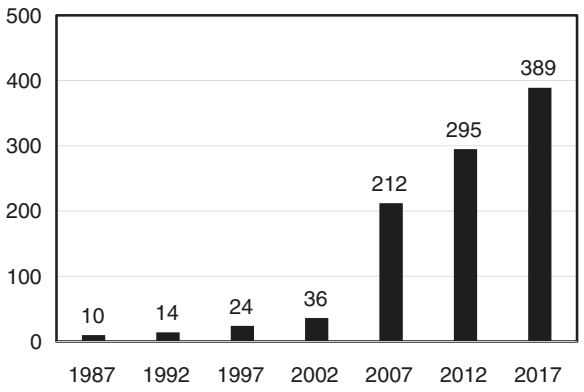


Fig. 1.8 The number of medical facilities with PET cameras (modification of Fig. 1–1 in Reference [17])

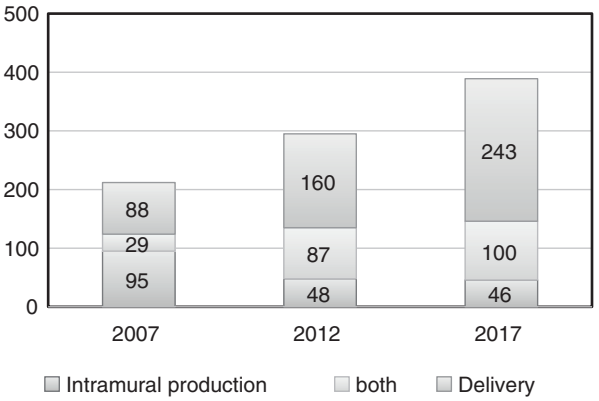


Fig. 1.9 The number of medical facilities according to the source of PET drugs (modification of Fig. 1–2 in Reference [17])

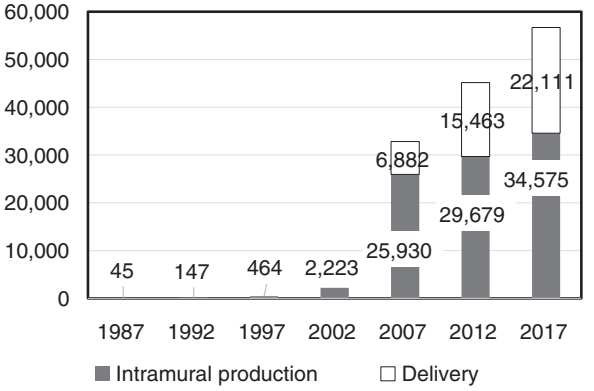


Fig. 1.10 The number of FDG PET per month (modification of Fig. 8 in Reference [17])

As for the number of facilities with PET scanners, only 10 facilities had PET scanners in 1987 and 389 facilities have installed PET scanners in 2017. The number of facilities with PET scanners increased approximately 40 times in these 30 years.

As for the number of FDG PET tests, only 45 tests were performed in 1 month in 1987 and 56,686 tests were done in 1 month in 2017. The number of FDG PET tests increased more than 1000 times, compared to the first data obtained in 1987. It was found that more than 97% of FDG PET tests were performed as oncology tests in 2017. FDG PET test is also useful to evaluate the metabolic activity of brain and myocardium and this test can be applied to diagnose dementia and myocardial disorder such as ischemic heart disease. However, the ratio of FDG PET tests used for these purposes are less than 3%.

This marked increase of PET tests in Japan owes to the broad coverage of FDG PET tests by public health insurance and the introduction of commercial distribution system of this PET agent. The commercial distribution system of FDG started in Japan in 2005. The number of FDG drugs provided by this system is increasing and approximately 40% of these PET tests (22,111 tests of total 56,686 tests) were performed using commercially distributed drugs in 2017.

1.5 The Coverage of FDG PET by Public Health Insurance in Japan

The wide coverage by public health insurance is one of the unique features of FDG PET tests in Japan.

The FDG PET tests for malignant tumors were first covered by public health insurance in Japan in 2002. The following ten kinds of malignant tumors were covered: lung cancer, breast cancer, colon cancer, head and neck cancer, brain tumor, pancreatic cancer, malignant lymphoma, metastatic liver tumors, malignant melanoma, and primary unknown cancer. Many additional conditions were also indicated. The detailed conditions are shown in Table 1.1.

As described in the previous section, this wide coverage by public health insurance facilitated the spread of FDG PET for malignant tumors in Japan. Although the number of FDG PET tests performed in a month in 1997 was only 464, the numbers in 2002 and 2007 dramatically increased up to 2223 and 32,812, respectively.

The coverage of FDG PET by public health insurance was revised in 2006. Three kinds of additional cancer, esophageal cancer, uterine cancer, and ovarian cancer, were covered and some conditions for previously covered tumors were also changed (Table 1.1).

The coverage of FDG PET by public health insurance was revised in 2010 again and all malignant tumors except for the early stage of gastric cancer are now covered when other clinical tests including CI tests failed to confirm the stage of malignant tumors or the diagnoses of metastases and/or recurrences.

Recently, FDG PET has been one of the most popular imaging tests in the field of clinical oncology in Japan due to this broad coverage by public health insurance. However, there is a problem in the coverage of FDG PET test by public health insurance in Japan. As previously mentioned, there are many reports to demonstrate the usefulness of FDG PET in the evaluation of the therapeutic effects of nonsurgical cancer treatments such as chemotherapy and radiotherapy. But, FDG PET for this purpose is not covered well by public health insurance in Japan. In 2012, the Ministry of Health, Labour and Welfare in Japan notified that FDG PET to evaluate the therapeutic effects of patients suffering from malignant lymphoma is covered by public health insurance. However, no notification for other malignancies has been promulgated yet.

As mentioned previously, a pharmaceutical company started commercial distribution of FDG in Japan in 2005 and another company also initiate the sale of this PET drug in 2017. The clinical indication of these commercially available drugs is limited to the following tumors: lung cancer, breast cancer, colon cancer, head and neck cancer, brain tumor, pancreatic cancer, malignant lymphoma, malignant melanoma, and primary unknown cancer (Table 1.2).

When institutes and hospitals have their own cyclotrons, FDG is produced using their in-house synthesis system. To perform PET using this homemade FDG under public health insurance, it is necessary to use an approved FDG synthesizer. This would be a unique rule in Japan.

Table 1.1 Coverage of FDG PET for malignant tumors by public health insurance in Japan

Year	Events	Tumors covered by health insurance
2002	First coverage of F-18 FDG PET tests by public health insurance	Lung cancer Breast cancer Colon cancer Head and neck cancer The following conditions are required: 1. Although these malignant tumors are suspected by other clinical tests and imaging tests, it is difficult to confirm the pathological diagnosis. 2 It is difficult to confirm the diagnosis of staging and recurrence and/or metastasis by other clinical tests and imaging tests.
		Brain tumor The following condition is required: 1 It is difficult to confirm the diagnosis of recurrence and/or metastasis by other clinical tests and imaging tests.
		Pancreatic cancer The following condition is required: 1 Although other clinical tests and imaging tests suggest pancreatic cancer, mass forming pancreatitis cannot be ruled out.
		Malignant lymphoma The following condition is required: 1 It is difficult to confirm the diagnosis of staging and recurrence and/or metastasis by other clinical tests and imaging tests.
		Metastatic liver tumors The following conditions are required: 1 Although metastatic liver tumors are suspected by other clinical tests and imaging tests, it is difficult to confirm the pathological diagnosis. 2 Primary unknown case.
		Primary unknown cancer The following condition is required: 1 Although the results of pathological diagnosis of lymph node biopsy and/or those of CT tests strongly suggest metastatic tumors and there is strong evidence suggesting malignant tumors such as elevated tumor markers, no primary tumors are identified.
		Malignant melanoma The following condition is required: 1 It is difficult to confirm the diagnosis of staging and recurrence and/or metastasis by other clinical tests and imaging tests.

2006	Addition of 3 kinds of tumors to the coverage of F-18 FDG PET tests by public health insurance	Lung cancer Breast cancer Colon cancer Head and neck cancer The following conditions are required: 1 Although these malignant tumors are suspected by other clinical tests and imaging tests, it is difficult to confirm the pathological diagnosis. 2 It is difficult to confirm the diagnosis of staging and recurrence and/or metastasis by other clinical tests and imaging tests.
		Brain tumor The following condition is required: 1 It is difficult to confirm the diagnosis of recurrence and/or metastasis by other clinical tests and imaging tests.
		Pancreatic cancer The following conditions are required: 1 Although other clinical tests and imaging tests suggest pancreatic cancer, mass forming pancreatitis cannot be ruled out. 2 It is difficult to confirm the diagnosis of staging and recurrence and/or metastasis by other clinical tests and imaging tests.
		Metastatic liver tumors The following conditions are required: 1 Although metastatic liver tumors are suspected by other clinical tests and imaging tests, it is difficult to confirm the pathological diagnosis. 2 Primary unknown case.
		Primary unknown cancer The following condition is required: 1 Although the results of pathological diagnosis of lymph node biopsy and/or those of CT tests strongly suggest metastatic tumors and there is strong evidence suggesting malignant tumors such as elevated tumor markers, no primary tumors are identified.
		Malignant lymphoma Malignant melanoma Esophageal cancer Uterine cancer Ovarian cancer The following condition is required: 1 It is difficult to confirm the diagnosis of staging and recurrence and/or metastasis by other clinical tests and imaging tests.
2010	Wide coverage of F-18 FDG PET tests by public health insurance	All malignant tumor except for early gastric cancer The following condition is required: 1 It is difficult to confirm the diagnosis of staging and recurrence and/or metastasis by other clinical tests and imaging tests.

Table 1.2 The clinical indication of commercially available FDG

Company	Clinical indications and their conditions
Nihon Medi-physics co., ltd. (2005~) FUJIFILM Toyama chemical co., ltd. (2017~)	Lung cancer Breast cancer The following conditions are required: 1 Although these malignant tumors are suspected by other clinical tests and imaging tests, it is difficult to confirm the pathological diagnosis. 2 It is difficult to confirm the diagnosis of staging and recurrence and/or metastasis by other clinical tests and imaging tests.
	Colon cancer Head and neck cancer The following condition is required: 1 It is difficult to confirm the diagnosis of staging and recurrence and/or metastasis by other clinical tests and imaging tests.
	Brain tumor The following condition is required: 1 it is difficult to confirm the diagnosis of recurrence and/or metastasis by other clinical tests and imaging tests.
	Pancreatic cancer The following condition is required: 1 Although these malignant tumors are suspected by other clinical tests and imaging tests, it is difficult to confirm the pathological diagnosis.
	Malignant lymphoma Malignant melanoma The following condition is required: 1 It is difficult to confirm the diagnosis of staging and recurrence and/or metastasis by other clinical tests and imaging tests.
	Primary unknown cancer The following condition is required: 1 Although the results of pathological diagnosis of lymph node biopsy and/or those of CT tests strongly suggest metastatic tumors and there is strong evidence suggesting malignant tumors such as elevated tumor markers, no primary tumors are identified.

Recently, PET/MRI combined scanners are commercially available in Japan and PET/MRI tests have been covered by public health insurance since 2013. But, tumors that are covered by insurance is limited to the following 12 kinds of tumors: brain tumor, head and neck cancer, mediastinal tumor, pleural tumors, breast cancer, rectal cancer, urological cancer, ovarian cancer, uterus cancer, bone and soft tissue tumor, hematological malignancy, and malignant melanoma. PET/MRI tests can be performed when it is difficult to confirm the diagnosis of staging and recurrence and/or metastasis by other clinical tests and imaging tests.

1.6 Cancer Screening Using FDG PET Tests

FDG PET or FDG PET/CT is performed for a unique purpose in Japan. PET is used in some cancer screening programs for healthy subjects.

Recent studies revealed that screening tests are useful to reduce the mortality of some kinds of cancer such as breast cancer, colorectal cancer, cervical cancer, and lung cancer [18]. Mammography is recommended to detect breast cancer and colonoscopy and/or fecal occult blood test is useful to find colorectal cancer. However, these conventional tests can detect limited types of cancer. Since FDG PET tests can detect many kinds of malignant tumors at a time, the usefulness of cancer screening using FDG PET would be worth investigating. The unique trial started at HIMEDIC Imaging Center at Lake Yamanaka in 1994 [19, 20]. The cancer screening program of this imaging center consisted of FDG PET and conventional modalities such as chest CT. This imaging center reported interesting results. Yasuda evaluated 3165 asymptomatic individuals by 5575 PET tests. Some examinees received multiple FDG PET tests. Finally, 67 cases of malignant tumors (2.1%) were detected in this cancer screening program. Among 67 cases, 36 tumors were detected by FDG PET and most of them could receive curative treatment [21]. After this successful report, many PET imaging centers for cancer screening were built in Japan. Minamimoto investigated the performance of FDG PET for cancer screening [22]. He reported that 50,558 healthy subjects received FDG PET for cancer screening at 46 facilities in Japan in 2005. He analyzed the results of 43,996 subjects at 38 facilities and found the detection rate of cancer was 1.14% and 79% among them showed positive PET findings. According to this report, thyroid cancer, colorectal cancer, lung cancer, and breast cancer are commonly found. Although cancer screening using FDG PET test seems useful to detect early stage of cancer that can receive curative treatment, the risk of radiation exposure should be considered. Murano evaluated the radiation exposure by cancer screening program using FDG PET test and performed risk-benefit analysis [23]. He reported that the benefit would be superior to the risk for men over 40 and women over 30 when dedicated PET scanner were used. When PET/CT combined scanner were used, the risk-benefit break-even age would be higher.

1.7 Summary and Key Points

In this chapter, we overviewed the important roles of FDG PET in current clinical oncology in the first half. In the latter half, we described the current situation of FDG PET in Japan, introducing the description about FDG PET in clinical cancer guidelines, the results of a nationwide survey of FDG PET, the coverage of FDG PET by public health insurance, and the unique application of FDG PET in cancer screening programs.

The followings are key points to understand the contents of this review.

- Imaging tests that can provide functional information about cancer such as FDG PET play an important role in current clinical oncology.
- There are four main roles in FDG PET for cancer patients as follows: (1) differential diagnosis of already-known lesions, (2) staging of malignant tumors, (3)

evaluation of therapeutic effects of non-surgical treatment, and (4) surveillance of recurrent tumors.
- There are many descriptions about the usefulness of FDG PET in Japanese clinical guidelines for various types of malignancy.
- Nationwide surveys of FDG PET performed every 5 years demonstrate the dramatic spread of this PET test in Japan due to wide coverage of FDG PET by public health insurance and commercial distribution of FDG.
- However, Japanese public health insurance does not cover FDG PET for evaluation of therapeutic effects except for malignant lymphoma.
- Unique application of FDG PET to cancer screening program is popular in Japan.

Although it is reported that FDG PET is a very useful tool in clinical oncology in the era of precision medicine, we should pile up reliable clinical evidence of this functional imaging test more and more and improve the contents about FDG PET in clinical guidelines for various kinds of cancer.

References

1. Suzuki C, Jacobsson H, Hatschek T, Torkzad MR, Boden K, Eriksson-Alm Y, et al. Radiologic measurements of tumor response to treatment: practical approaches and limitations. Radiographics. 2008;28(2):329–44. https://doi.org/10.1148/rg.282075068.
2. Ido T, Wan CN, Fowler JS, Wolf AP. Fluorination with molecular fluorine. A convenient synthesis of 2-deoxy-2-fluoro-D-glucose. J Org Chem. 1977;42(13):2341–2.
3. Yonekura Y, Benua RS, Brill AB, Som P, Yeh SD, Kemeny NE, et al. Increased accumulation of 2-deoxy-2-[^{18}F]Fluoro-D-glucose in liver metastases from colon carcinoma. J Nucl Med. 1982;23(12):1133–7.
4. Warburg O, Wind F, Negelein E. The metabolism of tumors in the body. J Gen Physiol. 1927;8(6):519–30. https://doi.org/10.1085/jgp.8.6.519.
5. Kubota K, Okasaki M, Minamimoto R, Miyata Y, Morooka M, Nakajima K, et al. Lesion-based analysis of ^{18}F-FDG uptake and ^{111}In-Pentetreotide uptake by neuroendocrine tumors. Ann Nucl Med. 2014;28(10):1004–10. https://doi.org/10.1007/s12149-014-0900-3.
6. Brierley J, Gospodarowicz MK, Wittekind C. TNM classification of malignant tumours. 8th ed. Chichester: Wiley-Blackwell; 2017.
7. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228–47. https://doi.org/10.1016/j.ejca.2008.10.026.
8. Van den Abbeele AD, Badawi RD. Use of positron emission tomography in oncology and its potential role to assess response to imatinib mesylate therapy in gastrointestinal stromal tumors (GISTs). Eur J Cancer. 2002;38(Suppl 5):S60–5. https://doi.org/10.1016/s0959-8049(02)80604-9.
9. Wahl RL, Jacene H, Kasamon Y, Lodge MA. From RECIST to PERCIST: evolving considerations for PET response criteria in solid tumors. J Nucl Med. 2009;50(Suppl 1):122S–50S. https://doi.org/10.2967/jnumed.108.057307.
10. The Japan Lung Cancer Society. Guidelines for diagnosis and treatment of the lung Cancer 2018. Tokyo: Kanehara; 2018.
11. Japan Society for Head and Neck Cancer. Japanese clinical practice guidelines for head and neck cancer 2018 (Japanese). Tokyo: Kanehara; 2017.

12. Hashiguchi Y, Muro K, Saito Y, Ito Y, Ajioka Y, Hamaguchi T, et al. Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2019 for the treatment of colorectal cancer. Int J Clin Oncol. 2020;25(1):1–42. https://doi.org/10.1007/s10147-019-01485-z.
13. Japanese Orthopaedic Association (JOA). Clinical practice guidelines on the management of soft tissue tumors 2020 (Japanese). Tokyo; 2020. https://www.joa.or.jp/topics/2019/files/guideline_2020.pdf. Accessed 30 Apr 2020.
14. Tsuchida T, Koga H, Uhara H, Kiyohara T, Takenouchi T, Anzai S, et al. Skin cancer clinical guidelines (version 2) (Japanese). Nihon Hifuka Gakkai Zasshi. 2015;125(1):5–75. https://doi.org/10.14924/dermatol.125.5.
15. Japanese Society of Hematology. Practical guidelines for hematological malignancies, 2018 (Japanese). Tokyo: Kanehara; 2018.
16. Nishiyama Y, Kinuya S, Kato T, Kayano D, Sato S, Tashiro M, et al. Nuclear medicine practice in Japan: a report of the eighth nationwide survey in 2017. Ann Nucl Med. 2019;33(10):725–32. https://doi.org/10.1007/s12149-019-01382-5.
17. Subcommittee on Survey of Nuclear Medicine Practice in Japan Japan Radioisotope Association. The present state of nuclear medicine practice in Japan—a report of the 8th nationwide survey in 2017—(Japanese with English abstract). Radioisotopes. 2018;67(7):339–87. https://doi.org/10.3769/radioisotopes.67.339.
18. Pinsky PF. Principles of cancer screening. Surg Clin North Am. 2015;95(5):953–66. https://doi.org/10.1016/j.suc.2015.05.009.
19. Ide M, Suzuki Y. Medical health club with clinical PET—a window on Japan. Eur J Nucl Med. 1996;23(12):1677–9. https://doi.org/10.1007/BF01249631.
20. Yasuda S, Shohtsu A. Cancer screening with whole-body ^{18}F-fluorodeoxyglucose positron-emission tomography. Lancet. 1997;350(9094):1819. https://doi.org/10.1016/s0140-6736(97)24051-1.
21. Yasuda S, Ide M, Fujii H, Nakahara T, Mochizuki Y, Takahashi W, et al. Application of positron emission tomography imaging to cancer screening. Br J Cancer. 2000;83(12):1607–11. https://doi.org/10.1054/bjoc.2000.1496.
22. Minamimoto R, Senda M, Uno K, Jinnouchi S, Iinuma T, Ito K, et al. Performance profile of FDG-PET and PET/CT for cancer screening on the basis of a Japanese Nationwide survey. Ann Nucl Med. 2007;21(9):481–98. https://doi.org/10.1007/s12149-007-0061-8.
23. Murano T, Minamimoto R, Senda M, Uno K, Jinnouchi S, Fukuda H, et al. Radiation exposure and risk-benefit analysis in cancer screening using FDG-PET: results of a Japanese nationwide survey. Ann Nucl Med. 2011;25(9):657–66. https://doi.org/10.1007/s12149-011-0511-1.

Chapter 2
The Role of ^{18}F-FDG-PET as Therapeutic Monitoring in Patients with Lung Cancer

Kyoichi Kaira

2.1 Introduction

In recent years, molecular targeted therapies such as epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI) and anaplastic lymphoma kinase (ALK) inhibitors have been proven to improve the treatment outcome and efficacy of patients with advanced non-small cell lung cancer (NSCLC) [1, 2]. Patients with advanced NSCLC harboring *EGFR* mutations who received EGFR-TKI (gefitinib, erlotinib, afatinib, and osimertinib) had a better prognosis than that in patients treated with platinum-based combination chemotherapy [1, 3, 4]. Although some targeting biomarkers are useful to predict the efficacy in patients administered suitable targeted drugs, there is no evidence of radiological modalities that provide early detection of response or non-response after the administration of molecular targeted therapy.

Recently, immunotherapy such as anti-programmed death-1 (PD-1)/programmed death-ligand 1 (PD-L1) antibodies has improved the clinical outcomes of patients with several types of cancers [5–7]. Clinical studies have also demonstrated that immune checkpoint inhibitors (ICIs) such as nivolumab, pembrolizumab, and atezolizumab provide significantly better prognosis in patients with previously treated NSCLC compared to docetaxel as standard treatment [5, 8, 9]. In advanced NSCLC patients with PD-L1 expression levels above 50%, pembrolizumab monotherapy was shown to have higher efficacy than that of platinum-based combination chemotherapy as first-line treatment [8]. However, the efficacy of ICIs differs according to PD-L1 expression level in patients with NSCLC [8]. The overall response rate (ORR) of ICI monotherapy is approximately 20% and approximately

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50% of patients with advanced NSCLC develop progressive disease (PD), indicating complete resistance to ICIs [5]. Therefore, early detection of ICI response for example, within 1 month, is critical. Previous evidence has demonstrated that computed tomography (CT) can differentiate responders from non-responders 9 weeks after ICI initiation [5]. At this time, progressive disease was observed in approximately 50% of NSCLC patients who received ICIs. Although it remains unknown whether positron emission tomography (PET) with 2′-deoxy-2′-[(18)F] fluoro-D-glucose (^{18}F-FDG) could be for the early detection of ICI efficacy, it may be a promising radiological modality compared to conventional evaluation such as CT.

This study discussed the usefulness and potential of PET as an imaging modality to predict the efficacy of molecularly targeted drugs and ICIs in patients with advanced NSCLC.

2.1.1 The Potential of ^{18}F-FDG-PET for Response Evaluation in EGFR-TKI

Patients with advanced NSCLC harboring sensitive *EGFR* mutations experience marked tumor shrinkage after the administration of EGFR-TKIs. However, it had remained unclear whether the response was significant in the early phase after treatment administration. Lee et al. recently reported the potential of ^{18}F-FDG-PET for early prediction of response to first-line treatment in 31 patients with advanced/metastatic NSCLC [10]. Their study included 26 patients administered cytotoxic regimens including platinum-based chemotherapy and five patients administered gefitinib. The authors concluded that ^{18}F-FDG-PET after one cycle of treatment could predict progressive disease earlier than standard radiographic assessment, but that an early metabolic response did not reflect better survival prognosis. However, there was no information on the role of the early prediction of response to gefitinib by ^{18}F-FDG-PET. Sunaga et al. described the potential of FDG-PET for early prediction of response to gefitinib in patients with advanced NSCLC [11]. The authors evaluated five patients with NSCLC for changes in ^{18}F-FDG uptake on day 2 and 4 weeks after the initiation of gefitinib treatment compared to ^{18}F-FDG-PET prior to therapy. Their results suggested that ^{18}F-FDG-PET could predict the therapeutic response to gefitinib at an early stage (day 2) regardless of preliminary assessment (Fig. 2.1). PET with both ^{18}F-FDG and 3′-[(18)F]fluoro-3′-deoxy-L-thymidine (FLT) was compared for the early prediction of nonprogression following erlotinib independent of EGFR mutation status in 34 patients with untreated stage IV NSCLC [12]. In that study, changes in ^{18}F-FDG uptake after 1 week of erlotinib could predict nonprogression after 6 weeks of therapy. Moreover, patients with an early metabolic response by FDG uptake had significantly longer progression-free survival (PFS) and overall survival (OS), whereas an early response by FLT predicted significantly longer PFS but not OS. The results of this study suggested the usefulness of early prediction by ^{18}F-FDG-PET to assess EGFR-TKI response. Benz et al. also reported that changes in FDG uptake at 2 weeks after the initiation of erlotinib

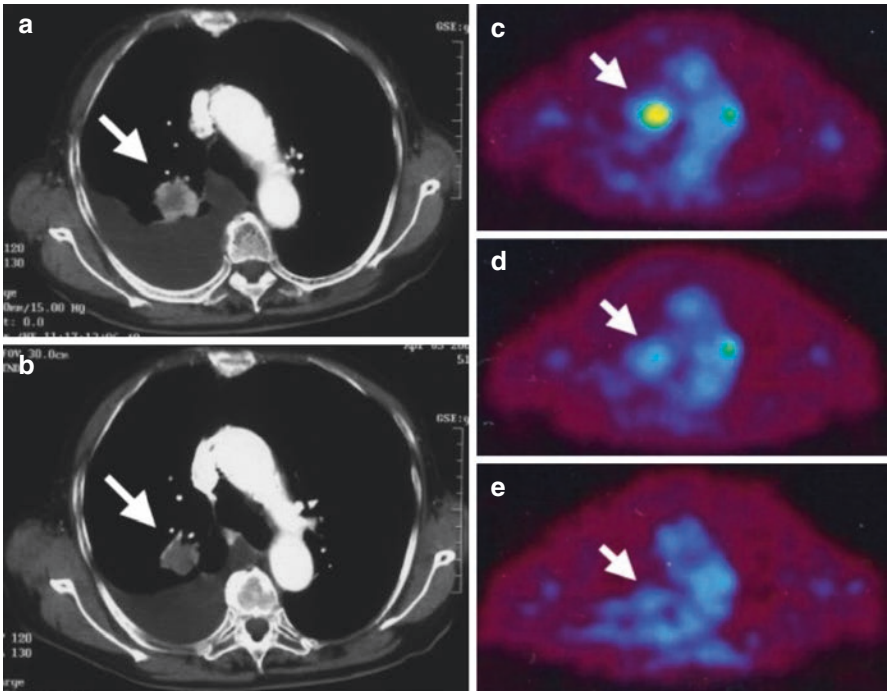

Fig. 2.1 A representative case referred from reference number 11 (Sunaga, et al.). The tumor in the right lung field (**a**, white arrow) yielded no shrinkage on CT after 4 weeks (**b**) from the start of gefitinib. FDG-PET corresponding to this tumor on CT showed increased accumulation (**c**, white arrow) before the initiation of gefitinib, then, the accumulation decreased on 2 days (**d**) and 4 weeks from the start of gefitinib (**e**)

treatment were helpful to identify patients who would benefit from EGFR-TKI [13]. Several previous studies support that the detection of early metabolic response by ^{18}F-FDG-PET can predict EGFR-TKI response in patients with advanced NSCLC. However, patients with NSCLC harboring *EGFR* mutations have a high response rate of approximately 70%; therefore, the prediction of tumor shrinkage by ^{18}F-FDG-PET at the early stage may be limited in daily practice. It is expected that ^{18}F-FDG-PET could predict a longer survival after the initiation of EGFR-TKI.

2.1.2 ^{18}F-FDG-PET in Angiogenetic Inhibitors

The combination of bevacizumab as a vascular epidermal growth factor (VEGF) inhibitor with cytotoxic chemotherapy significantly improved the response rate and PFS of patients with advanced non-squamous NSCLC [14]. Decreased ^{18}F-FDG uptake at 3 weeks from the start of bevacizumab plus erlotinib treatment was linked to a significantly favorable PFS in 47 patients with advanced non-squamous NSCLC [15]. Dingemans et al. also reported that a 30% decrease in maximal standardized

uptake value (SUV_{max}) by ^{18}F-FDG uptake at 3 weeks from the initiation of a combination chemotherapy of carboplatin and paclitaxel plus bevacizumab could identify responders compared to changes by CT in 223 patients with advanced non-squamous NSCLC [16]. Although little is known about the usefulness of ^{18}F-FDG-PET to predict the clinical benefit of bevacizumab as a single arm in patients with NSCLC, ^{18}F-FDG-PET may be useful to identify responders to angiogenetic inhibitors. Previous translational research showed a significant correlation between ^{18}F-FDG uptake and angiogenetic markers such as VEGF and microvessel density (MVD) in lung cancer [17]. Therefore, the amount of ^{18}F-FDG uptake within tumor cells reflects VEGF expression.

2.1.3 The Usefulness of ^{18}F-FDG-PET in Immunotherapy

According to two phase II studies, nivolumab as a single agent has a reported overall response rate (ORR) of approximately 20% and progressive disease (PD) rate of more than 40% in patients with previously treated NSCLC [5, 18]. In these studies, the ORR was initially assessed at 9 weeks after nivolumab administration. Therefore, it remains unknown whether tumor shrinkage appears in early phases such as 1 month after nivolumab initiation. When the therapeutic efficacy of nivolumab at 9 weeks was confirmed, approximately half of the patients who received ICI monotherapy had a therapeutic assessment of PD, contributing to their poor prognosis. Therefore, several studies reported the potential of ^{18}F-FDG-PET to predict the efficacy of ICI monotherapy at an early stage [19–21].

We have previously described that metabolic response by ^{18}F-FDG-PET was effective for the prediction of efficacy and survival at 1 month after nivolumab treatment initiation [19]. The predictive probability of partial response (100% versus 29%, $p = 0.021$) and progressive disease (100% versus 22.2%, $p = 0.002$) at 1 month after treatment initiation was significantly higher in ^{18}F-FDG-PET than in CT and ^{18}F-FDG uptake after nivolumab administration was an independent prognostic factor in multivariate analysis. Recently, Jreiqe et al. proposed the ratio of metabolic to morphological lesion volumes as a new ^{18}F-FDG-PET imaging biomarker to predict clinical benefit from ICI in NSCLC [20]. Although the clinical significance of therapeutic monitoring of early response following ICI administration by ^{18}F-FDG-PET remains uncertain, several studies have demonstrated its use for the assessment of ICI treatment efficacy [19, 20]. ^{18}F-FDG-PET may be a useful radiographic modality for immune monitoring to predict ICI efficacy; however, the optimal timing for assessing the efficacy and the measurement of ^{18}F-FDG uptake such as SUV_{max}, metabolic tumor volume (MTV) and total lesion glycolysis (TLG) remain unknown. We found that metabolic response according to ^{18}F-FDG uptake by measurement of TLG was a stronger biomarker for predicting response and survival at 1 month after nivolumab treatment than that of SUV_{max} and MTV [19]. Moreover, morphological changes on CT have a critical limitation in distinguishing between responders and non-responders. Figs. 2.2 and 2.3 show therapeutic monitoring by ^{18}F-FDG-PET. Several previous

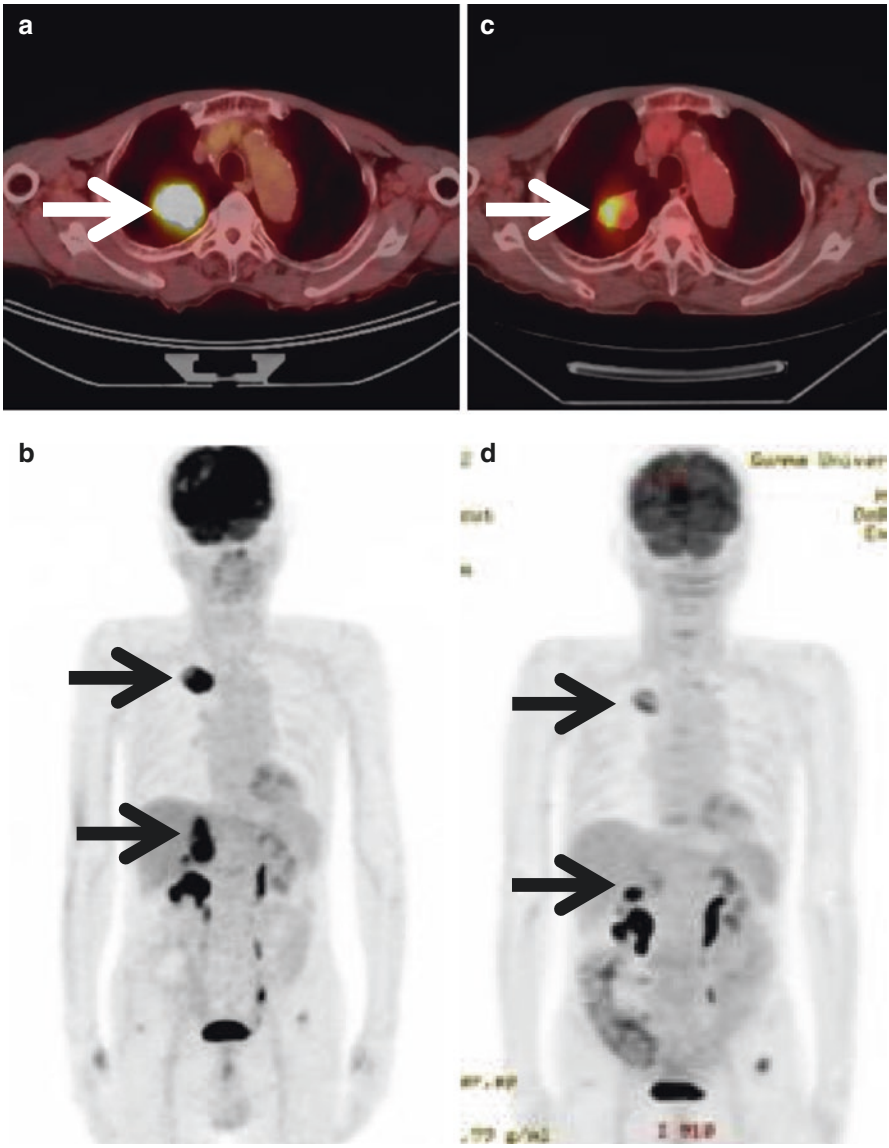

Fig. 2.2 A 74-year-old male with pulmonary squamous cell carcinoma who received nivolumab because of recurrence after platinum-based chemotherapy as first-line. PET imaging shows markedly decreased uptake of FDG in the primary site (white and black arrow) and right adrenal metastatic site (white arrow) between before (**a**, **b**) and after 1 month (**c**, **d**) from nivolumab initiation. The values of SUV_{max} in the primary and metastatic sites are 12.0 and 10.5, respectively, before nivolumab treatment, and 5.5 and 3.8, respectively, at 1 month after nivolumab

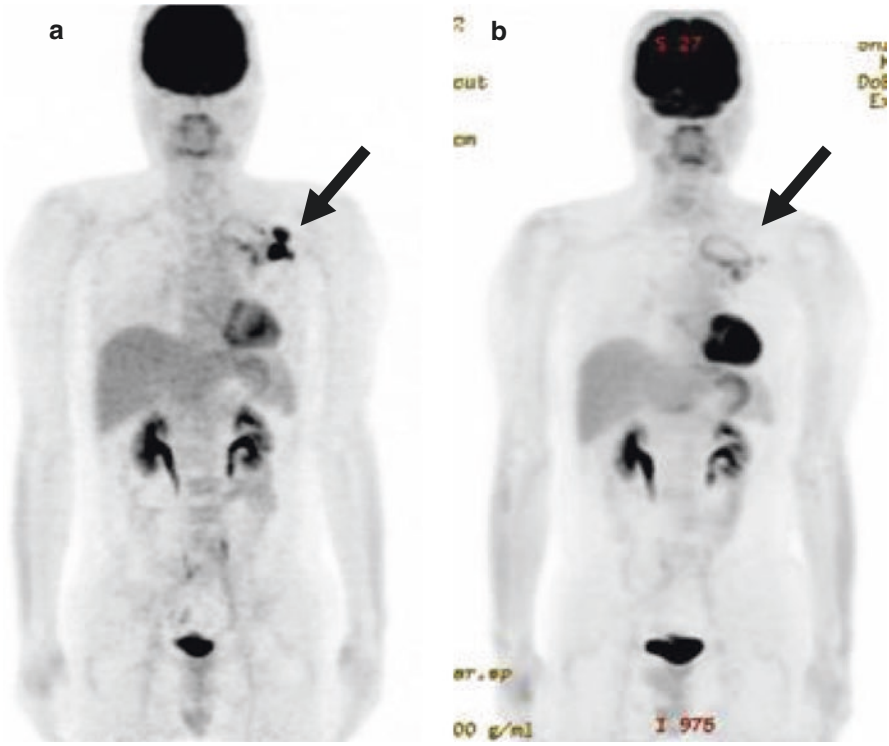

Fig. 2.3 A 48-year-old male with pulmonary adenocarcinoma who was treated with nivolumab as ninth-line treatment. PET imaging shows markedly decreased uptake of FDG in lymph node metastasis (black arrow) between before (**a**) and after 1 month (**b**) from nivolumab initiation. The values of SUV_{max} in the metastatic lesion before and after nivolumab are 17.1 and 1.9, respectively

studies included small sample sizes, which may have biased their results. Further investigation is warranted to assess the relationship between early ICI response and therapeutic efficacy and survival in patients with advanced or metastatic NSCLC.

2.1.4 The Relationship Between ^{18}F-FDG Uptake and PD-L1 Expression

PD-L1 expression within tumor cells is closely associated with tumor response after the administration of anti-PD-1/PD-L1 antibodies [5, 8, 9]. However, little is known about the relationship between PD-L1 expression and metabolic activity in human neoplasms. The mechanism by which tumor cells uptake ^{18}F-FDG requires glucose metabolism, hypoxia, and angiogenesis and the uptake of ^{18}F-FDG is closely associated with the expression of these markers [21]. Several researchers have reported

that PD-L1 expression is significantly related to the expression of glucose transporter 1 (Glut1) and hypoxia-inducible factor 1α (HIF-1α) in patients with pulmonary pleomorphic and renal cell carcinomas [22, 23]. The close correlation between SUV_{max} on ^{18}F-FDG uptake and PD-L1 expression in patients with NSCLC has been reported in different institutions [24–27]. A clinicopathological study with a large sample size of more than 500 patients with surgically resected NSCLC reported that high accumulation of ^{18}F-FDG was an independent predictor of PD-L1 positivity in multivariate analysis and a significant correlation between ^{18}F-FDG uptake and PD-L1 expression was observed regardless of histological type, including adenocarcinoma (AC) and squamous cell carcinoma (SQC) [24]. Two recent translational studies reported that PD-L1 expression was closely linked to the presence of glucose metabolism and hypoxia in patients with NSCLC [26, 27]. As the mechanism of ^{18}F-FDG uptake, HIF-1α is an essential factor linked to upregulated Glut1expression, which is supported by the evidence that suppression of HIF-1α decreased ^{18}F-FDG uptake and Glut1 expression [17]. Therefore, HIF-1α is an alternative marker for the measurement of ^{18}F-FDG accumulation. HIF-1α upregulation is significantly related to increased PD-L1 expression and contributes to the downregulation of T cell function and the activation of mitogen-activated protein kinase (MARK) and phosphoinositide 3-kinase (PI3K) signaling pathways as well as HIF-1 [28]. Moreover, HIF-1α directly binds to the hypoxia response element in the PD-L1 proximal promoter and controls its expression under hypoxic conditions [29]. Based on this evidence, PD-L1 is a potential marker for targeting HIF-1α and simultaneous inhibition of PD-L1 and HIF-1α may be a promising target for cancer immunotherapy. As there are a few reports regarding the relationship between PD-L1 and HIF-1α expression, further study is warranted to elucidate the detailed mechanism for the association between ^{18}F-FDG uptake and PD-L1 expression within tumor cells.

2.2 Future Directions of ^{18}F-FDG-PET as a Molecular Biomarker in Advanced NSCLC

^{18}F-FDG-PET is a useful radiographic modality for cancer diagnosis in relation to the presence of glucose metabolism of primary and metastatic lesions. Molecular imaging by ^{18}F-FDG-PET provides easy and clear visualization; thus, many oncologists usually utilize its modality in daily practice to assess the presence of recurrent sites and expansion of neoplasms, sometimes followed by pathological approaches. Although ^{18}F-FDG-PET is considered a cancer diagnostic device, its clinical significance for therapeutic monitoring of cancer treatment remains unclear. Among patients with different neoplasms, the clinical significance of therapeutic monitoring by ^{18}F-FDG-PET in those with malignant lymphoma has been established. However, the radiological role of ^{18}F-FDG-PET for therapeutic monitoring in patients with other cancers remains unclear.

The present review demonstrated that ^{18}F-FDG-PET may play a crucial role in the therapeutic monitoring of tumor response after the administration of molecularly targeted drugs, angiogenetic inhibitors, and ICIs in patients with NSCLC. Molecularly targeted therapies such as EGFR-TKI or combination chemotherapy including bevacizumab yielded better responses compared to those for other cytotoxic agents; therefore, evaluation of therapeutic response at an early stage from the start of any drugs may not be necessary. However, the ORR of anti-PD-1/PD-L1 antibodies as a single arm was approximately 20%, with a PD rate of more than 40%; thus, early detection of responders and non-responders is necessary to preserve the quality of life of patients with cancer. Considering the slight association between PD-L1 expression and ^{18}F-FDG uptake within tumor cells, ^{18}F-FDG-PET may be a useful modality for predicting the efficacy of cancer immunotherapy during the early phase from treatment initiation in patients with advanced NSCLC. Although metabolic indicators such as TLG or MTV for measurement of ^{18}F-FDG uptake may be better to measure tumor glucose metabolism than SUV_{max}, the development of established markers that accurately reflect the metabolic activity of ^{18}F-FDG accumulation is necessary. One future direction of ^{18}F-FDG-PET for therapeutic monitoring in addition to cancer diagnosis may be improvement of the efficacy of cancer treatment.

Amino acid PET tracers have been developed to overcome the limitation of false-positive findings on ^{18}F-FDG-PET [30–32]. PET imaging using these amino acid transporters exhibits higher specificity to detect malignant lesions than that using ^{18}F-FDG; however, the sensitivity to visualize tumor sites is higher in ^{18}F-FDG than that for amino acid tracers [30]. L-[3-^{18}F]-α-methyltyrosine (^{18}F-FAMT) has been developed as an amino acid tracer for PET imaging [33] and accumulates in tumor cells solely via L-type amino acid transporter 1 (LAT1) [30]. ^{18}F-FAMT is specific to neoplasms and ^{18}F-FAMT uptake was closely correlated with LAT1 expression in patients with NSCLC [30]. According to a recent report, ^{18}F-FAMT accumulation within the primary tumor is significantly linked to poor prognosis of NSCLC and ^{18}F-FAMT uptake was a stronger prognostic factor than ^{18}F-FDG uptake [34]. Since the clinical significance of the therapeutic monitoring of ^{18}F-FAMT-PET in advanced human neoplasms remains unknown, ^{18}F-FAMT-PET was recently compared to ^{18}F-FDG-PET regarding therapeutic response and outcome after systemic chemotherapy in 96 patients with advanced lung cancer [35]. Metabolic response and SUV_{max} in ^{18}F-FAMT-PET after one cycle of systemic chemotherapy were significantly associated with the response according to the Response Evaluation Criteria in Solid Tumors (RECIST) and metabolic response in ^{18}F-FAMT PET was an independent prognostic factor after one cycle of the first-line chemotherapy [35]. Therefore, ^{18}F-FAMT PET may be a useful radiographic modality for immune monitoring to predict ICI efficacy. Although ^{18}F-FAMT PET is an exploratory imaging modality, the relationship between PD-L1 expression and ^{18}F-FAMT accumulation within tumor cells requires further study. Moreover, further investigation is warranted to elucidate the biological association of PD-L1 with the upregulation of amino acid metabolism such as LAT1 within cancer cells.

2.3 Conclusion

^{18}F-FDG-PET is a useful modality for cancer diagnosis; moreover, its role will expand to therapeutic monitoring of cancer chemotherapy. While clinical data regarding the association between ICI treatment and glucose metabolism determined by ^{18}F-FDG uptake is immature, the clinical significance of therapeutic monitoring of the efficacy of ICI treatment by ^{18}F-FDG-PET in patients with lung cancer is expected to increase.

Key Points

- ^{18}F-FDG-PET is identified as a significant therapeutic monitoring on the molecular target agents, angiogenetic inhibitors, and immune checkpoint inhibitors in lung cancer patients.
- There are close relationship between ^{18}F-FDG uptake and PD-L1 expression within tumor cells.
- The changes in ^{18}F-FDG uptake were closely associated with an early response to immune checkpoint inhibitors in lung cancer.

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References

1. Maemondo M, Inoue A, Kobayashi K, Sugawara S, Oizumi S, Isobe H, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med. 2010;362:2380–8.
2. Kwak EL, Bang YJ, Camidge DR, Shaw AT, Solomon B, Maki RG, et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. N Engl J Med. 2010;363:1693–703.
3. Yang JC, Wu YL, Schuler M, Sebastian M, Popat S, Yamamoto N, et al. Afatinib versus cisplatin-based chemotherapy for EGFR mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): analysis of overall survival data from two randomised, phase 3 trials. Lancet Oncol. 2015;16:141–51.
4. Soria JC, Ohe Y, Vansteenkiste J, Reungwetwattana T, Chewaskulyong B, Lee KH, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. N Engl J Med. 2018;378:113–25.
5. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. N Engl J Med. 2015;373:1627–39.
6. Robert C, Long GV, Brady B, Dutriaux C, Maio M, Mortier L, et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med. 2015;372:320–30.
7. Motzer RJ, Escudier B, McDermott DF, George S, Hammers HJ, Srinivas S, et al. nivolumab versus everolimus in advanced renal-cell carcinoma. N Engl J Med. 2015;373:1803–13.
8. Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. N Engl J Med. 2016;375:1823–33.

9. Rittmeyer A, Barlesi F, Waterkamp D, Park K, Ciardiello F, von Pawel J, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet. 2017;389:255–65.
10. Lee DH, Kim SK, Lee HY, Lee SY, Park SH, Kim HY, et al. Early prediction of response to first-line therapy using integrated 18F-FDG PET/CT for patients with advanced/metastatic non-small cell lung cancer. J Thorac Oncol. 2009;4:816–21.
11. Sunaga N, Oriuchi N, Kaira K, Yanagitani N, Tomizawa Y, Hisada T, et al. Usefulness of FDG-PET for early prediction of the response to gefitinib in non-small cell lung cancer. Lung Cancer. 2008;59:203–10.
12. Zander T, Scheffler M, Nogova L, Kobe C, Engel-Riedel W, Hellmich M, et al. Early prediction of nonprogression in advanced non-small-cell lung cancer treated with erlotinib by using [(18)F]fluorodeoxyglucose and [(18)F]fluorothymidine positron emission tomography. J Clin Oncol. 2011;29:1701–8.
13. Benz MR, Herrmann K, Walter F, Garon EB, Reckamp KL, Figlin R, et al. (18)F-FDG PET/CT for monitoring treatment responses to the epidermal growth factor receptor inhibitor erlotinib. J Nucl Med. 2011;52:1684–9.
14. Niho S, Kunitoh H, Nokihara H, Horai T, Ichinose Y, Hida T, et al. Randomized phase II study of first-line carboplatin-paclitaxel with or without bevacizumab in Japanese patients with advanced non-squamous non-small-cell lung cancer. Lung Cancer. 2012;76:362–7.
15. Dingemans AM, de Langen AJ, van den Boogaart V, Marcus JT, Backes WH, Scholtens HT, et al. First-line erlotinib and bevacizumab in patients with locally advanced and/or metastatic non-small-cell lung cancer: a phase II study including molecular imaging. Ann Oncol. 2011;22:559–66.
16. de Jong EE, van Elmpt W, Leijenaar RT, Hoekstra OS, Groen HJ, Smit EF, et al. [18F]FDG PET/CT-based response assessment of stage IV non-small cell lung cancer treated with paclitaxel-carboplatin-bevacizumab with or without nitroglycerin patches. Eur J Nucl Med Mol Imaging. 2017;44:8–16.
17. Kaira K, Endo M, Abe M, Nakagawa K, Ohde Y, Okumura T, et al. Biologic correlates of ^{18}F-FDG uptake on PET in pulmonary pleomorphic carcinoma. Lung Cancer. 2011;71:144–50.
18. Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WE, Poddubskaya E, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med. 2015;373:123–35.
19. Kaira K, Higuchi T, Naruse I, Arisaka Y, Tokue A, Altan B, et al. Metabolic activity by $_{18}$F-FDG-PET/CT is predictive of early response after nivolumab in previously treated NSCLC. Eur J Nucl Med Mol Imaging. 2018;45:56–66.
20. Jreige M, Letovanec I, Chaba K, Renaud S, Rusakiewicz S, Cristina V, et al. $_{18}$F-FDG PET metabolic-to-morphological volume ratio predicts PD-L1 tumour expression and response to PD-1 blockade in non-small-cell lung cancer. Eur J Nucl Med Mol Imaging. 2019;46:1859–68.
21. Kaira K, Endo M, Abe M, Nakagawa K, Ohde Y, Okumura T, et al. Biologic correlation of 2-[18F]-fluoro-2-deoxy-D-glucose uptake on positron emission tomography in thymic epithelial tumors. J Clin Oncol. 2010;28:3746–53.
22. Chang YL, Yang CY, Lin MW, Wu CT, Yang PC. High co-expression of PD-L1 and HIF-1α correlates with tumour necrosis in pulmonary pleomorphic carcinoma. Eur J Cancer. 2016;60:125–35.
23. Ruf M, Moch H, Schraml P. PD-L1 expression is regulated by hypoxia inducible factor in clear renal cell carcinoma. Int J Cancer. 2016;139:396–403.
24. Takada K, Toyokawa G, Okamoto T, Baba S, Kozuma Y, Matsubara T, et al. Metabolic characteristics of programmed cell death-ligand 1-expressing lung cancer on ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography. Cancer Med. 2017;6:2552–61.
25. Zhang M, Wang D, Sun Q, Pu H, Wang Y, Zhao S, et al. Prognostic significance of PD-L1 expression and ^{18}F-FDG PET/CT in surgical pulmonary squamous cell carcinoma. Oncotarget. 2017;8:51630–40.

26. Kasahara N, Kaira K, Yamaguchi K, Masubuchi H, Tsurumaki H, Hara K, et al. Fluorodeoxyglucose uptake is associated with low tumor-infiltrating lymphocyte levels in patients with small cell lung cancer. Lung Cancer. 2019;134:180–6.
27. Kaira K, Shimizu K, Kitahara S, Yajima T, Atsumi J, Kosaka T, et al. 2-Deoxy-2-[fluorine-18] fluoro-d-glucose uptake on positron emission tomography is associated with programmed death ligand-1 expression in patients with pulmonary adenocarcinoma. Eur J Cancer. 2018;101:181–90.
28. Chen J, Jiang CC, Jin L, Zhang XD. Regulation of PD-1: a novel role of pro-survival signalling in cancer. Ann Oncol. 2016;27:409–16.
29. Noman MZ, Desantis G, Janji B, Hasmim M, Karray S, Dessen P, et al. PD-L1 is a novel direct target of HIF-1α, and its blockade under hypoxia enhanced MDSC-mediated T cell activation. J Exp Med. 2014;211:781–90.
30. Kaira K, Oriuchi N, Otani Y, Shimizu K, Tanaka S, Imai H, et al. Fluorine-18-alpha-methyltyrosine positron emission tomography for diagnosis and staging of lung cancer: a clinicopathologic study. Clin Cancer Res. 2007;13:6369–78.
31. Nishii R, Higashi T, Kagawa S, Kishibe Y, Takahashi M, et al. Diagnostic usefulness of an amino acid tracer, α-[N-methyl-^{11}C]-methylaminoisobutyric acid (11C-MeAIB), in the PET diagnosis of chest malignancies. Ann Nucl Med. 2013;27:808–21.
32. Leskinen-Kallio S, Ruotsalainen U, Någren K, Teräs M, Joensuu H, et al. Uptake of carbon-11-methionine and fluorodeoxyglucose in non-Hodgkin's lymphoma: a PET study. J Nucl Med. 1991;32:1211–8.
33. Tomiyoshi K, Amed K, Muhammad S, Higuchi T, Inoue T, Endo K, et al. Synthesis of isomers of 18F-labelled amino acid radiopharmaceutical: position 2- and 3-L-18F-alpha-methyltyrosine using a separation and purification system. Nucl Med Commun. 1997;18:169–75.
34. Kaira K, Oriuchi N, Shimizu K, Tominaga H, Yanagitani N, Sunaga N, et al. 18F-FMT uptake seen within primary cancer on PET helps predict outcome of non-small cell lung cancer. J Nucl Med. 2009;50:1770–6.
35. Kaira K, Higuchi T, Sunaga N, Arisaka Y, Hisada T, Tominaga H, et al. Usefulness of 18F-α-methyltyrosine PET for therapeutic monitoring of patients with advanced lung cancer. Anticancer Res. 2016;36:6481–90.

Chapter 3
F-18 FDG PET Tests in Breast Cancer

Rikako Hashimoto, Sadako Akashi-Tanaka, and Seigo Nakamura

Abbreviations

CT	Computed tomography (CT)
DM	Distant metastasis
ER	Estrogen receptor
FDG	Fluorodeoxyglucose
HER2	Human epithelial growth factor receptor 2
MG	Mammography (MG)
MRI	Magnetic resonance imaging
NAC	Neoadjuvant chemotherapy
PET	Positron emission tomography
PgR	Progesterone receptor
SUV	Standardized uptake value
SUVmax	Maximum SUV

3.1 Introduction

Breast cancer is the highest morbidity among women in the world. In Japan, it is also the highest morbidity rates. That age-specific morbidity trend peaked at 45–49, thereafter decreased with age in 2000–2010 [1]. The age-specific breast cancer mortality recently decreased older than 50s. The reasons of breast cancer mortality

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change may be improvement of diagnostic imaging modality and development of medications (endocrine therapy, chemotherapy, and molecular target drugs).

Perou et al. [2] have characterized gene expression profiling of breast cancer using cDNA microarray (gene expression profiling; GEP) and reported intrinsic subtypes classification based on GEP. Tumor morphology, proliferative ability, recurrence risk, and drug sensitivity differ among intrinsic subtypes. In recent years, alternative classification of intrinsic subtypes is defined using immunohistological definition and clinically it is widely used [3–5]. F-18 fluorodeoxyglucose positron emission tomography (FDG PET) can quantitatively assess and make an image mirroring tumor glucose metabolism as tumor activity differences among intrinsic subtype.

In this issue, We reviewed the positioning of FDG PET, dbPET, and some other possible radiopharmaceuticals in the management of breast cancer.

3.1.1 FDG Uptake Trend

3.1.1.1 FDG Uptake Trend of Normal or Benign Breast Tissue

On FDG PET, breast cancer with overexpression of the glucose transporter tends to show a high FDG uptake than normal mammary gland. On the other hand, when we read FDG PET images, it is very important to consider accumulation in normal mammary glands. The accumulation in normal mammary gland depends on the changes of their environments such as hormone status, age, and menstrual cycle. Individual differences in the concentration of normal mammary gland and benign changes associated with lactation and mastopathy also affect mammary uptake of FDG. Kumar et al. [6] reported on normal mammary gland, dense breast apparently showing higher FDG uptake (SUVs peak and average) compared to non-dense breast ($P = 0.003$ and 0.003, respectively). In the study, reported by Lin C. Y. et al. [7], there was no high-level FDG uptake in the normal breast tissues in menopause women without using exogenous hormones and in proliferative phase women the intensity of FDG uptake significantly correlated with normal breast tissues and menstrual cycle ($P < 0.001$). Moreover, lactating mammary gland takes significantly high FDG uptake because of the changes in hormone levels, development of mammary gland tissue with edema and inflammation [8]. About 60% of women have fibrocystic change in the breast, this would be assumed as change with estrogen and progesterone levels. Fibrocystic change is classified as non-proliferative lesions (fibrosis, fluid-filled cysts, apocrine metaplasia of the ductal epithelium, and adenoma) and proliferative adenosis (sclerosing adenosis, ductal epithelial hyperplasia, lobular epithelial hyperplasia) on pathological findings [9]. According to Tateishi U et al. [10], diffuse FDG accumulation in the background mammary gland is associated with fibrocystic change on FDG PET/CT. Litmanovich D et al. [11] analyzed 4038 women who underwent FDG PET/CT. In this study, 33 (0.82%) patients had unexpected FDG accumulation in the breast, 17 of 30 patients were

diagnosed with breast cancer, and 13 with benign; there was a borderline statistically significant difference in FDG uptake between malignant (3.13 +/− 2.25) and benign (1.85 +/− 1.18) lesions ($p = 0.05$).

3.1.1.2 The Association Between FDG Uptake and Histology or Prognostic Factors

First, breast cancer is classified into noninvasive cancer and invasive cancer. Second, histological type of invasive breast cancer is classified into invasive ductal carcinoma (53–75%), invasive lobular carcinoma (5–16%), and special types of invasive breast cancer [12–14]. FDG PET has high sensitivity and specificity for the detection of malignant lesions.

According to a meta-analysis on 13 published articles evaluating whole-body FDG PET and breast cancer detection performed by Samson et al. [15], FDG PET was 88% sensitive and 80% specific for breast cancer. False-negative detection by FDG PET and PET/CT is related to smaller size, histologic low-growing and well-differentiated histologic types; moreover, FDG uptake (SUVmax) is significantly correlated with pathological and immunohistological factors [16–21] (Table 3.1). However, due to the limited spatial resolution of PET, most of the breast tumors smaller than 10 mm are usually missed by PET. The PET/CT has spatial resolutions of approximately 4 mm [22]. Kumar and colleagues [23] showed a sensitivity of 23% in primary breast cancers, smaller than 10 mm.

Generally, invasive lobular carcinoma (ILC) shows lower sensitivity and SUVmax than invasive ductal carcinoma (IDC) on FDG PET or PET/CT [16–18, 24–26]. The reasons are caused by histopathological features such as diffuse scattering growth patterns, lower tumor cellularity, low glucose transporter 1 (GLUT-1) expression, and low proliferation rate [18, 27, 28].

One retrospective study by Molly P. H. et al. [29] compared the upstage rates by FDG PET and PET/CT between ILC ($n = 88$) and IDC ($n = 89$) of Stage III. The relative risk of PET/CT revealing unsuspected distant metastases in stage III IDC patients was 1.98 times (95% confidence interval, 0.98–3.98, $P = 0.049$) higher than ILC patients.

Poor prognostic factors including larger (≧2 cm) tumor size, negative estrogen receptor (ER), negative progesterone receptor (PgR), higher Ki67, and high histological grade are correlated with high-level SUVmax [16–21].

HER2 positive is known as one of the poor prognostic factors. However, HER2 positivity was not correlated with high SUVmax [16, 17, 20, 21] except for one analysis [18]. Higuchi et al. [30] analyzed the association between SUVmax and immunohistological subtypes in the 387 breast cancer patients, retrospectively. In this study, SUVmax of ER+/HER2+ (median: 5.15, 25–75 percentiles: 3.08–8.54, $p < 0.0001$), ER−/HER2+ (4.36, 2.73–9.08, $p = 0.0005$), and ER−/HER2− (6.30, 3.59–8.22, $p < 0.0001$) were significantly higher compared with those of ER+/HER2− (2.90, 1.70–5.10). In most of the studies, triple-negative breast cancer

Table 3.1 Correlation of primary tumor PET/CT FDG uptake with clinicopathologic prognostic factors in invasive carcinoma of the breast

		Characteristics SUVmax (mean ± SD)/P_{SUVmax}													
Study/Year	No. of patients	Tumor size		Histological type		ER Negative Positive		PgR Negative Positive		HER2 Negative Positive		Ki67 Low (<14%) High (≥14%)		Histological or nuclear grade	
Heudel et al. (2010) [16]	IDC37, ILC8	0.7–19.5 1.2–16.5 (T1 or T2)	*	1.2–19.5 0.7–2.9	**	2.4–19.5 0.7–11.7	**	0.7–7.8 0.9–19.5	**	1.2–10.1 0.7–19.5	n.s.	N/A		1.2–10.1 0.7–19.5 2.7–19.5	**
Jo et al. (2015) [21]	IDC96	2.8 ± 1.4 4.3 ± 2.1 (1 < T≦2, >2)	**	N/A		4.0 ± 1.9 3.2 ± 1.9	*	4.2 ± 1.9 3.0 ± 1.7	*	3.4 ± 1.8 4.1 ± 2.1	n.s.	2.9 ± 1.4 4.3 ± 2.2	**	3.0 ± 0.9 3.7 ± 2.1 (G1 or 2,3)	**
Ugurluer G. et al. (2016) [17]	IDC112 ILC27	4.5 ± 0.8 6.7 ± 0.4 (1 < T≦2, >2)	*	6.6 ± 0.4 4.7 ± 0.8	*	8.7 ± 0.7 5.4 ± 0.4	**.	8.0 ± 0.6 5.4 ± 0.4		5.9 ± 0.4 6.8 ± 0.6	n.s.	N/A		3.3 ± 1.5 5.4 ± 0.6 7.0 ± 0.5	**
Song et al. (2011) [20]	IDC55	1.8 ± 0.9 3.7 ± 2.0 7.2 ± 4.1 12.4 ± 5.0 (T1b, 1c, 2 or 3)	*	N/A		4.5 ± 3.4 10.3 ± 5.0	**	4.3 ± 2.7 10.4 ± 5.4	**	7.8 ± 5.9 5.6 ± 4.0	n.s.	N/A		2.1 ± 0.6 3.9 ± 2.1 8.0 ± 4.0	**
Shigeto U. et al. (2008) [18]	IDC136 ILC9 Others7	3.3 + 2.7 5.8 + 3.6 (≦2, >2)	**	4.8 + 3.5 1.4 + 1.5 (IDC or ILC)	**	4.0 + 3.0 6.4 + 4.1	**	4.1 + 2.9 5.4 + 4.2	*	4.0 + 3.1 6.2 + 4.2	**	N/A		2.9 + 3.0 4.8 + 2.4 6.2 + 3.5	**
Lee et al. (2018) [19]	IDC89	3.5 (2.7–4.6) 7.1 (5.9–8.6) (1 < T≦2, >2)	**	N/A		6.5 (5.2–8.1) 4.4 (3.4–5.5)	*	6.7 (5.3–8.1) 4.2 (3.3–5.4)	**	5.1 (4.1–6.2) 6.1 (4.6–8.0)	n.s.	3.5 (2.9–4.2) 7.4 (5.9–8.9)	**	3.3 (2.5–4.2) 5.8 (4.8–6.8 (G1 or 2,3)	**

*: $p < 0.05$, **: $p < 0.01$
n.s. Not significant
IDC Invasive ductal carcinoma, *ILC* Invasive lobular carcinoma

(ER−/HER2−) reported as showing highest SUVmax level compared with the other subtypes [16, 21, 24, 31–34].

3.1.2 Staging and Detection of Distant Metastases

3.1.2.1 Locoregional Staging with FDG PET or PET/CT

Breast cancer metastasizes in the ipsilateral axillary lymph nodes as a first site. Evaluation of the axillary lymph node before surgery is definitely diagnosed by performing cytology if the metastasis is suspected by US and CT. About 30% of cases diagnosed as cN0 by US or CT changes positive when sentinel lymph node biopsy (SNB) is performed [35]. Diagnostic performance for axillary lymph node metastasis by FDG PET and PET/CT tends to be lower sensitive and higher specificity. In the systematic review for assessment of axillary lymph node status in early breast cancer on FDG PET, Cooper et al. [36] reported that across 26 studies (n = 2591 patients), the mean sensitivity was 63% (95% confidence interval (CI): 52–74%; range 20–100%) and mean specificity was 94% (95% CI: 91–96%; range 75–100%). Mean sensitivity was 11% (5–22%) for micro-metastases (≦2 mm; five studies; n = 63) and 57% (47–66%) for macro-metastases (>2 mm; four studies; n = 111). Clinical N3 diagnosis (infra- or supraclavicular and internal mammary nodes) is very important for operable patients because it is strongly related to the treatment procedure and the determination of radiation area. Groheux [37] reported that ^{18}F-FDG PET/CT confirmed N3 nodal involvement in stage 3C patients and revealed 32% unsuspected N3 in 117 local advanced breast cancer patients; therefore, they had lymph node dissection and radiation fields were adapted on the basis of the PET/CT results.

3.1.2.2 Role of Staging with FDG PET or PET/CT

Routine systemic staging is not indicated for early breast cancer in absence of symptoms. When signs or symptoms exist in operative breast cancer patient (within stage3C), the staging is directed to add conventional modalities (CT, MRI, US, chest X-P, bone scan), and using PET/CT is optional and limited by National Comprehensive Cancer Network (NCCN) guidelines (Table 3.2) [38]. In the study by Bonner ME and colleagues [39], median sensitivity/specificity for distant metastasis were 78.0%/91.4% with combined conventional imaging, bone scintigraphy 98.0%/93.5%, chest X-ray 100%/97.9%, liver ultrasound 100%/96.7%, CT chest/abdomen 100%/93.1%, FDG PET 100.0%/96.5%, FDG PET/CT 100%/98.1%, respectively. From those results, FDG PET and PET/CT is sufficiently useful if they are used for distant metastasis diagnosis.

In early operable breast cancer patients, there are certain cases diagnosed as distant metastasis unexpectedly by systemic staging tests [40–43] (Table 3.3).

Table 3.2 Recommended systemic imaging tests to evaluate distant metastasis for breast cancer patients (Modified from National Comprehensive Cancer Network (NCCN) guidelines)

	Recommended systemic imaging tests to evaluate distant metastasis
Preoperative workup (initial clinical stage1–3)	Consider additional studies only if directed by signs or symptoms • Chest diagnostic CT with contrast (if pulmonary symptoms present) • Abdominal ± pelvic diagnostic CT with contrast or MRI with contrast indicated if elevated alkaline phosphatase, abnormal liver function tests, abdominal symptoms or abdominal physical examination of the abdomen or pelvis • Bone scan indicate if localized bone pain or elevated alkaline phosphatase or sodium fluoride PET/CT (category 2B) • FDG PET/CT[a,b] (optional)
Recurrent or stage 4	• Chest diagnostic CT with contrast Abdominal±pelvic diagnostic CT with contrast or MRI with contrast • Bone scan or sodium fluoride PET/CT[c] (category 2B) • Spine MRI, brain MRI with contrast if suspicious, symptoms. • FDG PET/CT[a, b] (optional)

[a]FDG PET/CT is not indicated in the staging of clinical stage I, II or operable stage III breast cancer. FDG PET/CT is most helpful in situations where standard staging studies are equivocal or suspicious, especially in the setting of locally advanced or metastatic disease

[b]FDG PET/CT may also be helpful in identifying unsuspected regional nodal disease and/or distant metastases in locally advanced breast cancer when used in addition to standard staging studies

[c]If FDG PET/CT is performed and clearly indicates bone metastasis, on both the PET and CT component, bone scan or sodium fluoride PET/CT may not be needed

Table 3.3 Upstaged rates to stage 4 by PET/CT in operable breast cancer patients

	Initial stage						
	Stage1	Stage2A	Stage2B	Stage3A	Stage3B	Stage3C	Total upstaged rates to stage 4
Riedl et al. 2014 [40] *n* = 134 (only younger than 40 y)	5% (1/20)	5% (2/44)	17% (8/47)	31% (4/13)	50% (4/8)	50% (1/2)	14.9% (20/134)
Ulaner et al. 2016 [41] *n* = 232 (only TN breast cnacer)	0% (0/23)	5% (4/82)	15% (13/87)	17% (4/23)	57% (8/14)	33% (1/3)	12.9% (30/232)
Caballero Ontanaya et al. 2012 [42] *n* = 254	N/R	2.3% (1/44)	10.7% (6/56)	17.5% (11/63)	36.5% (27/74)	47.1% (8/17)	20.8% (53/254)
Yararbas et al. 2018 [66] *n* = 234	0% (0/3)	18.6% (7/43)	30.3% (18/66)	46.3% (24/82)	68.8% (10/16)	20.8% (5/24)	27.3% (64/234)
David et al. 2011 [43] *n* = 131	N/R	2.8% (1/36)	8.3% (4/48)	21.3% (10/47)	N/R	N/R	11.4% (14/131)

N/R Not reported

According to the studies, 8–30% breast cancer patients in stage 2B were revealed distant metastasis by PET/CT. If operable early breast cancer patients upstage to stage 4, the management of treatment will be modified.

Gnerlich et al. [44] reported that younger women (younger than 40 years of age) diagnosed with early-stage breast cancer had higher breast cancer mortality rate compared with older women, stage 1 (adjusted HR (aHR) = 1.44; CI: 1.27–1.64), stage 2 (aHR = 1.09; CI: 1.03–1.15), and stage 4 disease (aHR = 0.85; CI: 0.76–0.95). Riedl CC and colleagues [40] reported on asymptomatic breast cancer patients younger than 40 years of age, PET/CT revealed distant metastases in 17% of asymptomatic stage IIB. According to this study, the systemic staging for asymptomatic younger patients with early breast cancer would be more important than older patients.

Breast cancer subtypes are strongly correlated to prognosis and high-grade breast cancer, even if they are in early stage, require accurate staging and qualified treatment options. Jones et al. [45] reported that 10-year outcomes differed by breast cancer subtype, with early-stage (stage1 and 2) TN and HER2 subtypes having the worse overall, disease-free and distant metastasis-free survival. In the study by Ulaner GA and colleagues [41], 15% (n = 13/87) initial stage 2B triple-negative breast cancer patients revealed distant metastasis by PET/CT, and they have significantly shorter survival compared to initial stage 2B patients not upstaged (3 years Kaplan Meier estimate 33%, 95% CI: 13–55 vs. 97%, CI: 76–93, $p < 0.0001$).

3.1.3 Evaluation for Recurrence and Follow-Up

For postoperative breast cancer patients, there is no significant difference in survival rate and recurrence-free survival rate between only MMG and intensive follow-up using conventional imaging (US, CT, MRI). Moreover, no significant difference was found in subgroup analysis according to age, tumor diameter, and lymph node metastasis status [46]. In meta-analysis including 12 studies, 5045 patients [47], pooling data showed 40% of isolated locoregional recurrences diagnosed during routine visits or routine tests in asymptomatic patients (95% CI: 35–45). Even if distant metastasis or relapse is detected in very early stage, very few patients will be cured, unfortunately [48]. Cochet et al. [49] reported that 30 (21%) of 142 preoperative patients were upstaged by PET/CT, including 12 (8%) from stage II or III to stage IV. On the other hand, 23 patients (16%) were downstaged by PET/CT, including 4 (3%) from stage IV to stage II or III.

Among distant metastasis of breast cancer, bone metastasis is the most frequent in metastatic organs of breast cancer. Accurate diagnosis and monitoring for bone metastasis is important to decrease the risk of fracture and loss of quality of life due to pain. There are osteoblastic and osteolytic changes in breast cancer bone metastasis. Conventionally, screening of bone metastases has used bone scan (BS) with $^{99\,m}$Tc-methylene bisphosphonate. Bone scintigraphy relies on the

osteoblastic response to bone destruction by cancer cells. Moreover, benign processes (such as osteoarthritis, fractures, and degenerative changes) may lead to a high false-positive rate and decrease the specificity of BS [50]. FDG PET can detect both osteoblastic and osteolytic change [51]. In the meta-analysis across seven studies (668 patients) [52], sensitivity and specificity for detection of bone metastases in breast cancer patients of PET/CT were 93% (95% CI: 82–98%) and 99% (95% CI: 95–100%), and that of bone scintigraphy were 81% (95% CI: 58–93%) and 96% (95% CI: 76–100%), respectively. In addition to lesion detection and staging, it is feasible to quantify skeletal tumor burden using FDG PET [53, 54]. Ana et al. [53] reported that skeletal tumor burden was significantly and independently associated with overall survival ($p < 0.0001$) and progression-free survival ($p < 0.0001$).

3.1.4 Breast PET

Dedicated breast PET (dbPET) scans were included in the Japanese medical insurance coverage from July 2013 under the combination with whole-body PET on the same day. dbPET scanners are classified into two types: Opposing detector type and ring-shaped detector type. The former is positron emission tomography (PEM) and the latter is tomographic technique performed with ring-shaped scanner. Furthermore, ring-shaped detectors are classified into two basic types: C-shaped type and O-shaped type. The PEM compresses the breast like X-ray mammography and it is possible to obtain multiple plane slices with a mobile detector. On the other hand, with the newly developed ring-shaped scanner with arranged detectors circumferentially, it is possible to image the breast in the sitting position or supine position, comparable to the tomographic images of MRI and create MIP images.

The dbPET has shown higher sensitivity than whole-body PET, especially small tumors less than 10 mm and noninvasive lesions. Nishimatsu et al. [55] reported a study comparing of sensitivity and specificity of dbPET and whole-body PET/CT for a total of 179 histologically proven breast cancer lesions. In the study, lesion-based sensitivity of dbPET and whole-body PET/CT were 92% and 88%, respectively ($p = 0.06$). SUVmax mean of dbPET and whole-body PET/CT were 13.0 ± 9.7 and 6.4 ± 4.8, respectively ($p < 0.0001$). Raylman and colleagues [56] performed Positron emission mammography-guided breast biopsy and reported its potential for guiding the biopsy of breast lesions optimally detected with PEM. We studied the sensitivity and utility of preoperative breast cancer patient with O type ring-shaped detector (Elmammo®) (Fig. 3.1). The image mirrored the pathological invasive and ductal component.

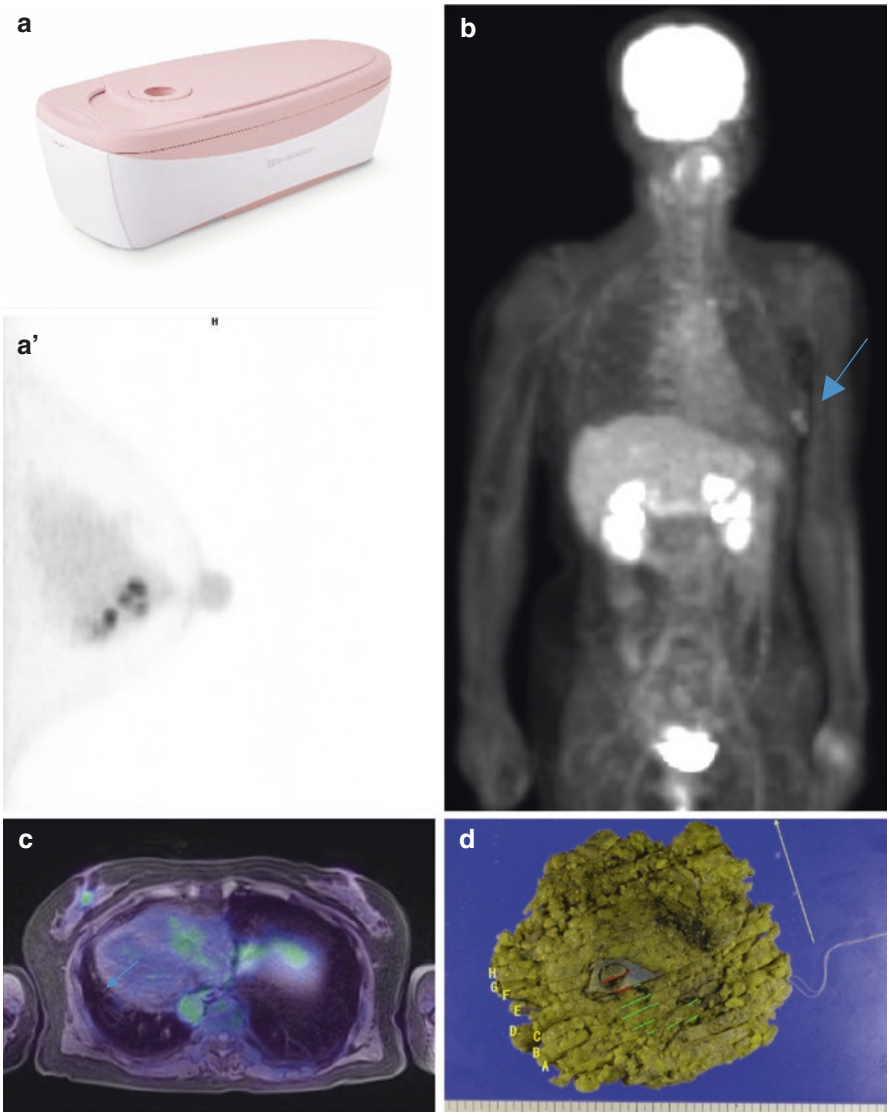

Fig. 3.1 Comparison between FDG uptake of each FDG PET, PET/MRI, and dbPET. 60-year-old woman with Lt. invasive ductal carcinoma. (**a**, **a′**) dbPET (Elmammo®) and imaging: Multiple FDG hot spots in lower bottom area from nipple to peripheral site (SUVmax5.81). (**b**, **c**) Whole-body FDG PET and FDG PET/MRI: Lower FDG hot spot in Lt breast (SUVmax 1.8). (**d**) Pathological findings: invasive ductal carcinoma (Red: 1.5 cm invasive lesion, Green: 4.5 cm ductal carcinoma in situ) ER90%, PgR30%, HER2 1+, Ki67 2o%. *Source:* Hashimoto R. et al. The usefulness and future aspect of Dedicated Breast Positron Emission Tomography in the clinical settings. Shiniryo 2016, 43(11), 33

3.1.5 Evaluation of Treatment Response

3.1.5.1 Evaluation of Neoadjuvant Setting

There are mainly two purposes of neoadjuvant chemotherapy (NAC) for breast cancer patients. First, it is to reduce the tumor volume and to increase the chance of breast-conserving surgery. The second is to enable to have surgery for inoperable patients by downstage as well as the improvement of long-term prognosis.

Breast cancer patients who achieved pathological complete response (pCR) after NAC have better prognosis than those with non-pCR. Moreover, if we can diagnose precisely pCR after NAC, they could avoid surgery in the future.

In a meta-analysis by Chen et al. [57], for PET/CT and breast MRI, the pooled sensitivity was 87% (95% CI: 71–95%) and 79% (95% CI: 68–87%), respectively. The diagnostic performance of PET/CT is similar to that of MRI for the assessment of breast cancer response to NAC.

Sometimes, it is difficult to evaluate accurately pCR or non-pCR by imaging, due to pathological changes with the response to chemotherapy, including inflammation, fibrosis, and edema in tumor. Breast MRI has been generally used to assess the response to NAC.

3.1.5.2 Early Evaluation of Response to NAC

The optimal parameters for evaluating response to NAC have not been determined yet and varied among subtypes. SUVmax, SUVmean, SUVpeak, metabolic tumor volume (MTV), and total lesion glycolysis (TLG) have been used as the imaging parameters of PET/CT for NAC. Groheux et al. [58] reported that the mean change in SUVmax (ΔSUVmax) after two cycles of NAC in triple-negative breast cancer was 72% in patients who achieved PCR vs. 42% in patients who did not ($P < 0.0001$). There was no significant difference in the evaluation parameter's AUC (AUC for ΔSUVmax vs. ΔSUVpeak). In HER2-positive phenotype, absolute SUVmax (or SUVpeak) values at PET imaging after two cycles of chemotherapy (AUC for each cycle, 0.93) were better correlated with pCR than ΔSUVmax (AUC, 0.78; $P = 0.11$) or ΔTLG (AUC, 0.62; $P = 0.005$). Cheng et al. [59] showed similar results in the HER2-positive group, ΔSUV could predict neither overall nor ALN pCR. Hence, the ΔSUV after two cycles of neoadjuvant therapy could predict pCR in HER2-negative patients treated with Cytotoxic NAC alone.

PET/CT has superior specificity to MRI [94% (95% CI: 78–98%) vs. 83% (95% CI: 81–87%), respectively, $p = 0.015$]. When the second imaging scan is performed before three cycles of NAC, PET/CT is similar or more sensitive than MRI and more specific [57, 60]. In recent years, several clinical trials with response guided design using the early evaluation of FDG PET have been attempted (Table 3.4). In the AVATAXHER trial [61], patients with HER2-positive breast cancer who received

Table 3.4 Clinical trials to evaluate early response of neoadjuvant chemotherapy or endocrine therapy

Study	Target patients	Protocol	*N*	Timing of InterimPET	pCR %	PET parameter
AVATAXHER Coudert et al. (2014) [61] in France	Stage T2/3, N 0/1 HER2:+		*142*	*After 1 cycle*	*24%*[*a] *43.8%*[*b] *53.6%* [*c]	*ΔSUVmax*
Groheux et al. (2016) [67] in France	Triple-negative With stage 2 & 3	4 cycles of epirubicin + cyclophosphamide followed by 4 cycles of docetaxel at conventional doses [*d] Or Dose-intensified, dose-dense concomitant regimen of epirubicin + cyclophosphamide for six cycles[*e]	22[*d] 55[*e] (77)	*After 2 cycles* *After 2 cycles*	22% [*d] 44%[*e] *P* = 0.078	ΔSUVmax[a]after two cycles (pCR: 72% vs. Non Pcr 42%; *P* = 0.0001)
TBCRC008 Connolly et al. (2015) [68] in USA	HER2:− With stage 2–3	12 weeks of preoperative carboplatinand + weekly nab-paclitaxel + Vorinostator[*f] or placebo[*g]	6[*f] 12[*g] (18)	*After 1 cycle*	25.8%[*f] 29.0%[*g]	ΔSUVmax LBM[a] (SUmax)
Ueda S. et al. (2011) [69] in Japan	ER: +	Letrozole for 12 weeks	12	4 weeks after	NA Responder 6	ΔSUVmax

[a]Lean body mass

neoadjuvant trastuzumab plus docetaxel scanned PET/CT after two cycle. When ΔSUV is less than 70%, which means low likelihood of achieving pCR, patients were randomized to receive two more cycles of the same regimen or to receive adding bevacizumab. As a result, adding bevacizumab rose pCR rate from 24.0 to 42.5% of the same regimen group. This means early evaluation of response using FDG PET is effective to reach higher pCR rates by optimizing regimen in breast cancer.

Early prediction of monitoring the response to chemotherapy or endocrine therapy is important for optimal management by improving the ability to individual therapies, such as avoiding ineffective chemotherapy or additional effective one in nonresponding patients [62].

3.1.5.3 Other Promising Tracers for Breast Cancer

In recent years, various tracers such as ^{18}F-fluoro-L thymidine (FLT), 16α–:^{18}F-fluoro-17β-estradiol (FES), and ^{64}Cu-DOTA-trastuzumab have been developed for specific molecular targets in breast cancer [63]. Although approximately 70% of breast cancers are hormone receptor positive, not every HR-positive tumor respond to endocrine therapy. FES was developed as a receptor ligand for ER [64]. FES PET can reflect ER status. There is a report suggesting the usefulness of FES-dbPET in evaluating the neoadjuvant endocrine treatment [65]. FES PET and these new tracers would predict the response to each therapy and could advance personalized treatment.

Summary and Key Points

We overviewed the important roles of FDG PET in current clinical breast oncology in this chapter. We have described the roles and features of FDG PET in each of the clinical settings that are diagnosis, staging, recurrence assessment, evaluation for response to chemotherapy, and prognosis prediction.

The following are key points to understand the contents of this review.

- FDG uptake trend of normal, benign breast tissue and histological factors of breast cancer.
- The roles of FDG PET for breast cancer patients are as follows: (1) locoregional or systemic staging, (2) Dedicated breast PET, (3) evaluation for recurrence and follow-up, and (4) evaluation of therapeutic effects.
- Routine systemic staging is not indicated for early breast cancer in the absence of symptoms. However high-grade breast cancer subtypes such as triple-negative or HER2 are required accurate staging and qualified treatment options, even if they are in early stage.
- Dedicated breast PET has been developed to find small tumors less than 10 mm and noninvasive lesions and shown higher sensitivity than whole-body PET.
- In japan, evaluation of therapeutic effects of breast cancer is not covered with Japanese public health insurance. However, achieving pathological complete response after neoadjuvant chemotherapy shows better prognosis than non-

pCR. Therefore, in recent years, several clinical trials with response guided design using the early evaluation of FDG PET have been attempted and various tracers have been developed for specific molecular targets in breast cancer.

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References

1. Katanoda K, Hori M, Matsuda T, et al. An updated report on the trends in cancer incidence and mortality in Japan, 1958-2013. Jpn J Clin Oncol. 2015;45(4):390–401.
2. Perou CM, Sorlie T, Eisen MB, et al. Molecular portraits of human breast tumours. Nature. 2000;406(6797):747–52.
3. Goldhirsch A, Winer EP, Coates AS, et al. Personalizing the treatment of women with early breast cancer: highlights of the St Gallen international expert consensus on the primary therapy of early breast Cancer 2013. Ann Oncol. 2013;24(9):2206–23.
4. Curigliano G, Burstein HJ, et al. De-escalating and escalating treatments for early-stage breast cancer: the St. Gallen international expert consensus conference on the primary therapy of early breast Cancer 2017. Ann Oncol. 2017;28(8):1700–12.
5. Coates AS, Winer EP, Goldhirsch A, et al. Tailoring therapies—improving the management of early breast cancer: St Gallen international expert consensus on the primary therapy of early breast Cancer 2015. Ann Oncol. 2015;26(8):1533–46.
6. Kumar R, Mitchell S, Alavi A. 18F-FDG uptake and breast density in women with normal breast tissue. J Nucl Med. 2004;45(8):1423; author reply −4.
7. Lin CY, Ding HJ, Liu CS, Chen YK, Lin CC, Kao CH. Correlation between the intensity of breast FDG uptake and menstrual cycle. Acad Radiol. 2007;14(8):940–4.
8. Hicks RJ, Binns D, Stabin MG. Pattern of uptake and excretion of (18)F-FDG in the lactating breast. J Nucl Med. 2001;42(8):1238–42.
9. Guinebretiere JM, Menet E, Tardivon A, Cherel P, Vanel D. Normal and pathological breast, the histological basis. Eur J Radiol. 2005;54(1):6–14.
10. Tateishi U, Terauchi T, Akashi-Tanaka S, et al. Comparative study of the value of dual tracer PET/CT in evaluating breast cancer. Cancer Sci. 2012;103(9):1701–7.
11. Litmanovich D, Gourevich K, Israel O, Gallimidi Z. Unexpected foci of 18F-FDG uptake in the breast detected by PET/CT: incidence and clinical significance. Eur J Nucl Med Mol Imaging. 2009;36(10):1558–64.
12. Fisher ER, Gregorio RM, Fisher B, Redmond C, Vellios F, Sommers SC. The pathology of invasive breast cancer. A syllabus derived from findings of the National Surgical Adjuvant Breast Project (protocol no. 4). Cancer. 1975;36(1):1–85.
13. Rosen PP. The pathological classification of human mammary carcinoma: past, present and future. Ann Clin Lab Sci. 1979;9(2):144–56.
14. Ellis IO, Galea M, Broughton N, Locker A, Blamey RW, Elston CW. Pathological prognostic factors in breast cancer. II. Histological type. Relationship with survival in a large study with long-term follow-up. Histopathology. 1992;20(6):479–89.
15. Samson DJ, Flamm CR, Pisano ED, Aronson N. Should FDG PET be used to decide whether a patient with an abnormal mammogram or breast finding at physical examination should undergo biopsy? Acad Radiol. 2002;9(7):773–83.
16. Heudel P, Cimarelli S, Montella A, Bouteille C, Mognetti T. Value of PET-FDG in primary breast cancer based on histopathological and immunohistochemical prognostic factors. Int J Clin Oncol. 2010;15(6):588–93.

17. Ugurluer G, Yavuz S, Calikusu Z, et al. Correlation between 18F-FDG positron-emission tomography 18F-FDG uptake levels at diagnosis and histopathologic and immunohistochemical factors in patients with breast cancer. J Breast Health. 2016;12(3):112–8.
18. Ueda S, Tsuda H, Asakawa H, et al. Clinicopathological and prognostic relevance of uptake level using 18F-fluorodeoxyglucose positron emission tomography/computed tomography fusion imaging ([18]F-FDG PET/CT) in primary breast cancer. Jpn J Clin Oncol. 2008;38(4):250–8.
19. Lee SJ, Chung MS, Shin SJ, Choi YY. Correlation of tumor uptake on breast-specific gamma imaging and fluorodeoxyglucose PET/CT with molecular subtypes of breast cancer. Medicine. 2018;97(43):e12840.
20. Song BI, Hong CM, Lee HJ, et al. Prognostic value of primary tumor uptake on F-18 FDG PET/CT in patients with invasive ductal breast Cancer. Nucl Med Mol Imaging. 2011;45(2):117–24.
21. Jo I, Zeon SK, Kim SH, et al. Correlation of primary tumor FDG uptake with clinicopathologic prognostic factors in invasive ductal carcinoma of the breast. Nucl Med Mol Imaging. 2015;49(1):19–25.
22. Kumar R, Rani N, Patel C, Basu S, Alavi A. False-negative and false-positive results in FDG-PET and PET/CT in breast cancer. PET Clin. 2009;4(3):289–98.
23. Kumar R, Chauhan A, Zhuang H, Chandra P, Schnall M, Alavi A. Clinicopathologic factors associated with false negative FDG-PET in primary breast cancer. Breast Cancer Res Treat. 2006;98(3):267–74.
24. Groheux D, Giacchetti S, Moretti JL, et al. Correlation of high [18]F-FDG uptake to clinical, pathological and biological prognostic factors in breast cancer. Eur J Nucl Med Mol Imaging. 2011;38(3):426–35.
25. Fujii T, Yajima R, Kurozumi S, et al. Clinical significance of [18]F-FDG-PET in invasive lobular carcinoma. Anticancer Res. 2016;36(10):5481–5.
26. Gil-Rendo A, Martinez-Regueira F, Zornoza G, Garcia-Velloso MJ, Beorlegui C, Rodriguez-Spiteri N. Association between [[18]F]fluorodeoxyglucose uptake and prognostic parameters in breast cancer. Br J Surg. 2009;96(2):166–70.
27. Jung NY, Kim SH, Choi BB, Kim SH, Sung MS. Associations between the standardized uptake value of [18]F-FDG PET/CT and the prognostic factors of invasive lobular carcinoma: in comparison with invasive ductal carcinoma. World J Surg Oncol. 2015;13:113.
28. Bos R, Hoeven JJMVD, Wall EVD, et al. Biologic correlates of [18]fluorodeoxyglucose uptake in human breast cancer measured by positron emission tomography. J Clin Oncol. 2002;20(2):379–87.
29. Hogan MP, Goldman DA, Dashevsky B, et al. Comparison of [18]F-FDG PET/CT for systemic staging of newly diagnosed invasive lobular carcinoma versus invasive ductal carcinoma. J Nucl Med. 2015;56(11):1674–80.
30. Higuchi T, Nishimukai A, Ozawa H, et al. Prognostic significance of preoperative [18]F-FDG PET/CT for breast cancer subtypes. Breast (Edinburgh, Scotland). 2016;30:5–12.
31. Koolen BB, Vrancken Peeters MJ, Wesseling J, et al. Association of primary tumour FDG uptake with clinical, histopathological and molecular characteristics in breast cancer patients scheduled for neoadjuvant chemotherapy. Eur J Nucl Med Mol Imaging. 2012;39(12):1830–8.
32. Sasada S, Masumoto N, Suzuki E, et al. Prediction of biological characteristics of breast cancer using dual-phase FDG PET/CT. Eur J Nucl Med Mol Imaging. 2019;46(4):831–7.
33. Garcia Vicente AM, Soriano Castrejon A, Leon Martin A, et al. Molecular subtypes of breast cancer: metabolic correlation with [18]F-FDG PET/CT. Eur J Nucl Med Mol Imaging. 2013;40(9):1304–11.
34. Kitajima K, Fukushima K, Miyoshi Y, et al. Association between (1)(8)F-FDG uptake and molecular subtype of breast cancer. Eur J Nucl Med Mol Imaging. 2015;42(9):1371–7.
35. Krag DN, Anderson SJ, Julian TB, et al. Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial. Lancet Oncol. 2010;11(10):927–33.
36. Cooper KL, Harnan S, Meng Y, et al. Positron emission tomography (PET) for assessment of axillary lymph node status in early breast cancer: a systematic review and meta-analysis. Eur J Surg Oncol. 2011;37(3):187–98.

37. Groheux D, Giacchetti S, Delord M, et al. ^{18}F-FDG PET/CT in staging patients with locally advanced or inflammatory breast cancer: comparison to conventional staging. J Nucl Med. 2013;54(1):5–11.
38. Network NCC. Breast Cancer (version1.2019); 2019.
39. Brennan ME, Houssami N. Evaluation of the evidence on staging imaging for detection of asymptomatic distant metastases in newly diagnosed breast cancer. Breast (Edinburgh, Scotland). 2012;21(2):112–23.
40. Riedl CC, Slobod E, Jochelson M, et al. Retrospective analysis of 18F-FDG PET/CT for staging asymptomatic breast cancer patients younger than 40 years. J Nucl Med. 2014;55(10):1578–83.
41. Ulaner GA, Castillo R, Goldman DA, et al. (18)F-FDG-PET/CT for systemic staging of newly diagnosed triple-negative breast cancer. Eur J Nucl Med Mol Imaging. 2016;43(11):1937–44.
42. Caballero Ontanaya L, Hindie E, Delord M, et al. Prognostic impact of (18)FDG-PET-CT findings in clinical stage III and IIB breast cancer. J Natl Cancer Inst. 2012;104(24):1879–87.
43. Groheux D, Giacchetti S, Espie M, et al. The yield of 18F-FDG PET/CT in patients with clinical stage IIA, IIB, or IIIA breast cancer: a prospective study. J Nucl Med. 2011;52(10):1526–34.
44. Gnerlich JL, Deshpande AD, Jeffe DB, Sweet A, White N, Margenthaler JA. Elevated breast cancer mortality in women younger than age 40 years compared with older women is attributed to poorer survival in early-stage disease. J Am Coll Surg. 2009;208(3):341–7.
45. Jones T, Neboori H, Wu H, et al. Are breast cancer subtypes prognostic for nodal involvement and associated with clinicopathologic features at presentation in early-stage breast cancer? Ann Surg Oncol. 2013;20(9):2866–72.
46. Moschetti I, Cinquini M, Lambertini M, Levaggi A, Liberati A. Follow-up strategies for women treated for early breast cancer. Cochrane Database Syst Rev. 2016;(5):Cd001768.
47. de Bock GH, Bonnema J, van der Hage J, Kievit J, van de Velde CJ. Effectiveness of routine visits and routine tests in detecting isolated locoregional recurrences after treatment for early-stage invasive breast cancer: a meta-analysis and systematic review. J Clin Oncol. 2004;22(19):4010–8.
48. Hortobagyi GN. Can we cure limited metastatic breast cancer? J Clin Oncol. 2002;20(3):620–3.
49. Cochet A, David S, Moodie K, et al. The utility of 18 F-FDG PET/CT for suspected recurrent breast cancer: impact and prognostic stratification. Cancer Imaging. 2014;14:13.
50. Tryciecky EW, Gottschalk A, Ludema K. Oncologic imaging: interactions of nuclear medicine with CT and MRI using the bone scan as a model. Semin Nucl Med. 1997;27(2):142–51.
51. Abe K, Sasaki M, Kuwabara Y, et al. Comparison of 18FDG-PET with 99mTc-HMDP scintigraphy for the detection of bone metastases in patients with breast cancer. Ann Nucl Med. 2005;19(7):573–9.
52. Rong J, Wang S, Ding Q, Yun M, Zheng Z, Ye S. Comparison of 18 FDG PET-CT and bone scintigraphy for detection of bone metastases in breast cancer patients. A meta-analysis. Surg Oncol. 2013;22(2):86–91.
53. Brito AE, Santos A, Sasse AD, et al. 18F-fluoride PET/CT tumor burden quantification predicts survival in breast cancer. Oncotarget. 2017;8(22):36001–11.
54. Etchebehere EC, Araujo JC, Fox PS, Swanston NM, Macapinlac HA, Rohren EM. Prognostic factors in patients treated with 223Ra: the role of skeletal tumor burden on baseline 18F-fluoride PET/CT in predicting overall survival. J Nucl Med. 2015;56(8):1177–84.
55. Nishimatsu K, Nakamoto Y, Miyake KK, et al. Higher breast cancer conspicuity on dbPET compared to WB-PET/CT. Eur J Radiol. 2017;90:138–45.
56. Raylman RR, Majewski S, Weisenberger AG, et al. Positron emission mammography-guided breast biopsy. J Nucl Med. 2001;42(6):960–6.
57. Chen L, Yang Q, Bao J, Liu D, Huang X, Wang J. Direct comparison of PET/CT and MRI to predict the pathological response to neoadjuvant chemotherapy in breast cancer: a meta-analysis. Sci Rep. 2017;7(1):8479.
58. Groheux D, Majdoub M, Sanna A, et al. Early metabolic response to neoadjuvant treatment: FDG PET/CT criteria according to breast cancer subtype. Radiology. 2015;277(2):358–71.
59. Cheng J, Wang Y, Mo M, et al. 18F-fluorodeoxyglucose (FDG) PET/CT after two cycles of neoadjuvant therapy may predict response in HER2-negative, but not in HER2-positive breast cancer. Oncotarget. 2015;6(30):29,388–95.

60. Sheikhbahaei S, Trahan TJ, Xiao J, et al. FDG-PET/CT and MRI for evaluation of pathologic response to neoadjuvant chemotherapy in patients with breast cancer: a meta-analysis of diagnostic accuracy studies. Oncologist. 2016;21(8):931–9.
61. Coudert B, Pierga JY, Mouret-Reynier MA, et al. Use of [(18)F]-FDG PET to predict response to neoadjuvant trastuzumab and docetaxel in patients with HER2-positive breast cancer, and addition of bevacizumab to neoadjuvant trastuzumab and docetaxel in [(18)F]-FDG PET-predicted non-responders (AVATAXHER): an open-label, randomised phase 2 trial. Lancet Oncol. 2014;15(13):1493–502.
62. Thomas E, Holmes FA, Smith TL, et al. The use of alternate, non-cross-resistant adjuvant chemotherapy on the basis of pathologic response to a neoadjuvant doxorubicin-based regimen in women with operable breast cancer: long-term results from a prospective randomized trial. J Clin Oncol. 2004;22(12):2294–302.
63. Kurihara H, Shimizu C, Miyakita Y, et al. Molecular imaging using PET for breast cancer. Breast Cancer (Tokyo, Japan). 2016;23(1):24–32.
64. Yoo J, Dence CS, Sharp TL, Katzenellenbogen JA, Welch MJ. Synthesis of an estrogen receptor beta-selective radioligand: 5-[18F]fluoro-(2R,3S)-2,3-bis(4-hydroxyphenyl) pentanenitrile and comparison of in vivo distribution with 16alpha-[18F]fluoro-17beta-estradiol. J Med Chem. 2005;48(20):6366–78.
65. Jones EF, Ray KM, Li W, et al. Initial experience of dedicated breast PET imaging of ER+ breast cancers using [F-18]fluoroestradiol. NPJ Breast Cancer. 2019;5:12.
66. Yararbas U, Avci NC, Yeniay L, Argon AM. The value of 18F-FDG PET/CT imaging in breast cancer staging. Bosn J Basic Med Sci. 2018;18(1):72–9.
67. Groheux D, Biard L, Giacchetti S, et al. (1)(8)F-FDG PET/CT for the early evaluation of response to neoadjuvant treatment in triple-negative breast cancer: influence of the chemotherapy regimen. J Nucl Med. 2016;57(4):536–43.
68. Connolly RM, Leal JP, Goetz MP, et al. TBCRC 008: early change in 18F-FDG uptake on PET predicts response to preoperative systemic therapy in human epidermal growth factor receptor 2-negative primary operable breast cancer. J Nucl Med. 2015;56(1):31–7.
69. Ueda S, Tsuda H, Saeki T, et al. Early metabolic response to neoadjuvant letrozole, measured by FDG PET/CT, is correlated with a decrease in the Ki67 labeling index in patients with hormone receptor-positive primary breast cancer: a pilot study. Breast Cancer (Tokyo, Japan). 2011;18(4):299–308.

Chapter 4
F-18 FDG PET Tests in Head and Neck Cancer

Masahiro Kikuchi

4.1 FDG PET/CT for HNSCC

4.1.1 Utility During Initial Staging

4.1.1.1 T Staging

For T staging, contrast-enhanced magnetic resonance imaging (MRI) or CT is generally preferred over FDG PET/CT because the resolution of the latter is relatively poor. However, PET/CT is superior in the detection of bone invasion. Li et al. reported that the mean sensitivity and specificity of PET/CT for the detection of mandibular invasion were 83% and 90%, respectively [1]. Therefore, PET/CT is more useful than MRI or CT for T stage assessment in cases of oral/oropharyngeal carcinoma with clinically suspected mandibular invasion. Moreover, hybrid PET/MRI or fused PET/MRI may be superior to PET/CT because of lesser influence from dental artifacts [2] (Fig. 4.1a).

4.1.1.2 N Staging

PET/CT is useful for clinical N staging [3, 4], with a meta-analysis [4] showing sensitivity and specificity values of 79% [95% confidence interval (CI): 72–85%] and 86% (95% CI: 83–89%), respectively.

However, the detection of occult lymph node (LN) metastasis by PET/CT remains a diagnostic challenge in clinically node-negative (cN0) cases of HNSCC subjected to clinical examinations such as neck palpation, CT, MRI, and

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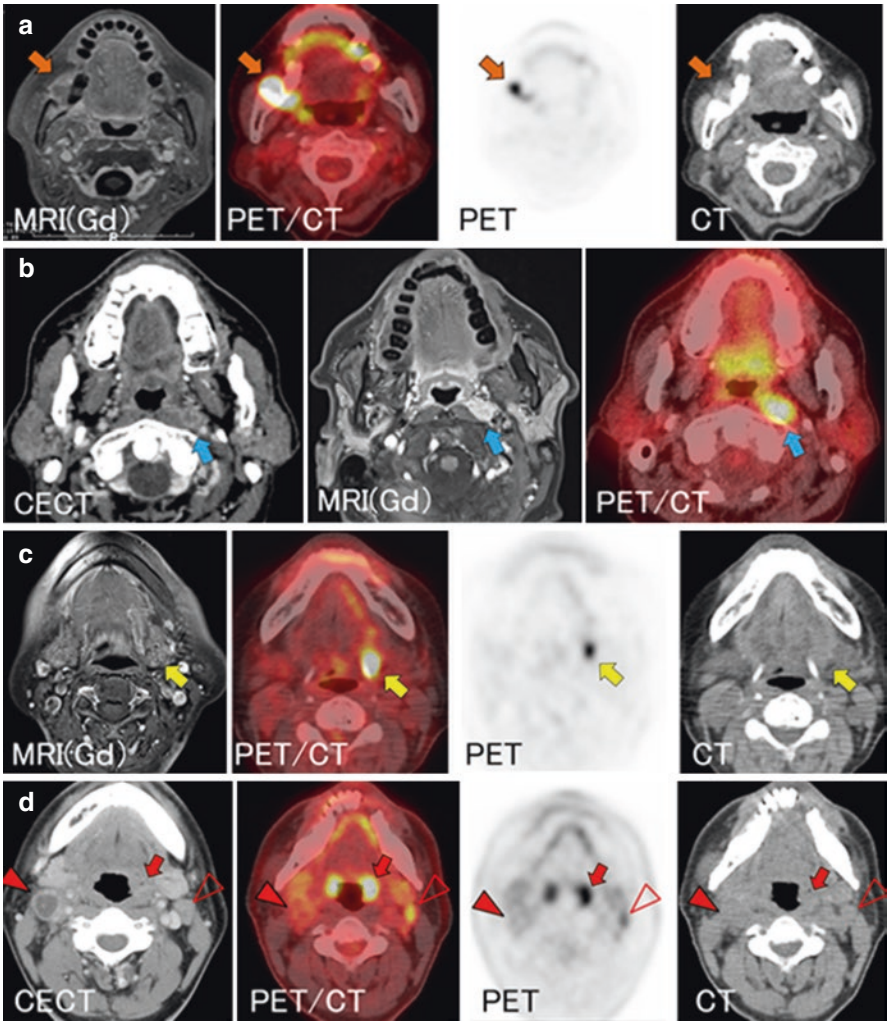

Fig. 4.1 Initial staging of head and neck cancer using PET/CT. (**a**) An 85-year-old woman with a right lower gingival SCC (UICC eighth edition: cT4aN1M0). Contrast-enhanced MRI (left), PET/CT (second left), PET (second right), and CT (right). PET/CT clearly shows the tumor which invades into the mandible (orange arrow). (**b**) A 62-year-old man with a p16-positive oropharyngeal SCC involving the left tonsil. Contrast-enhanced CT (left), contrast-enhanced MRI (middle), and PET/CT (right) were performed. Retropharyngeal node metastasis on the left side (blue arrow) is most clearly identified by PET/CT, followed by MRI and CT. (**c**) A 79-year-old woman with a left tongue SCC (UICC eighth edition: cT4aN2bM0). Contrast-enhanced MRI (left), PET/CT (second left), PET (second right), and CT (right). A lateral lingual lymph node on the left side (yellow arrow) is not detected by contrast-enhanced MRI, while it is clearly identified by PET/CT. (**d**) A 52-year-old man with a left p16 positive oropharyngeal SCC (UICC eighth edition: cT1N2M0). Contrast-enhanced CT (left), PET/CT (second left), PET (second right), and CT (right). The primary tumor was in the left palatine tonsil (red arrow) with bilateral cervical lymph node metastases (arrowhead and hollow arrowhead). Contrast-enhanced CT shows cystic lymph node metastasis on the right side (arrowhead). This lymph node is not FDG-avid on PET/CT. In contrast, metastatic lymph node on the left side (hollow arrowhead) is clearly identified by contrast-enhanced CT and PET/CT

ultrasonography [5]. In a recently reported meta-analysis of 18 studies including 1044 patients with cN0 HNSCC, the pooled sensitivity, specificity, positive predictive value, and negative predictive value of PET or PET/CT for the detection of occult cervical LN metastasis were 58% (95% CI: 42–72%), 87% (95% CI: 79–92%), 62% (95% CI: 55–69%), and 83% (95% CI: 79–86%), respectively [6]. Thus, the sensitivity was low while the specificity was moderate. The authors suggested that elective neck dissection should be considered when the pretest probability of LN metastasis is 30% because the posttest probability would be as high as 87% as per the level analysis [6]. In a recently reported prospective, nonrandomized, multicenter cohort study of PET/CT performed for 212 patients with clinical T2–T4N0 HNSCC (oral cavity, oropharynx, and larynx), the sensitivity, specificity, positive predictive value, and negative predictive value specific to visual assessments for the clinical N0 sides were 75%, 64%, 56%, and 87%, respectively [7]. The authors suggested that PET/CT may assist the clinician in making decisions about the optimal treatment for clinically N0 neck (elective neck dissection or observation) in HNSCC [7].

In addition, PET/CT is extremely useful for the detection of retropharyngeal LNs [8] or lingual LNs [9], which are located outside the boundaries of routine neck dissections (Figs. 4.1b,c). The most common primary tumor site associated with retropharyngeal LN metastasis is the nasopharynx, followed by the posterior pharyngeal wall. Lingual LN metastases mostly originate from tumors in the oral cavity.

Clinicians should note that necrotic LNs are occasionally overlooked by PET/CT because of the lack of FDG uptake by the necrotic tissue. Oropharyngeal carcinoma with HPV positivity has been proposed as an additional factor for cystic/necrotic LN transformation [10] (Fig. 4.1d), and contrast-enhanced PET/CT may be better than nonenhanced PET/CT for the detection of cystic LN metastasis in such cases [11].

4.1.1.3 M Staging

The lung is the most frequent site of distant metastasis (approximately 70% cases), followed by the bone and liver [12]. The incidence of brain metastases is only 0.4%; however, it can increase to 2–8% if distant metastases are already present at other sites [13].

In a meta-analysis of 12 studies involving the use of PET/CT for the detection of distant metastasis and second primary cancers before and after treatment in patients with HNSCC, the pooled sensitivity and specificity values were 89% (95% CI: 80–95%) and 93% (95% CI: 91–95%), respectively [14]. Subgroup analysis showed similar pooled estimates for initial staging and restaging.

PET/CT is also useful for the diagnosis of pulmonary nodules; however, it should be noted that small lung nodules measuring <1 cm are often non-FDG-avid and can result in false-negative findings [15].

4.1.2 Utility for the Diagnosis of Primary Unknown Carcinoma with Cervical Node Metastasis

The term HNSCC of unknown primary (HNSCCUP) is used for cases of HNSCC with cervical node metastasis where the primary site cannot be identified after initial clinical evaluation. It accounts for 2–10% of all presenting HNSCCs [16].

PET/CT is highly recommended for the identification of the primary site in HNSCCUP [17]. In a meta-analysis of seven studies with 246 cases of HNSCCUP subjected to PET/CT for the detection of primary sites, the primary tumor detection rate and the sensitivity and specificity of PET/CT were 44% (95% CI: 31–58%), 97% (95% CI: 63–99%), and 68% (95% CI: 49–83%), respectively [18].

In patients whose primary sites are not initially detected but finally known, the most common primary site is the tonsil (lateral tonsil or base of tongue), which is associated with HPV infection (Figs. 4.2a, b). HPV is occasionally detected in metastatic cervical LNs; the expression of its surrogate marker p16 in metastatic cervical LNs can help in the identification of oropharyngeal primary lesions in patients with HNSCCUP [19]. In a systematic review of 14 studies including 416 patients with HNSCCUP who underwent palatine tonsillectomies, occult tonsillar malignancies were identified in 34% patients [20]. Among these, 89% lesions were ipsilateral, 1% were contralateral, and 10% were synchronous bilateral. Therefore, bilateral palatine tonsillectomy is recommended for the identification of the primary lesion. Other primary sites include the hypopharynx (Fig. 4.2c) and nasopharynx. Confirmation by panendoscopy and biopsy after PET/CT is of utmost importance [16].

4.1.3 Utility for the Detection of Recurrence

4.1.3.1 Early Detection of Recurrence and Superiority to CT and MRI

Despite aggressive treatment, the locoregional recurrence rate is as high as 45% [21], and most recurrences develop within the first 2 years after treatment [22]. The prognosis of patients with recurrent HNSCC is poor, with a median survival duration of <1 year [23]; however, the average 5-year survival rate was found to be 39% if salvage surgery was successfully performed for the recurrence [24]. Thus, early detection of recurrent lesions is important because it may improve the curative salvage treatment [25]. PET/CT is beneficial for the early detection of recurrence and can facilitate appropriate salvage treatments for recurrences [26].

Furthermore, PET/CT is superior to CT or MRI in the detection of recurrent lesions [3]. In a meta-analysis of 1195 patients with residual or recurrent HNSCC, the pooled sensitivity and specificity of PET or PET/CT for the detection of residual or recurrent disease at the primary site were 86% (95% CI: 80–91%) and 82% (95% CI: 79–85%), respectively. These values were 72% (95% CI: 63–80%) and 88% (95% CI: 85–91%),

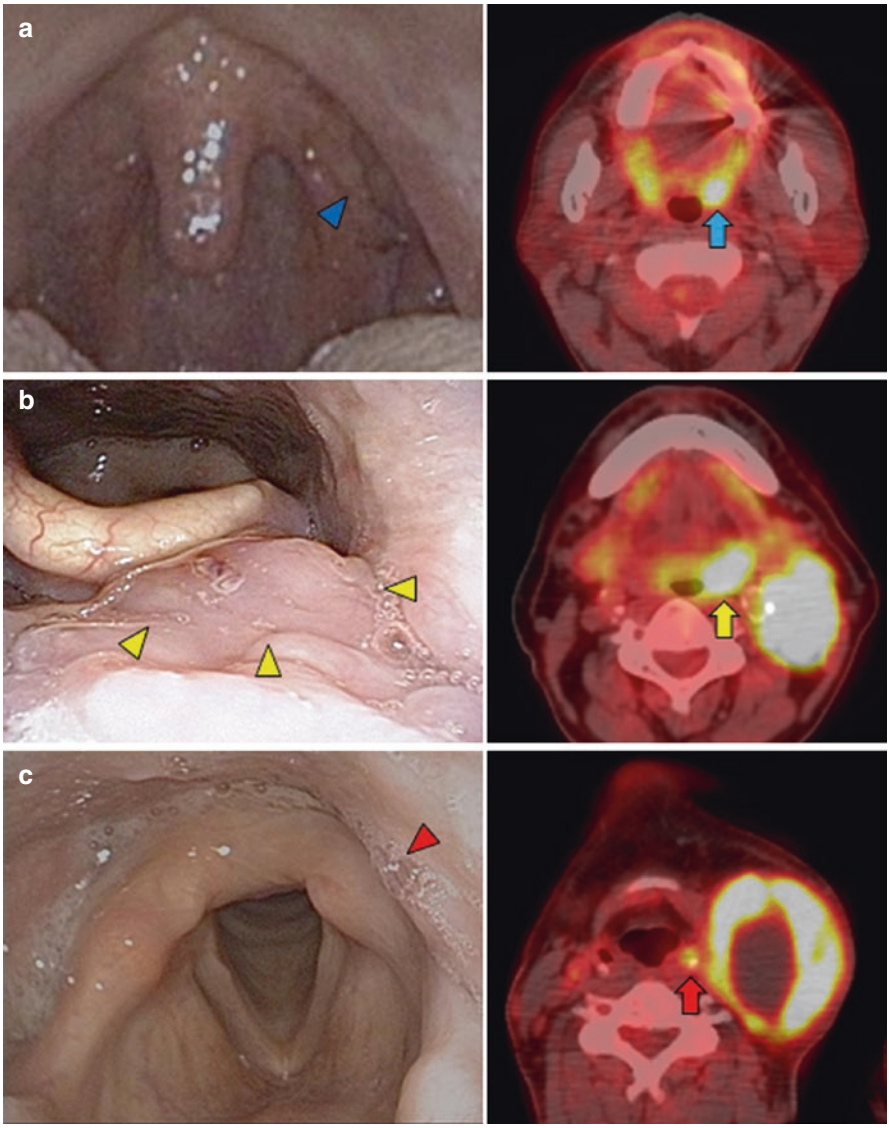

Fig. 4.2 Detection of the unknown primary tumor in cases of head and neck squamous cell carcinoma of unknown primary (HNSCCUP) using FDG PET/CT. (**a**) A 55-year-old man with a left cervical lymph node metastasis from SCC. The left palatine tonsil is not swollen (blue arrowhead). In PET/CT, FDG accumulation is more intense in the left palatine tonsil than in the right one (blue arrow). The patient underwent tonsillectomy, and histopathological analyses revealed a p16-positive oropharyngeal SCC (3 mm). (**b**) A 65-year-old man with a left cervical lymph node metastasis from SCC. A fiberscope shows a slightly swollen base of tongue on the left side (yellow arrowheads), with equivocal findings for malignancy. In contrast, PET/CT shows apparent FDG uptake at the base of tongue. Subsequent biopsy revealed a p16-positive oropharyngeal SCC. (**c**) A 65-year-old man with multiple left cervical LN metastases from SCC. A fiberscope shows no abnormal findings in the laryngopharyngeal regions. PET/CT shows the primary tumor in the left pyriform sinus (red arrow). Subsequent biopsy of the correspondent area (red arrowhead) revealed a hypopharyngeal SCC

respectively, for residual and recurrent neck disease and 85% (95% CI: 65–96%) and 95% (95% CI: 90–98%), respectively, for distant metastases [27].

4.1.3.2 Recurrence After Surgery

Clinical follow-up after surgery for HNSCC is difficult, particularly if the surgery involves defect reconstruction using regional or free tissue transfer [28]. Moreover, treatment-related anatomical changes complicate accurate CT or MRI assessments. PET/CT is the most reliable tool for locoregional surveillance after surgery with or without reconstruction (Fig. 4.3a).

4.1.3.3 Perineural Tumor Spread (PNTS)

Head and neck malignancies, including adenoid cystic carcinoma, salivary ductal carcinoma, and HNSCC, can relapse along a cranial nerve (V1, V2, V3, VII, XII, etc.) extending from the primary tumor; this is known as PNTS and associated with poor outcomes. The early detection of PNTS is important for patient management. Although MRI is the most sensitive imaging tool for the detection of PNTS, recent studies have investigated the role of PET/CT [29, 30] (Fig. 4.3b). It was found that the detection of PNTS at the skull base using PET/CT can be difficult because of high physiological FDG uptake in the nearby brain tissue. However, coronal PET/CT may be helpful for the detection of PNTS (Fig. 4.3c).

4.1.3.4 Follow-Up PET/CT for Patients Without Clinical Symptoms

Surveillance PET/CT can detect subclinical lesions in 5–36% patients without symptoms after definitive therapy [31–33]. The optimal timing for the initial surveillance PET/CT procedure after treatment appears to be 3–6 months; this maximizes the time for the resolution of inflammation and identifies the need for salvage treatment as early as possible [34]. Further studies evaluating the cost-effectiveness of surveillance PET/CT and its efficacy in terms of survival are necessary [34].

4.1.4 Utility for Assessment of the Response to Radiotherapy

4.1.4.1 Detection of Residual Lymph Nodes After Radiotherapy

There is a general consensus that PET/CT should be performed at least 12 weeks after radiotherapy, in accordance with the NCCN Clinical Practice Guidelines for the detection of residual node disease in head and neck cancer [35]. This is because early PET/CT performed <12 weeks after the completion of radiotherapy would generate high false-positive rates caused by radiotherapy-induced inflammation

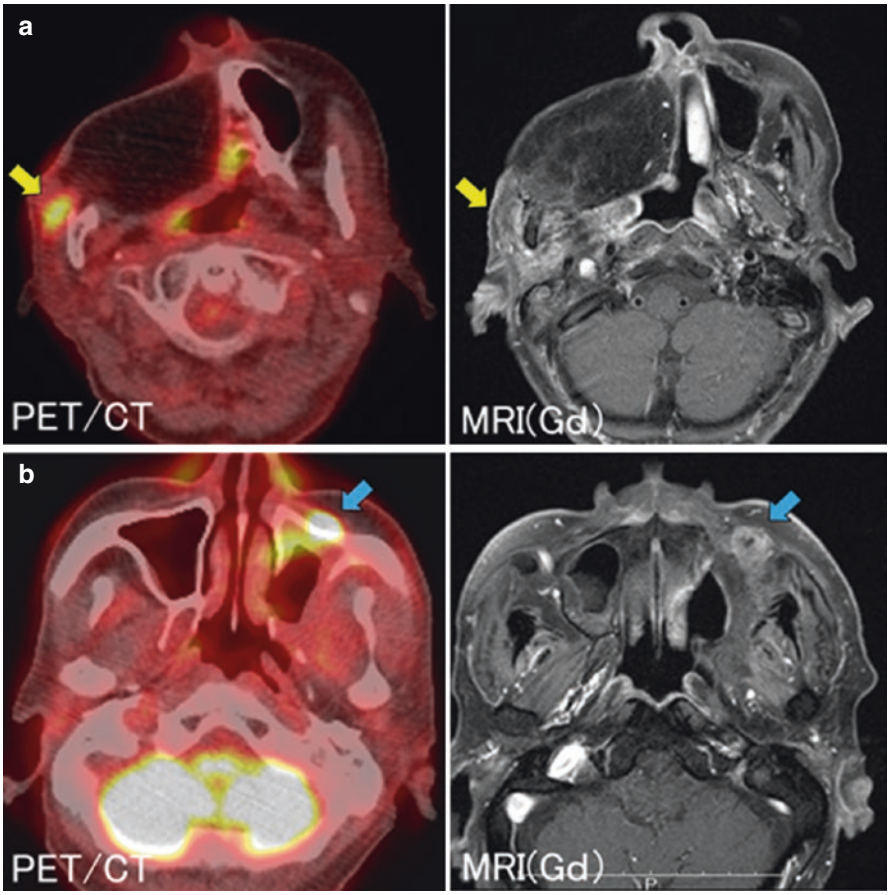

Fig. 4.3 Detection of recurrence of head and neck cancer using FDG PET/CT. (**a**) An 84-year-old woman with a right maxillary sinus squamous cell carcinoma (SCC). The patient underwent right total maxillectomy with reconstruction using a free rectus abdominis myocutaneous flap. Follow-up PET/CT at 8 months (left) shows local recurrence (yellow arrow). Contrast-enhanced MRI shows equivocal findings (right). (**b**) An 81-year-old man with a left superior gingival SCC. The patient underwent left partial maxillectomy without reconstruction. Follow-up PET/CT at 9 months (left) reveals perineural spread of a recurrent tumor along the left inferior orbital nerve (blue arrow). Contrast-enhanced MRI (right) also clearly identifies the perineural spread. (**c**) A 49-year-old woman with a right parotid gland adenocarcinoma not otherwise specified. The patient underwent right total parotidectomy. Follow-up PET/CT at 4 months reveals perineural spread of a recurrent tumor along the right mandibular nerve (V3) beneath the foramen ovale (red arrow). The tumor is located near the brain, where there is high physiological FDG uptake; however, coronal PET/CT images can clearly identify the lesion

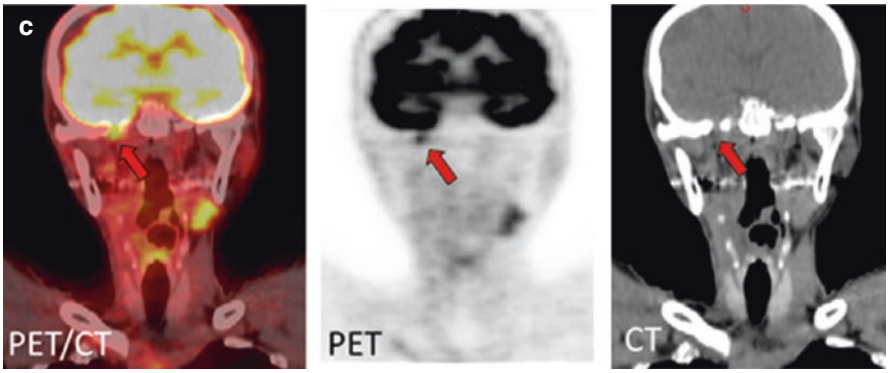

Fig. 4.3 (continued)

[36–38]. In a meta-analysis of 1293 patients with HNSCC who received radiotherapy with or without chemotherapy and underwent PET/CT for residual neck disease within 6 months after treatment, the pooled sensitivity and specificity of PET/CT were 72% (95% CI: 63–80%) and 88% (95% CI: 85–91%), respectively [39]. In this meta-analysis, HPV-positive tumors were associated with lower sensitivity and specificity values than HPV-negative tumors and the authors suggested that PET/CT may be less reliable in cases involving HPV-positive tumors than in those involving HPV-negative tumors [39].

In a prospective, randomized controlled trial for assessing the noninferiority of PET/CT-guided surveillance (performed 12 weeks after the end of chemoradiotherapy) in HNSCC cases involving stage N2 or N3 disease, neck dissection was planned or performed only if PET/CT showed an incomplete or equivocal response. The authors found similar survival data for patients who underwent PET/CT-guided surveillance and those who underwent planned neck dissection, which indicated that PET/CT-guided surveillance was noninferior to planned neck dissection. Moreover, it was equally effective in both HPV-positive and HPV-negative patient groups [40].

4.1.4.2 Detection of Residual Primary Lesions After Radiotherapy

There is no consensus regarding the optimal timing for PET/CT for the detection of the residual primary lesions after definitive radiotherapy with or without chemotherapy. However, PET/CT is generally performed at least 12 weeks after therapy, similar to the recommended timing for nodal assessment.

Laryngopharyngeal edema is a common side effect of radiotherapy for head and neck cancer, particularly when the mean laryngopharyngeal dose is ≥50 Gy [41]. Fibrotic changes, lymphatic vessel blockade, exogenous stimulation, infection [42], and increased thickening of the pharyngeal constrictors beneath the hypopharyngeal mucosa [43] may induce persistent laryngopharyngeal edema, which can be difficult to distinguish from a residual or recurrent tumor using a flexible rhino-pharyngo-laryngo-fiberscope, CT, or MRI, particularly in cases involving especially laryngeal

or hypopharyngeal cancer. In cases of HNSCC, PET/CT permits early and reliable assessment of the response to radiotherapy, performing better than CT or MRI in this regard [41, 44, 45]. However, false-positive PET findings at the primary site, particularly the larynx [44], are frequently observed because of persistent radiotherapy-induced inflammation or mucositis [46]. Schoder et al. [45] suggested that PET/CT should not be performed before 10–12 weeks after the completion of radiotherapy because posttreatment inflammatory changes increase the false-positive rate during this period. Small-volume residual disease may also escape detection on PET/CT, increasing the false-negative rate during the first 4–8 weeks after the completion of radiotherapy [47, 48]. Gupta et al. found that PET/CT identified residual disease at a primary site (oropharynx, hypopharynx, and larynx) at a median of 9 weeks after radiotherapy, with a sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of 50%, 92%, 50%, 92%, and 86%, respectively [49]. Thus, the overall diagnostic accuracy of PET/CT for the detection of residual primary lesions after radiotherapy is good, although the sensitivity and positive predictive value are relatively low. For patients with persistent laryngopharyngeal edema/mucositis and those with a region of focal and/or asymmetrical high FDG uptake in the primary lesion, biopsy should be performed to rule out local residual disease even if other examinations do not show a residual tumor (Fig. 4.4).

4.1.5 Utility for the Prediction of Survival Outcomes and/or Treatment Response

4.1.5.1 Prediction of Survival Outcomes

The maximum standardized uptake value (SUVmax) for the primary tumor is commonly used as a basis for the prognostic capacity of pretreatment PET/CT [50–53]. Two volume-based FDG parameters, namely the metabolic tumor volume (MTV) and total lesion glycolysis (TLG), have been described as better diagnostic and prognostic imaging biomarkers relative to SUVmax [54–59]. In two recently published systematic reviews, tumors with high volumetric parameters were associated with worse survival outcomes [60, 61].

Heterogeneity of FDG uptake may be another significant predictor of survival [62–68] in patients with head and neck cancer.

4.1.5.2 Prediction of the Treatment Response (Neoadjuvant Chemotherapy)

In the treatment of HNSCC, neoadjuvant chemotherapy (NAC) has not been associated with survival benefits [69]. Important roles of NAC include prediction of the further response to subsequent radiotherapy and selection of patients for treatment adaptation (i.e., radiotherapy or surgery). Conventional diagnostic imaging

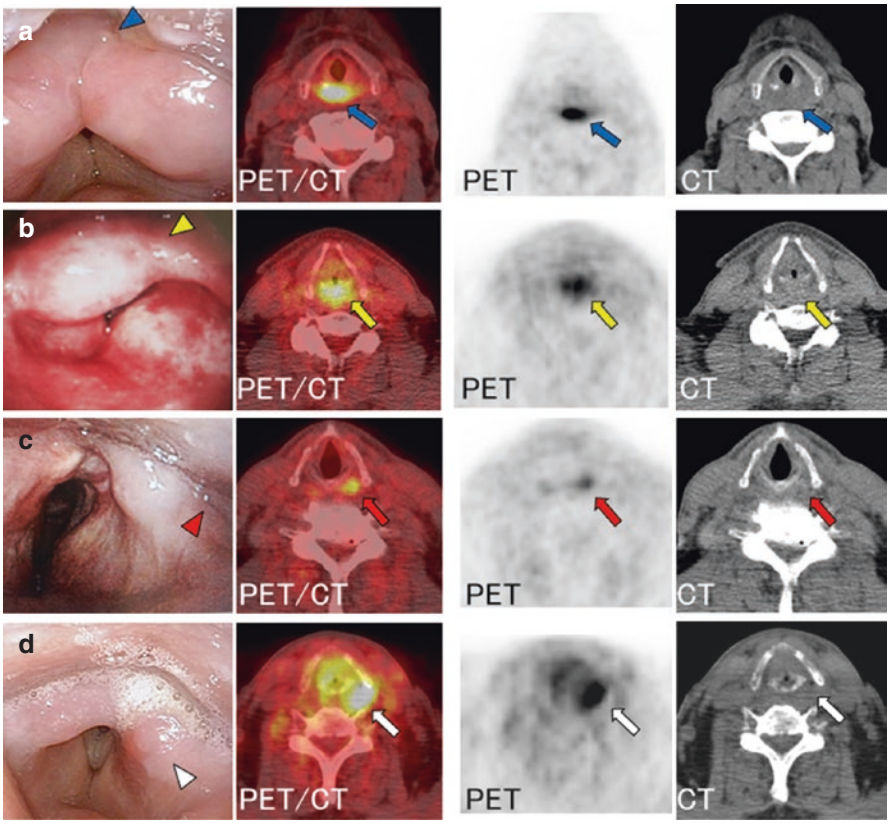

Fig. 4.4 All cases in **a**–**d** involved patients with hypopharyngeal SCC who underwent definitive radiotherapy with or without chemotherapy. PET/CT and fiberscopy were performed 3 months after the completion of therapy for evaluation of the treatment response. Moderate to intense FDG accumulation suggesting the existence of a residual tumor (arrows) can be seen on PET/CT; however, apparent residual tumors cannot be observed during fiberscopy because of moderate to severe laryngopharyngeal edema in each case (arrowheads). Cases **a**–**c** exhibit false-positive PET/CT findings. In cases **a** and **b**, FDG shows diffuse accumulation in the postcricoid region [maximum standardized uptake value (SUVmax), 6.1 and 3.8, respectively]. In case **c**, FDG shows focal accumulation in the left pyriform sinus (SUVmax, 3.6). These false-positive findings were caused by persistent radiation-induced mucositis. Only Case **d** shows true-positive findings on PET/CT. Intense FDG accumulation (SUVmax, 9.9) can be observed in the left pyriform sinus around the edematous laryngopharyngeal region, which shows diffuse/moderate FDG accumulation

modalities such as CT and MRI have been used for evaluation of the response to NAC, and the Response Evaluation Criteria in Solid Tumors' (RECIST) are widely accepted for this purpose [70]. However, evaluation requires the completion of at least two courses of chemotherapy [71], which is often time-consuming and leads to heavy financial and physical burdens for nonresponders. Therefore, response assessment should preferably be performed after only one cycle in order to avoid further unnecessary chemotherapy and the associated adverse effects [71, 72]. In a

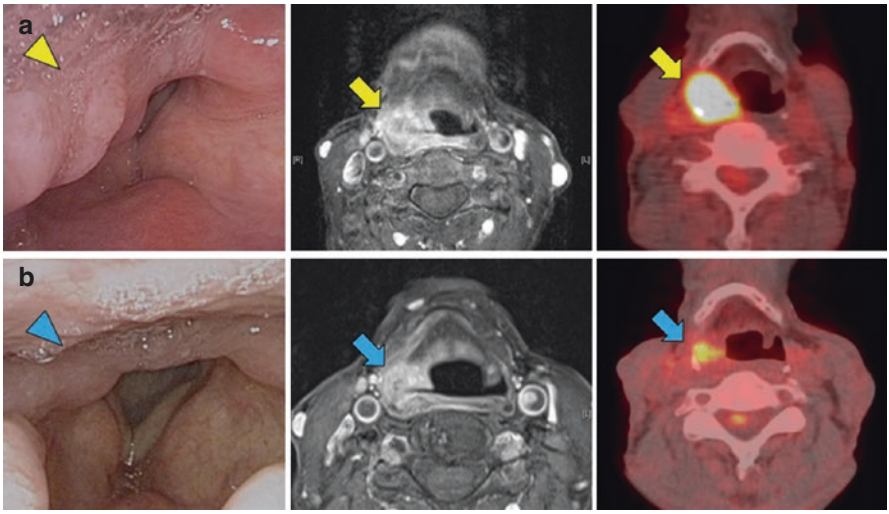

Fig. 4.5 Prediction of the response to neoadjuvant chemotherapy (NAC) for head and neck cancer using FDG PET/CT. A 75-year-old man with a right pyriform sinus squamous cell carcinoma (UICC eighth edition: cT4aN2aM0). The patient underwent fiberscopy, magnetic resonance imaging (MRI), and FDG PET/CT before (**a**) and 3 weeks after (**b**) one cycle of NAC (the platinum complex nedaplatin and the oral fluoropyrimidine derivate S-1). The arrowheads indicate a hypopharyngeal tumor observed with the fiberscope. The arrows indicate the tumor on the contrast-enhanced MR and PET/CT images. On MRI, the maximal diameter after NAC was almost comparable with that before NAC, whereas the maximum standardized uptake value in PET/CT showed a 79% decrease (from 21.7 to 4.5), indicating good response to NAC. The patient subsequently underwent definitive chemoradiotherapy and exhibited a complete response

systematic review [73], PET/CT allowed early evaluation of the NAC response and predicted the survival outcomes. A decline of 30–35% in the standardized uptake value (SUV) for the primary tumor is generally associated with a good outcome. Although there is no gold standard for the scan timing, PET/CT is a promising tool for early evaluation of the treatment response (even after one cycle) in patients receiving NAC [71, 74–77] (Fig. 4.5).

4.1.5.3 Prediction of the Treatment Response (Radiotherapy)

In a systematic review of 52 studies involving 1623 patients who underwent functional imaging, including PET/CT, within 4 weeks after the initiation of (chemo)radiotherapy, it was found that early tumoral changes induced by the treatment could be detected by PET/CT [78]. A low intra-treatment FDG uptake (SUVmax and TLG) was predictive of not only locoregional control but also overall survival. The optimal timing for PET/CT was 2–3 weeks after treatment initiation.

4.2 Clinical Pitfalls of FDG PET/CT

4.2.1 Physiological FDG Uptake in the Head and Neck

Physiological accumulation of FDG is commonly observed in several regions in the head and neck, with the most common sites being the brain, external ocular muscle, palatine tonsil, lingual tonsil, soft palate, salivary gland (sublingual gland > submandibular gland > parotid gland), and vocal cords [79]. Physiological uptake is generally symmetrical, although asymmetrical uptake is occasionally observed. As a result, differentiation of abnormal uptake from physiological uptake can be difficult in some cases.

4.2.2 PET/CT for Salivary Gland Tumors

A systematic review of 22 articles regarding PET/CT performed for patients with salivary gland tumors suggested that PET/CT was not useful for discriminating benign and malignant salivary gland tumors because of similar FDG uptake in both conditions [80]. For example, Warthin's tumor, which is the second most common benign parotid gland tumor, generally exhibits high FDG uptake [81], whereas intermediate-grade adenoid cystic carcinoma generally exhibits low FDG uptake. In a meta-analysis of incidental FDG uptake in the parotid glands, increased uptake in the salivary glands was more frequently observed in cases involving benign tumors than in those involving malignant tumors [82].

With regard to staging or restaging, PET/CT can be used as a complementary tool with conventional imaging for the detection of metastatic cervical LNs and distant metastasis, particularly in cases involving high-grade malignancies. However, there is no recommendation concerning the use of PET/CT for initial staging and/or follow-up [80].

4.2.3 PET/CT for Thyroid Gland Tumors

PET/CT is not recommended for the evaluation of patients with newly detected thyroid nodules [83]. Focal FDG uptake in the thyroid is incidentally detected in 1–2% patients, and fine needle aspiration cytology is recommended if the incidentaloma measures ≥1 cm.

Routine preoperative PET/CT is not recommended for differentiated thyroid cancer (DTC) [83] because of low sensitivity for the detection of cervical LN metastases (30–40%). In case of poor DTCs, PET/CT may be considered for initial staging.

In the postoperative setting, PET/CT should be considered for high-risk patients with DTC who are treated by total thyroidectomy and exhibit an elevated serum thyroglobulin level (>10 ng/mL) with negative findings in radioactive iodine (RAI) imaging [83]. FDG uptake in metastatic DTC is a major negative predictor of the response to RAI treatment and an independent prognostic factor for survival [84, 85].

Summary and Key Points

In this chapter, the clinical utilities and pitfalls of FDG PET in patients with head and neck cancer are overviewed. FDG PET is useful for staging, identification of unknown primary tumors, early detection of recurrent lesion after definitive therapy, early evaluation of chemotherapy/radiotherapy response, and prediction of survival outcomes for patients with head and neck squamous cell carcinoma. In contrast, FDG PET may not be recommended for the initial evaluation of patients with salivary gland tumors or thyroid gland tumors.

The followings are key points to understand the contents of this review.

- For T staging, contrast-enhanced MRI or CT is generally preferred over FDG PET.
- For N staging, FDG PET is useful but the sensitivity is low for the detection of occult cervical lymph node (LN) metastasis. Moreover, clinicians should note that necrotic/cystic LN metastasis is occasionally overlooked by FDG PET because of the lack of FDG uptake. Human papillomavirus (HPV) related oropharyngeal squamous cell carcinoma often produces necrotic/cystic LN metastasis.
- FDG PET is extremely useful for the detection of retropharyngeal LN or lingual LN, which are located outside the boundaries of routine neck dissections.
- The lung is the most frequent site of distant metastasis of HNSCC, but it should be noted that small lung nodules measuring <1 cm are often non-FDG-avid and can result in false-negative findings.
- FDG PET is useful to identify primary site in HNSCC of unknown primary. The most common site is the tonsil (lateral tonsil or base of tongue), which is associated with HPV infection.
- For patients who underwent head and neck surgery with reconstruction, FDG PET is useful for the early detection of recurrence because treatment-related anatomical changes complicate accurate assessments with CT or MRI.
- Coronal fusion image of FDG PET/CT can be helpful for the detection of a lesion at the skull base.
- For assessment of radiotherapy response, FDG PET should be performed at least 12 weeks after the completion of therapy to reduce the rate of false-positive and/or negative results.
- FDG PET can allow early evaluation of neoadjuvant chemotherapy/radiotherapy response and predict the survival outcomes.
- FDG PET is not useful for discriminating benign and malignant salivary gland tumors because of similar FDG uptake in both conditions. Warthin's tumor,

which is the second most common benign parotid gland tumor, generally exhibits high FDG uptake.

- Preoperative FDG PET is not recommended for differentiated thyroid cancer because of low sensitivity for the detection of cervical LN metastases.

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References

1. Li C, Sheng S, Men Y, Sun H, Xia H, Li L. Emission computed tomography for the diagnosis of mandibular invasion by head and neck cancers: a systematic review and meta-analysis. J Oral Maxillofac Surg. 2015;73(9):1875.e1–11. Epub May 11.
2. Hayashi K, Kikuchi M, Imai Y, Yamashita D, Hino M, Ito K, et al. Clinical value of fused PET/MRI for surgical planning in patients with oral/oropharyngeal carcinoma. Laryngoscope. 2019;21(10):27,911.
3. Fletcher JW, Djulbegovic B, Soares HP, Siegel BA, Lowe VJ, Lyman GH, et al. Recommendations on the use of 18F-FDG PET in oncology. J Nucl Med. 2008;49(3):480–508. https://doi.org/10.2967/jnumed.107.047787. Epub 2008 Feb 20.
4. Kyzas PA, Evangelou E, Denaxa-Kyza D, Ioannidis JP. 18F-fluorodeoxyglucose positron emission tomography to evaluate cervical node metastases in patients with head and neck squamous cell carcinoma: a meta-analysis. J Natl Cancer Inst. 2008;100(10):712–20. https://doi.org/10.1093/jnci/djn125. Epub 2008 May 13.
5. Schoder H, Carlson DL, Kraus DH, Stambuk HE, Gonen M, Erdi YE, et al. 18F-FDG PET/CT for detecting nodal metastases in patients with oral cancer staged N0 by clinical examination and CT/MRI. J Nucl Med. 2006;47(5):755–62.
6. Kim SJ, Pak K, Kim K. Diagnostic accuracy of F-18 FDG PET or PET/CT for detection of lymph node metastasis in clinically node negative head and neck cancer patients; a systematic review and meta-analysis. Am J Otolaryngol. 2019;40(2):297–305. https://doi.org/10.1016/j.amjoto.2018.10.013. Epub Oct 23.
7. Lowe VJ, Duan F, Subramaniam RM, Sicks JD, Romanoff J, Bartel T, et al. Multicenter trial of [(18)F]fluorodeoxyglucose positron emission tomography/computed tomography staging of head and neck cancer and negative predictive value and surgical impact in the n0 neck: results from ACRIN 6685. J Clin Oncol. 2019;37(20):1704–12. Epub 2019 Feb 15.
8. Coskun HH, Ferlito A, Medina JE, Robbins KT, Rodrigo JP, Strojan P, et al. Retropharyngeal lymph node metastases in head and neck malignancies. Head Neck. 2011;33(10):1520–9. Epub 2010 Aug 24.
9. Tomblinson CM, Nagel TH, Hu LS, Zarka MA, Hoxworth JM. Median lingual lymph nodes: prevalence on imaging and potential implications for oral cavity cancer staging. J Comput Assist Tomogr. 2017;41(4):528–34. https://doi.org/10.1097/RCT.0000000000000568.
10. Goldenberg D, Begum S, Westra WH, Khan Z, Sciubba J, Pai SI, et al. Cystic lymph node metastasis in patients with head and neck cancer: An HPV-associated phenomenon. Head Neck. 2008;30(7):898–903. https://doi.org/10.1002/hed.20796.
11. Haerle SK, Strobel K, Ahmad N, Soltermann A, Schmid DT, Stoeckli SJ. Contrast-enhanced (1)(8)F-FDG-PET/CT for the assessment of necrotic lymph node metastases. Head Neck. 2011;33(3):324–9. https://doi.org/10.1002/hed.21447.
12. Takes RP, Rinaldo A, Silver CE, Haigentz M Jr, Woolgar JA, Triantafyllou A, et al. Distant metastases from head and neck squamous cell carcinoma. Part I basic aspects. Oral Oncol. 2012;48(9):775–9. https://doi.org/10.1016/j.oraloncology.2012.03.013. Epub Apr 18.

13. de Bree R, Mehta DM, Snow GB, Quak JJ. Intracranial metastases in patients with squamous cell carcinoma of the head and neck. Otolaryngol Head Neck Surg. 2001;124(2):217–21. https://doi.org/10.1067/mhn.2001.112478.
14. Xu GZ, Guan DJ, He ZY. (18)FDG-PET/CT for detecting distant metastases and second primary cancers in patients with head and neck cancer. A meta-analysis. Oral Oncol. 2011;47(7):560–5. https://doi.org/10.1016/j.oraloncology.2011.04.021. Epub May 28.
15. Gould MK, Maclean CC, Kuschner WG, Rydzak CE, Owens DK. Accuracy of positron emission tomography for diagnosis of pulmonary nodules and mass lesions: a meta-analysis. JAMA. 2001;285(7):914–24. https://doi.org/10.1001/jama.285.7.914.
16. Mani N, George MM, Nash L, Anwar B, Homer JJ. Role of 18-Fludeoxyglucose positron emission tomography-computed tomography and subsequent panendoscopy in head and neck squamous cell carcinoma of unknown primary. Laryngoscope. 2016;126(6):1354–8. Epub 2015 Dec 16.
17. Bochtler T, Loffler H, Kramer A. Diagnosis and management of metastatic neoplasms with unknown primary. Semin Diagn Pathol. 2018;35(3):199–206. https://doi.org/10.1053/j.semdp.2017.11.013. Epub Nov 26.
18. Zhu L, Wang N. 18F-fluorodeoxyglucose positron emission tomography-computed tomography as a diagnostic tool in patients with cervical nodal metastases of unknown primary site: a meta-analysis. Surg Oncol. 2013;22(3):190–4. https://doi.org/10.1016/j.suronc.2013.06.002. Epub Jul 11.
19. Park GC, Lee M, Roh JL, Yu MS, Choi SH, Nam SY, et al. Human papillomavirus and p16 detection in cervical lymph node metastases from an unknown primary tumor. Oral Oncol. 2012;48(12):1250–6. Epub Jun 23.
20. Di Maio P, Iocca O, De Virgilio A, Ferreli F, Cristalli G, Pellini R, et al. Role of palatine tonsillectomy in the diagnostic workup of head and neck squamous cell carcinoma of unknown primary origin: a systematic review and meta-analysis. Head Neck. 2019;41(4):1112–21. Epub 2018 Dec 21.
21. Ang KK, Trotti A, Brown BW, Garden AS, Foote RL, Morrison WH, et al. Randomized trial addressing risk features and time factors of surgery plus radiotherapy in advanced head-and-neck cancer. Int J Radiat Oncol Biol Phys. 2001;51(3):571–8. https://doi.org/10.1016/s0360-3016(01)01690-x.
22. Leemans CR, Tiwari R, Nauta JJ, van der Waal I, Snow GB. Recurrence at the primary site in head and neck cancer and the significance of neck lymph node metastases as a prognostic factor. Cancer. 1994;73(1):187–90. https://doi.org/10.1002/97-0142(19940101)73:1<187::aid-cncr2820730132>3.0.co;2-j.
23. Vermorken JB, Mesia R, Rivera F, Remenar E, Kawecki A, Rottey S, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med. 2008;359(11):1116–27.
24. Goodwin WJ Jr. Salvage surgery for patients with recurrent squamous cell carcinoma of the upper aerodigestive tract: when do the ends justify the means? Laryngoscope. 2000;110(3 Pt 2 Suppl 93):1–18. https://doi.org/10.1097/00005537-200003001-00001.
25. de Visscher AV, Manni JJ. Routine long-term follow-up in patients treated with curative intent for squamous cell carcinoma of the larynx, pharynx, and oral cavity. Does it make sense? Arch Otolaryngol Head Neck Surg. 1994;120(9):934–9.
26. Kim JW, Roh JL, Kim JS, Lee JH, Cho KJ, Choi SH, et al. (18)F-FDG PET/CT surveillance at 3-6 and 12 months for detection of recurrence and second primary cancer in patients with head and neck squamous cell carcinoma. Br J Cancer. 2013;109(12):2973–9. https://doi.org/10.1038/bjc.2013.668. Epub Oct 22.
27. Cheung PK, Chin RY, Eslick GD. Detecting residual/recurrent head neck squamous cell carcinomas using PET or PET/CT: systematic review and meta-analysis. Otolaryngol Head Neck Surg. 2016;154(3):421–32. https://doi.org/10.1177/0194599815621742. Epub 2015 Dec 29.
28. Muller J, Hullner M, Strobel K, Huber GF, Burger IA, Haerle SK. The value of (18)F-FDG-PET/CT imaging in oral cavity cancer patients following surgical reconstruction. Laryngoscope. 2015;125(8):1861–8. Epub 2015 Apr 17.

29. Dercle L, Hartl D, Rozenblum-Beddok L, Mokrane FZ, Seban RD, Yeh R, et al. Diagnostic and prognostic value of 18F-FDG PET, CT, and MRI in perineural spread of head and neck malignancies. Eur Radiol. 2018;28(4):1761–70. Epub 2017 Oct 30.
30. Bakst RL, Glastonbury CM, Parvathaneni U, Katabi N, Hu KS, Yom SS. Perineural invasion and perineural tumor spread in head and neck cancer. Int J Radiat Oncol Biol Phys. 2019;103(5):1109–24. Epub Dec 15.
31. Roman BR, Goldenberg D, Givi B. AHNS series—do you know your guidelines? Guideline recommended follow-up and surveillance of head and neck cancer survivors. Head Neck. 2016;38(2):168–74. https://doi.org/10.1002/hed.24100.
32. Kikuchi M, Shinohara S, Hino M, Itoh K, Tona R, Kishimoto I, et al. Detection of subclinical recurrence or second primary cancer using (18) F-FDG PET/CT in patients treated curatively for head and neck squamous cell carcinoma. Head Neck. 2016;38(Suppl 1):E511–8. https://doi.org/10.1002/hed.24032. Epub 2015 Jul 14.
33. Abgral R, Querellou S, Potard G, Le Roux PY, Le Duc-Pennec A, Marianovski R, et al. Does 18F-FDG PET/CT improve the detection of posttreatment recurrence of head and neck squamous cell carcinoma in patients negative for disease on clinical follow-up? J Nucl Med. 2009;50(1):24–9. https://doi.org/10.2967/jnumed.108.055806. Epub 2008 Dec 17.
34. Zhao X, Rao S. Surveillance imaging following treatment of head and neck cancer. Semin Oncol. 2017;44(5):323–9. https://doi.org/10.1053/j.seminoncol.2018.01.010. Epub Feb 9.
35. National Comprehensive Cancer Network. NCCN clinical practice guidelines: head and neck cancers, version 2.2019. Ft. NCCN: Washington, PA; 2019.
36. Ong SC, Schoder H, Lee NY, Patel SG, Carlson D, Fury M, et al. Clinical utility of 18F-FDG PET/CT in assessing the neck after concurrent chemoradiotherapy for Locoregional advanced head and neck cancer. J Nucl Med. 2008;49(4):532–40. https://doi.org/10.2967/jnumed.107.044792. Epub 2008 Mar 14.
37. Isles MG, McConkey C, Mehanna HM. A systematic review and meta-analysis of the role of positron emission tomography in the follow up of head and neck squamous cell carcinoma following radiotherapy or chemoradiotherapy. Clin Otolaryngol. 2008;33(3):210–22. https://doi.org/10.1111/j.749-4486.2008.01688.x.
38. Gupta T, Master Z, Kannan S, Agarwal JP, Ghsoh-Laskar S, Rangarajan V, et al. Diagnostic performance of post-treatment FDG PET or FDG PET/CT imaging in head and neck cancer: a systematic review and meta-analysis. Eur J Nucl Med Mol Imaging. 2011;38(11):2083–95. Epub 2011 Aug 19.
39. Helsen N, Van den Wyngaert T, Carp L, Stroobants S. FDG-PET/CT for treatment response assessment in head and neck squamous cell carcinoma: a systematic review and meta-analysis of diagnostic performance. Eur J Nucl Med Mol Imaging. 2018;45(6):1063–71. Epub 2018 Feb 24.
40. Mehanna H, Wong WL, McConkey CC, Rahman JK, Robinson M, Hartley AG, et al. PET-CT surveillance versus neck dissection in advanced head and neck cancer. N Engl J Med. 2016;374(15):1444–54. Epub 2016 Mar 23.
41. Bae JS, Roh JL, Lee SW, Kim SB, Kim JS, Lee JH, et al. Laryngeal edema after radiotherapy in patients with squamous cell carcinomas of the larynx and hypopharynx. Oral Oncol. 2012;48:853.
42. Ichimura K, Sugasawa M, Nibu K, Takasago E, Hasezawa K. The significance of arytenoid edema following radiotherapy of laryngeal carcinoma with respect to residual and recurrent tumour. Auris Nasus Larynx. 1997;24(4):391–7.
43. Popovtzer A, Cao Y, Feng FY, Eisbruch A. Anatomical changes in the pharyngeal constrictors after chemo-irradiation of head and neck cancer and their dose-effect relationships: MRI-based study. Radiother Oncol. 2009;93(3):510–5.
44. Yao M, Smith RB, Hoffman HT, Funk GF, Lu M, Menda Y, et al. Clinical significance of postradiotherapy [18F]-fluorodeoxyglucose positron emission tomography imaging in management of head-and-neck cancer-a long-term outcome report. Int J Radiat Oncol Biol Phys. 2009;74(1):9–14.

45. Schoder H, Fury M, Lee N, Kraus D. PET monitoring of therapy response in head and neck squamous cell carcinoma. J Nucl Med. 2009;50(Suppl 1):74S–88S.
46. Kim GJ, Fiskum GM, Morgan WF. A role for mitochondrial dysfunction in perpetuating radiation-induced genomic instability. Cancer Res. 2006;66(21):10377–83.
47. Andrade RS, Heron DE, Degirmenci B, Filho PA, Branstetter BF, Seethala RR, et al. Posttreatment assessment of response using FDG-PET/CT for patients treated with definitive radiation therapy for head and neck cancers. Int J Radiat Oncol Biol Phys. 2006;65(5):1315–22.
48. Greven KM, Williams DW 3rd, McGuirt WF Sr, Harkness BA, D'Agostino RB Jr, Keyes JW Jr, et al. Serial positron emission tomography scans following radiation therapy of patients with head and neck cancer. Head Neck. 2001;23(11):942–6.
49. Gupta T, Jain S, Agarwal JP, Rangarajan V, Purandare N, Ghosh-Laskar S, et al. Diagnostic performance of response assessment FDG-PET/CT in patients with head and neck squamous cell carcinoma treated with high-precision definitive (chemo)radiation. Radiother Oncol. 2010;97(2):194–9.
50. Connell CA, Corry J, Milner AD, Hogg A, Hicks RJ, Rischin D, et al. Clinical impact of, and prognostic stratification by, F-18 FDG PET/CT in head and neck mucosal squamous cell carcinoma. Head Neck. 2007;29(11):986–95. https://doi.org/10.1002/hed.20629.
51. Liao CT, Chang JT, Wang HM, Ng SH, Hsueh C, Lee LY, et al. Pretreatment primary tumor SUVmax measured by FDG-PET and pathologic tumor depth predict for poor outcomes in patients with oral cavity squamous cell carcinoma and pathologically positive lymph nodes. Int J Radiat Oncol Biol Phys. 2009;73(3):764–71. https://doi.org/10.1016/j.ijrobp.2008.05.004. Epub Oct 2.
52. Machtay M, Natwa M, Andrel J, Hyslop T, Anne PR, Lavarino J, et al. Pretreatment FDG-PET standardized uptake value as a prognostic factor for outcome in head and neck cancer. Head Neck. 2009;31(2):195–201. https://doi.org/10.1002/hed.20942.
53. Torizuka T, Tanizaki Y, Kanno T, Futatsubashi M, Naitou K, Ueda Y, et al. Prognostic value of 18F-FDG PET in patients with head and neck squamous cell cancer. AJR Am J Roentgenol. 2009;192(4):W156–60. https://doi.org/10.2214/AJR.08.1429.
54. Cheng NM, Chang JT, Huang CG, Tsan DL, Ng SH, Wang HM, et al. Prognostic value of pretreatment (1)(8)F-FDG PET/CT and human papillomavirus type 16 testing in locally advanced oropharyngeal squamous cell carcinoma. Eur J Nucl Med Mol Imaging. 2012;39(11):1673–84. Epub 2012 Aug 2.
55. Dibble EH, Alvarez AC, Truong MT, Mercier G, Cook EF, Subramaniam RM. 18F-FDG metabolic tumor volume and total glycolytic activity of oral cavity and oropharyngeal squamous cell cancer: adding value to clinical staging. J Nucl Med. 2012;53(5):709–15. https://doi.org/10.2967/jnumed.111.099531. Epub 2012 Apr 9.
56. Lim R, Eaton A, Lee NY, Setton J, Ohri N, Rao S, et al. 18F-FDG PET/CT metabolic tumor volume and total lesion glycolysis predict outcome in oropharyngeal squamous cell carcinoma. J Nucl Med. 2012;53(10):1506–13. https://doi.org/10.2967/jnumed.111.101402. Epub 2012 Aug 14.
57. Tang C, Murphy JD, Khong B, La TH, Kong C, Fischbein NJ, et al. Validation that metabolic tumor volume predicts outcome in head-and-neck cancer. Int J Radiat Oncol Biol Phys. 2012;83(5):1514–20. Epub 2 Jan 21.
58. Moon SH, Choi JY, Lee HJ, Son YI, Baek CH, Ahn YC, et al. Prognostic value of 18F-FDG PET/CT in patients with squamous cell carcinoma of the tonsil: comparisons of volume-based metabolic parameters. Head Neck. 2013;35(1):15–22. https://doi.org/10.1002/hed.22904. Epub 2012 Feb 6.
59. Kikuchi M, Koyasu S, Shinohara S, Usami Y, Imai Y, Hino M, et al. Prognostic value of pretreatment 18F-fluorodeoxyglucose positron emission tomography/CT volume-based parameters in patients with oropharyngeal squamous cell carcinoma with known p16 and p53 status. Head Neck. 2015;37(10):1524–31. Epub 2014 Jul 21.
60. Wang L, Bai J, Duan P. Prognostic value of 18F-FDG PET/CT functional parameters in patients with head and neck cancer: a meta-analysis. Nucl Med Commun. 2019;40(4):361–9. https://doi.org/10.1097/MNM.0000000000000974.

61. Pak K, Cheon GJ, Nam HY, Kim SJ, Kang KW, Chung JK, et al. Prognostic value of metabolic tumor volume and total lesion glycolysis in head and neck cancer: a systematic review and meta-analysis. J Nucl Med. 2014;55(6):884–90. https://doi.org/10.2967/jnumed.113.133801. Epub 2014 Apr 21.
62. Koyasu S, Nakamoto Y, Kikuchi M, Suzuki K, Hayashida K, Itoh K, et al. Prognostic value of pretreatment 18F-FDG PET/CT parameters including visual evaluation in patients with head and neck squamous cell carcinoma. AJR Am J Roentgenol. 2014;202(4):851–8. https://doi.org/10.2214/AJR.13.11013.
63. Jang JY, Pak KJ, Yi KI, Ki YK, Kim WT, Kim H, et al. Differential prognostic value of metabolic heterogeneity of primary tumor and metastatic lymph nodes in patients with pharyngeal cancer. Anticancer Res. 2017;37(10):5899–905. https://doi.org/10.21873/anticanres.12036.
64. Kim BS, Pak K, Yi KI, Kim IJ, Roh HJ, Cho KS. Prognostic value of tumoral heterogeneity and volumetric parameters as measured by F18-FDG PET/CT in sinonasal cancer. Eur Arch Otorhinolaryngol. 2016;274:1437.
65. Oh JS, Kang BC, Roh JL, Kim JS, Cho KJ, Lee SW, et al. Intratumor textural heterogeneity on pretreatment (18)F-FDG PET images predicts response and survival after chemoradiotherapy for hypopharyngeal cancer. Ann Surg Oncol. 2015;22(8):2746–54.
66. Kwon SH, Yoon JK, An YS, Shin YS, Kim CH, Lee DH, et al. Prognostic significance of the intratumoral heterogeneity of (18) F-FDG uptake in oral cavity cancer. J Surg Oncol. 2014;110(6):702–6.
67. Ryu IS, Kim JS, Roh JL, Lee JH, Cho KJ, Choi SH, et al. Prognostic value of preoperative metabolic tumor volume and total lesion glycolysis measured by 18F-FDG PET/CT in salivary gland carcinomas. J Nucl Med. 2013;54(7):1032–8.
68. Huang B, Chan T, Kwong DL, Chan WK, Khong PL. Nasopharyngeal carcinoma: investigation of intratumoral heterogeneity with FDG PET/CT. AJR Am J Roentgenol. 2012;199(1):169–74.
69. Pignon JP, le Maitre A, Maillard E, Bourhis J. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. Radiother Oncol. 2009;92(1):4–14. https://doi.org/10.1016/j.radonc.2009.04.014. Epub May 14.
70. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228–47. https://doi.org/10.1016/j.ejca.2008.10.026.
71. Kikuchi M, Nakamoto Y, Shinohara S, Fujiwara K, Yamazaki H, Kanazawa Y, et al. Early evaluation of neoadjuvant chemotherapy response using FDG-PET/CT predicts survival prognosis in patients with head and neck squamous cell carcinoma. Int J Clin Oncol. 2013;18:402.
72. Kikuchi M, Shinohara S, Nakamoto Y, Usami Y, Fujiwara K, Adachi T, et al. Sequential FDG-PET/CT after neoadjuvant chemotherapy is a predictor of histopathologic response in patients with head and neck squamous cell carcinoma. Mol Imaging Biol. 2011;13(2):368–77.
73. Dos Anjos RF, Dos Anjos DA, Vieira DL, Leite AF, Figueiredo PT, de Melo NS. Effectiveness of FDG-PET/CT for evaluating early response to induction chemotherapy in head and neck squamous cell carcinoma: a systematic review. Medicine (Baltimore). 2016;95(32):e4450. https://doi.org/10.1097/MD.0000000000004450.
74. de Bree R, Wolf GT, de Keizer B, Nixon IJ, Hartl DM, Forastiere AA, et al. Response assessment after induction chemotherapy for head and neck squamous cell carcinoma: from physical examination to modern imaging techniques and beyond. Head Neck. 2017;39(11):2329–49. https://doi.org/10.1002/hed.24883. Epub 2017 Aug 17.
75. Brun E, Kjellen E, Tennvall J, Ohlsson T, Sandell A, Perfekt R, et al. FDG PET studies during treatment: prediction of therapy outcome in head and neck squamous cell carcinoma. Head Neck. 2002;24(2):127–35.
76. Chepeha DB, Sacco AG, Oxford LE, Karamchandani R, Miller TH, Teknos TN, et al. Advanced squamous cell carcinoma of the oropharynx: efficacy of positron emission tomography and computed tomography for determining primary tumor response during induction chemotherapy. Head Neck. 2009;31(4):452–60. https://doi.org/10.1002/hed.21006.

77. Semrau S, Schmidt D, Lell M, Waldfahrer F, Lettmaier S, Kuwert T, et al. Results of chemoselection with short induction chemotherapy followed by chemoradiation or surgery in the treatment of functionally inoperable carcinomas of the pharynx and larynx. Oral Oncol. 2013;49(5):454–60. https://doi.org/10.1016/j.oraloncology.2012.12.008. Epub 3 Jan 12.
78. Martens RM, Noij DP, Ali M, Koopman T, Marcus JT, Vergeer MR, et al. Functional imaging early during (chemo)radiotherapy for response prediction in head and neck squamous cell carcinoma; a systematic review. Oral Oncol. 2019;88:75–83. https://doi.org/10.1016/j.oraloncology.2018.11.005. Epub Nov 22.
79. Nakamoto Y, Tatsumi M, Hammoud D, Cohade C, Osman MM, Wahl RL. Normal FDG distribution patterns in the head and neck: PET/CT evaluation. Radiology. 2005;234(3):879–85. https://doi.org/10.1148/radiol.2343030301.
80. Bertagna F, Nicolai P, Maroldi R, Mattavelli D, Bertoli M, Giubbini R, et al. Diagnostic role of (18)F-FDG-PET or PET/CT in salivary gland tumors: a systematic review. Rev Esp Med Nucl Imagen Mol. 2015;34(5):295–302.
81. Rassekh CH, Cost JL, Hogg JP, Hurst MK, Marano GD, Ducatman BS. Positron emission tomography in Warthin's tumor mimicking malignancy impacts the evaluation of head and neck patients. Am J Otolaryngol. 2015;36(2):259–63. https://doi.org/10.1016/j.amjoto.2014.11.008. Epub Nov 27.
82. Treglia G, Bertagna F, Sadeghi R, Muoio B, Giovanella L. Prevalence and risk of malignancy of focal incidental uptake detected by fluorine-18-fluorodeoxyglucose positron emission tomography in the parotid gland: a meta-analysis. Eur Arch Otorhinolaryngol. 2015;272(12):3617–26. https://doi.org/10.1007/s00405-014-3308-8. Epub 2014 Sep 28.
83. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid Cancer: the American Thyroid Association guidelines task force on thyroid nodules and differentiated thyroid cancer. Thyroid. 2016;26(1):1–133. https://doi.org/10.1089/thy.2015.0020.
84. Robbins RJ, Wan Q, Grewal RK, Reibke R, Gonen M, Strauss HW, et al. Real-time prognosis for metastatic thyroid carcinoma based on 2-[18F]fluoro-2-deoxy-D-glucose-positron emission tomography scanning. J Clin Endocrinol Metab. 2006;91(2):498–505. https://doi.org/10.1210/jc.2005-1534. Epub 2005 Nov 22.
85. Deandreis D, Al Ghuzlan A, Leboulleux S, Lacroix L, Garsi JP, Talbot M, et al. Do histological, immunohistochemical, and metabolic (radioiodine and fluorodeoxyglucose uptakes) patterns of metastatic thyroid cancer correlate with patient outcome? Endocr Relat Cancer. 2011;18(1):159–69. https://doi.org/10.1677/ERC-10-0233. Print 2011 Feb.

Chapter 5
Positron Emission Tomography/Computed Tomography in Colorectal Cancer

Yoshiko Bamba and Michio Itabashi

Compared with other modalities, positron emission tomography/computed tomography (PET/CT) has higher sensitivity and specificity in the diagnosis and treatment of colorectal cancer. PET/CT is a whole-body imaging and qualitative diagnostic technique. However, owing to the high cost, it must be used cost-effectively.

Based on the lesion size and degree of fluorine-18 deoxyglucose (FDG) accumulation, it is possible to diagnose the presence and degree of the primary lesion using PET/CT (Fig. 5.1). In the interpretation of PET/CT findings, it should be noted that there is a physiological accumulation in benign neoplastic lesions such as in colon polyps. However, it is difficult to distinguish between benign and malignant lesions depending on the degree of accumulation. Because taking laxatives can increase such accumulation in the large intestine, careful consideration is required. PET examination was performed in 1750 cases of colon cancer or suspected colon cancer, and 53 cases (3.3%) showed non-primary FDG accumulation [1]. Based on histological examination, malignant tumors were present in 42 cases (71%). In order to prevent false positives, accumulation patterns, standard uptake values (SUV), and anatomical features must be considered during assessment. Size of the tumor is important, and detection of those ≤1 cm is difficult. At our hospital, in 169 cases before surgery for colorectal cancer 160 cases (94.7%) were found to show clustering, but 9 cases that did not show clustering were those whose tumor diameter was ≤25 mm.

In the diagnosis of lymph node metastasis, proximal lymph node diagnosis is more difficult than that of distant lymph node metastasis (Fig. 5.2). In colorectal cancer, the lymph nodes are classified as three types based on the extent of metastasis according to the Japanese Classification of Colorectal, Appendiceal, and Anal Carcinoma. Moreover, the Japanese Society for Cancer of the Colon and Rectum

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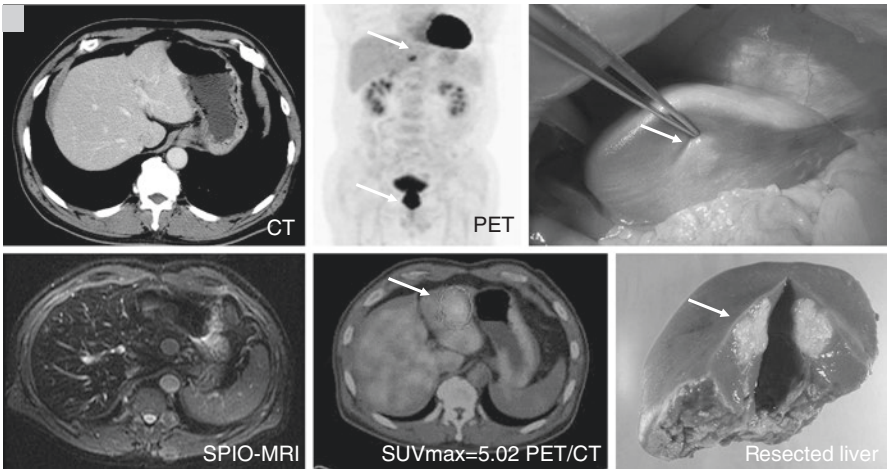

Fig. 5.1 The patient was a 55-year-old man with rectal cancer and liver metastasis. The liver metastasis was undetectable on CT and MRI, but was revealed from a PET/CT

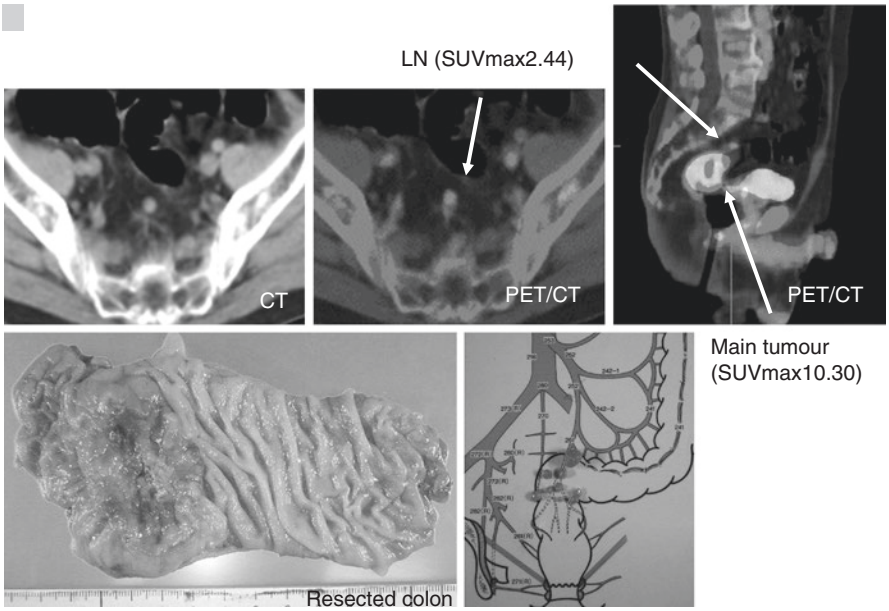

Fig. 5.2 The patient was a 78-year-old man with rectal cancer with proximal lymph node metastasis. Accumulation of FDG-PET was detected in the proximal lymph node

has established a set of guidelines for the management of colorectal cancer in Japan [2]. The sensitivity of diagnosis of group 3 lymph nodes using PET/CT is about 35–60%. The difficulty in the diagnosis of proximal lymph node metastasis is due to its proximity to the primary lesion. Lowering the cut-off value may improve the

Table 5.1 Diagnostic ability of lateral lymph node dissection

		Accuracy (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Right lateral LN	CT	61.9	50.0	66.7	37.5	76.9
	MRI	66.7	100	53.3	46.2	100
	PET	90.5	66.7	100	100	88.2
Left lateral LN	CT	72.0	57.1	77.8	50.0	82.4
	MRI	76.0	85.7	72.2	54.5	92.9
	PET	88.0	57.1	100	100	65.7

diagnosis of lymph node metastasis. In the diagnostic ability of lateral pelvic lymph, a qualitative diagnosis by PET/CT is useful. The diagnostic results of CT, magnetic resonance imaging (MRI), and PET/CT were high in sensitivity and negative predictive value of MRI, and high in specificity and positive predictive value of PET/CT test (Table 5.1).

In the evaluation of the recurrence of metastasis in colorectal cancer, the whole-body scan is preferable and its sensitivity and specificity are excellent, and the treatment strategy was changed to 29% by performing PET/CT examination [3]. There are reports of correctly diagnosing 90% of unresectable cases using PET examination [4].

In the diagnosis of colorectal liver metastases, the sensitivity was 94% and 87% and the specificity was 98% and 90% when compared with PET/CT and other modalities [5]. There are reports in which PET/CT was the best compared to MRI in liver metastases [6].

In a meta-analysis of lung metastases, the sensitivity and specificity of CT were 59% and 79%, respectively, compared with 55.6% and 99.1% for PET/CT [5]. One of the factors associated with low sensitivity is the volume of metastases, and the size detected by PET is approximately 10 mm [7]. Diagnosis of early lung metastases is made by chest CT examination, and chest CT examination is important for follow-up after surgery for colorectal cancer.

In the diagnosis of local recurrence, it is often difficult to distinguish between postoperative scar and recurrence. The sensitivity and specificity in the diagnosis of local recurrence, in our hospital, were 95.5% and 100%, respectively, by PET/CT [8]. Possibility of qualitative diagnosis is the difference between PET/CT examinations and other modalities such as MRI; additionally, it is possible to have important information regarding the potential for recurrence

Peritonitis carcinomatosis, peritoneal and lymph node recurrence, and metastasis are difficult to diagnose [9]. Therefore, it is important to avoid unnecessary surgery by making a qualitative diagnosis using PET/CT.

For the response assessment of colorectal cancer, SUVmax and SUV response index are reported to be the best predictors of radiation chemotherapy (Fig. 5.3). Especially, early metabolic response assessment performed after one cycle of targeted therapy in metastatic colorectal cancer is highly predictive of non-response at a standard response assessment time [10].

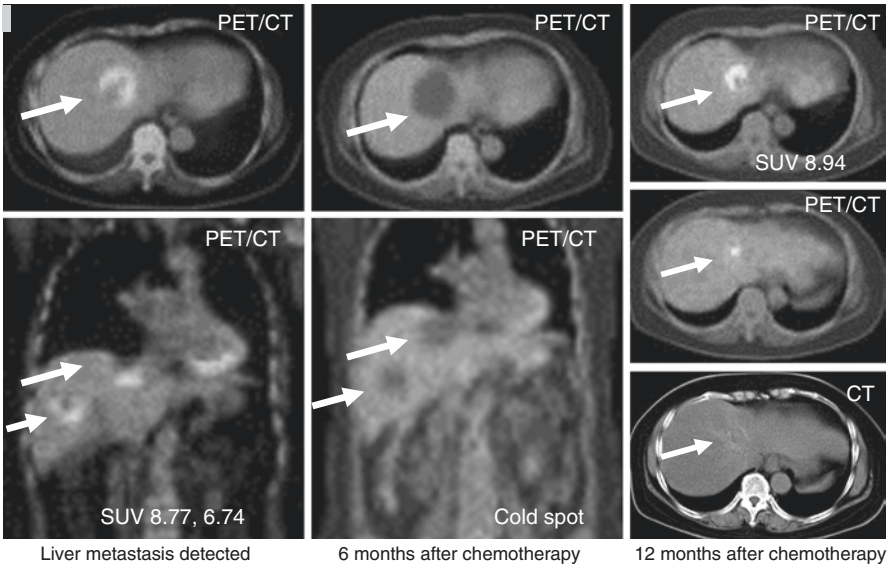

Fig. 5.3 The patient was a 59-year-old woman with postoperative sigmoid colon cancer. Chemotherapy was performed for liver metastases. They were negative of accumulation in 6 months after chemotherapy and became positive for SUV in 12 months

5.1 Summary and Key Points

In this chapter, we overviewed the roles of PET/CT in colorectal cancer diagnosis and treatment. PET/CT is a whole-body imaging and qualitative diagnostic technique. We should use it cost-effectively.

The following are key points to understand the contents of this review.

- It is possible to diagnose the presence and degree of the primary lesion of colorectal cancer using PET/CT. In order to prevent false positives, accumulation patterns, standardized uptake values (SUV), and anatomical features must be considered to make an accurate evaluation.
- In the diagnosis of lymph node metastasis, proximal lymph node diagnosis is more difficult than that of distant lymph node metastasis, because the difficulty in the diagnosis of proximal lymph node metastasis is due to its proximity to the primary lesion.
- In the evaluation of the recurrence of metastasis in colorectal cancer, the whole-body scan is preferable and its sensitivity and specificity are excellent.
- SUVmax and SUV response index are reported to be the best predictors of radiation chemotherapy for the response assessment.

References

1. Agress HJ, Cooper B. Detection of clinically unexpected malignant and premalignant tumors with whole-body FDG PET: histopathologic comparison. Radiology. 2004;230:417–22.
2. Hashiguchi Y, Muro K, Saito Y, et al. Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2019 for the treatment of colorectal cancer. Int J Clin Oncol. 2020;25:1–42.
3. Huebner RH, Park KC, Shepherd JE, et al. A meta-analysis of the literature for whole-body FDG PET detection of recurrent colorectal cancer. J Nucl Med. 2000;41:1177–89.
4. Wang JY, Tang R, Chiang JM. Value of carcinoembryonic antigen in the management of colorectal cancer. Dis Colon Rectum. 1994;37:272–7.
5. Watson AJM, Lolohea S, Frizelle FA. The role of positron emission tomography in the management of recurrent colorectal cancer: a review. Dis Colon Rectum. 2006;50:102–14.
6. Maninenti PP, Mancini M, Mainolfi C, et al. Detection of colo-rectal liver metastases: prospective comparison of contrast enhanced US, multidetector CT, PET/CT, and 1.5 Tesla MR with extracellular and reticulo-endothelial cell specific contrast agents. Abdom Imaging. 2010;35:511–21.
7. Bamba Y, Itabashi M, Kameoka S. Value of PET/CT imaging for diagnosing pulmonary metastasis of colorectal cancer. Hepatogastroenterology. 2011;58(112):1972–4.
8. Bamba Y, Itabashi M, Kameoka S. Management of local recurrence of colorectal cancer the role of PET/CT. Abdom Imaging. 2011;36(3):322–6.
9. Bamba Y, Itabashi M, Kameoka S. Clinical use of PET/CT in peritoneal carcinomatosis from colorectal cancer. Hepatogastroenterology. 2012;59(117):1408–11.
10. Woff E, Hendlisz A, Garcia C, et al. Monitoring metabolic response using FDG PET-CT during targeted therapy for metastatic colorectal cancer. Eur J Nucl Med Mol Imaging. 2016;43:1792–801.

Chapter 6
Urological Cancer

Noboru Nakaigawa

6.1 Introduction

Cancer cells switch their energy source from mitochondrial oxidative phosphorylation to a glycolytic pathway which does not require oxygen. This metabolic phenomenon in cancer cells is well known as the Warburg effect [1]. As a result, cancer cells accelerate glucose uptake to maintain their survival and proliferation. ^{18}F-2-fluoro-2-deoxyglucose positron emission (FDG PET) is a useful noninvasive tool to evaluate glucose accumulation status and applied mainly as a local diagnosis method for various malignant disease using this metabolic phenomenon in cancer cells. But, FDG PET was not generally used for urological cancer, because the FDG accumulation in targeted cancer was masked by tracer excreted into urinary tract. The development of positron emission tomography/computed tomography (PET/CT), which provided precise anatomic localization of suspicious areas of increased FDG uptake resolved this problem to some extent. Recently, the validlity of FDG PET/CT for the local diagnosis of urological cancer has becoming recognized. Additionally, many investigators reported the potencies of FDG PET/CT as the tool for the qualitative diagnosis of various urological cancers. In this chapter, various attempts using FDG PET or FDG PET/CT effectively were reviewed, especially focusing on renal cell carcinoma (RCC) for which we have investigated the usefulness of FDG PET/CT under various conditions for the recent decade.

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6.2 Renal Cell Carcinoma

Renal cell carcinoma (RCC) accounts for 3% of all adult cancers [2]. The standard treatment for localized RCC is radical or partial nephrectomy with curative intent, but approximately 30% of patients are diagnosed with metastases and an additional 20–40% of patients develop metastases after nephrectomy [3, 4]. The recommended treatments for metastatic RCC were molecular targeted therapy including vascular endothelial growth factor-receptor tyrosine kinase (VEGFr-TKI) and mammalian target of rapamycin inhibitor (mTORi) for the last decade, and recently the immune checkpoint inhibitors are applied and attracting the most attention as novel therapies. The antitumor effect of these systematic therapies is evaluated by CT imaging mainly, and MRI or bone scintigram occasionally, because the blood biomarker which can evaluate the response of RCC to systematic therapies has not been developed.

6.3 The Diagnostic Ability of FDG PET/CT for RCC

FDG PET has not been generally used for renal cell carcinoma (RCC) for two reasons. The first reason is that the urinary excretion of the radiotracer masks the presence of primary lesions, and the second is that the individual RCC demonstrates various degree of FDG accumulation and the accumulation of FDG is too weak to detect in some RCC. Actually, Aide et al. indicated the high rate of false-negative results, when they evaluated the 35 primary renal tumors by FDG PET prospectively. They reported that the sensitivity, specificity, and accuracy of FDG PET were 47%, 80%, and 51%, respectively [5]. Kang et al. reviewed 66 patients retrospectively and reported that the sensitivity for primary RCC was 60% [6]. However, FDG PET/CT is useful for the diagnosis of metastatic lesions from RCC, which is not masked by the tracer excreted in urinary tract. Majhail et al. evaluated the 33 distant RCC metastases by FDG PET and investigated the usefulness of FDG PET histologically using the samples obtained by following biopsy or surgical resection. They reported that sensitivity and specificity were 63.6% and 100%, respectively [7]. There were several reports suggesting the availability of FDG PET/CT as the localizing diagnostic tool of metastatic lesions from RCC. Aide et al. reported that the sensitivity and specificity for RCC metastasis were 100% and 99% [5]. Kang et al. reported that the sensitivity and specificity for retroperitoneal lymph node metastases and/or renal bed recurrence was 75.0% and 100.0%, those for lung metastases were 75.0% and 97.1%, and those for bone metastases were 77.3% and 100.0% [6]. The development of an inline PET/CT system which provides not only functional imaging but also anatomical information improved the diagnostic ability. When we evaluated 243 lesions in 26 patients with metastatic RCC using FDG PET/CT, FDG uptake was detected in 230 of 243 lesions (94.7%) excluding lung or liver metastases with diameters less than 1 cm [8].

6.4 The Prediction of Survival by FDG PET/CT

One of the unique characteristics of metastatic RCC is the variation of their prognosis. Some patients show aggressive progression of disease and die within a few months, and some patients can survive for a few years without treatment. In the era of molecular targeted therapy, Heng et al. advocated the prognostic classification using the following six risk factors; low-performance status, anemia, short interval between the initial diagnosis and treatment, hypercalcemia, hyperplateletemia, and neutrophilia [9]. The median overall survival (OS) of the patients with three or more risk factors (26% of all patients) was between 8.8 months and 2 years and OS rate was only 7%. The median OS of the patients with one or two risk factors (51%) was between 27 months and 2 years and OS was 53%. The median OS of the patients with no risk factor (23%) was not reached in their study in which median follow-up period was 24.5 months, and 2 years OS was 75% (log-rank $P < 0.0001$).

We speculated that the difference in glucose metabolism could be associated with the prognostic diversity of metastatic RCC and evaluated 101 patients with treatment-naïve metastatic RCC by FDG PET/CT and investigated the association of OS and max SUVmax, as which the maximum standardized uptake value in the individual patients [10]. In this study, the patients with higher max SUVmax showed shorter OS (Fig. 6.1a). The multivariate analysis with the standard clinical risk factors revealed that max SUVmax was an independent predictor of survival ($p < 0.001$; hazard ratio 1.265; 95% confidence interval 1.159–1.380). We then divided the 101 patients into three subgroups by max SUVmax. The max SUVmax of 51 patients (50 %) was < 7.0 and the median OS of this subgroup was 41.9 months (95 % CI 34.12–49.68). The max SUVmax of 32 patients (32 %) were ≥ 7.0 and < 12.0, and median OS was 20.6 months (95 % CI 12.4–28.8). The max SUVmax of 18 patients (18 %) was ≥ 12.0, and median OS was 4.2 months (95 % CI 0.7–7.7). Differences in OS for these patient subgroups were statistically significant (< 7.0 vs. ≥ 7.0 and < 12.0: p=0.0001, ≥ 7.0 and < 12.0 vs. ≥ 12.0: p=0.0004) (Fig. 6.1b).

Many investigators reported that pretreatment FDG PET/CT assessment could predict the prognosis of the patient with metastatic RCC [11–13]. Hwang et al. evaluated 65 patients with RCC before treatment by VEGFr-TKI (31 sunitinib, 16 sorafenib, and 9 pazopanib) and reported that metabolic tumor volume (MTV) and total lesion glycolysis (TLG) were independent prognostic factors for predicting progression free survival (PFS) and OS [14].

Next, we investigated prospectively the association between the max SUVmax and OS focusing 81 patients with advanced RCC previously treated by molecular targeted therapy and revealed that the patients with high max SUVmax had a poor prognosis, and multivariate analysis with the clinical risk factors showed that max SUVmax was an independent predictor of survival ($p < 0.001$; hazard ratio 1.156; 95% confidence interval 1.080–1.239) [15]. Subclassification of patients by max SUVmax showed that the median OS of patients with max SUVmax <7.0 (48% of all patients), 7.0–12.0 (37%), and ≥12.0 (15%) were 32.8 months, 15.2 months, and 6.0 months, respectively. These differences are statistically significant (<7.0 versus 7.0–12.0: $p = 0.0333$, 7.0–12.0 versus ≥12.0: $p = 0.0235$) (Fig. 6.1c).

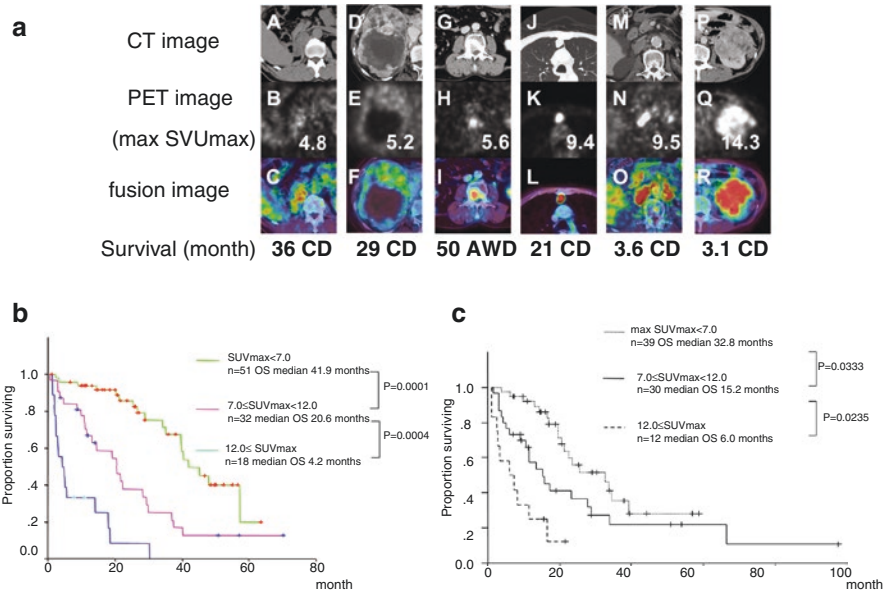

Fig. 6.1 The association of max SUVmax of advanced RCC and survival. (**a**) The features of FDG PET/CT and prognoses: the cases with treatment-naïve advanced RCC. (**A**, **B**, **C**) A case with local recurrence and a max SUVmax of 4.8. (**D**, **E**, **F**) A case with a primary tumor and a max SUVmax of 5.2. (**G**, **H**, **I**) A case with bone metastasis and a max SUVmas of 5.6 (**J**, **K**, **L**) A case with lung metastasis and a max SUVmax of 9.4. (**M**, **N**, **O**) A case with local recurrence and a max SUVmax of 9.5. (**P**, **Q**, **R**) A case with a primary tumor and a max SUVmax of 14.3. **a d g j m p**: CT imaging. **b e h k n q**: PET images. **c f i l o r**: fusion images. *CD* Cancer death. *AWD* Alive with cancer [10]. (**b**) Overall survival curve of 101 patients with treatment-naïve advanced RCC stratified by the pretreatment max SUVmax [10]. (**c**) Overall survival curve of 81 patients with advanced RCC after the first molecular targeted therapy stratified by the max SUVmax before the second molecular targeted therapy [15]

Although most studies focused the patients with metastatic RCC, Nakajima et al. reviewed 139 patients with RCC treated by nephrectomy. In their cohort, 121 patients did not present metastasis. They reported that MTV, TLG assessed by FDG PEET/CT before nephrectomy and pTNM stage were the significant prognostic factors for disease progression [12].

6.5 Tyrosine Kinase Inhibitor and FDG PET/CT

The prognosis of advanced RCC was dramatically improved with the development of VEGFr-TKI targeting angiogenesis in the last decade, but the best responses to VEGFr-TKI were usually found in stable diseases (SD) according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Indeed, the objective response rates of RCC to four VEGFr-TKIs, sunitinib, pazopanib, axitinib, and sorafenib were 31%, 31%, 19%, and 2% in phase III clinical trials, respectively [16–19]. Some RCCs treated with VEGFr-TKIs do not decrease in tumor volume

but maintain long-term dormancy without enlargement of volume or novel metastasis. There have been no clinical answers to the question of whether an individual case treated with VEGFr-TKIs whose tumors did not decrease in size should continue the treatment or change to other therapeutic options.

In order to answer this question, we investigated the relation of the early assessment by FDG PET/CT and long-term prognosis [20]. Thirty patients treated by VEGFr-TKI (sunitinib 16 cases, sorafenib 14 cases) were evaluated by FDG PET/CT before VEGFr-TKI treatment and after 1 month of VEFr-TKI treatment. The progression-free survival (PFS) of the patients whose max SUVmax decreased <20% was shorter than that of the patients whose max SUVmax decreased ≥20% ($P = 0.027$) (Fig. 6.2a, b). The PFS of patients whose tumor diameter sum increased

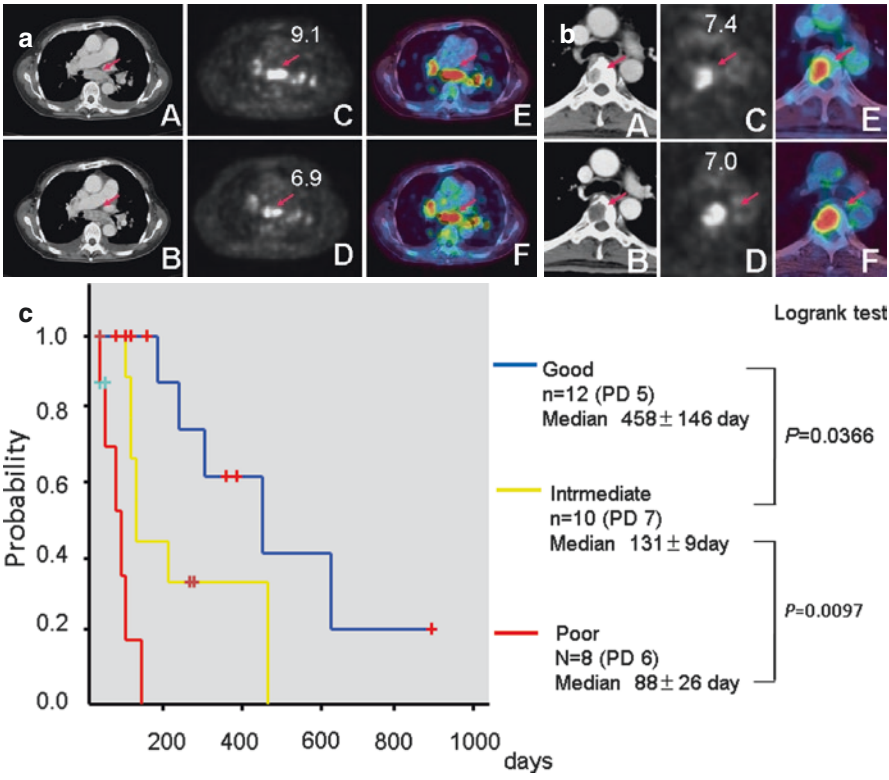

Fig. 6.2 Early assessment of RCC treated with VEGFr-TKI by FDG PET/CT and progression-free survival [20]. (**a**) A patient with lymph node metastasis. The SUVmax decreased 20% at 1 month after VEGFr-TKI treatment started. She maintained an SD for 887 days. Upper lane: assessment before treatment. Lower lane: assessment at 1 month after VEGFr-TKI treatment started. (A, B) CT images (C, D) PET images (E, F) fusion images. (**b**) A patient with bone metastasis. The SUVmax decreased only 5% at 1 month after VEGFr-TKI treatment started. He died on day 88. Upper lane: assessment before treatment. Lower lane: assessment at 1 month after VEGFr-TKI treatment started. (A, B) CT images (C, D) PET images (E, F) fusion images. (**c**) Kaplan-Meier curves of progression-free survival in 30 patients classified by the FDG PET/CT assessment at 1 month after VEGFr-TKI treatment started according to the criteria as below. Good responder: Diameter sum did not increase and SUVmax decreased ≥20%. Intermediate responder: Diameter sum did not increase and SUVmax decreased <20%. Poor responder: Diameter sum increased, or one or more new lesions appeared

was shorter than that of the patient with tumors whose diameter sum did not ($P = 0.006$). The patients were classified into three response groups: good responder (diameter sum did not increase, and SUVmax decreased ≥20%), intermediate responder (diameter sum did not increase, and SUVmax decreased <20%), and poor responder (diameter sum increased, or one or more new lesions appeared). The median PFS of good, intermediate, and poor responders were 458 days, 131 days, and 88 days, respectively (Fig. 6.2c). There was a statistic difference. This work suggested that the early assessment of response to VEGFr-TKIs using a combination of FDG uptake and tumor size could predict long-term antitumor effect of VEGFr-TKIs by expressing the biological dormancy induced by VEGFr-TKIs.

When we investigated the differences in the FDG accumulation change at 1 month after VEGFr-TKI treatment started among various organs where RCC metastases were located focusing 190 RCC lesions including 49 lung metastases, 40 bone metastases, 37 lymph node metastases, 29 abdominal organ metastasis, and others in 48 patients, the response was not influenced by the organs [21].

Some investigators reported the studies about the assessment of the VEGFr-TKI antitumor effect using FDG PET/CT [22, 23]. Kayani et al. reported that 40 patients treated by sunitinib were assessed by FDG PET/CT after 16 weeks and the change in FDG uptake could predict the disease course [24]. Farnebo reported that the assessment of changes standardized uptake normalized to lean body mass (SUL) and TLG after 14 days could predict PFS and OS in patients with RCC treated by VEGFr-TKI (18 sunitinib, 19 sorafenib, and 2 pazopanib) [25].

Additionally, we reported that FDG PET/CT could monitor the real-time antitumor effect during the VEGFr-TKI treatment [26]. We monitored the FDG accumulation in RCC of 38 patients treated with VEGFr-TKI by 162 FDG PET/CT sequentially until they were judged to demonstrate progressive disease (PD) according to RECIST criteria (Fig. 6.3a,b). The 10 patients with RCC whose FDG accumulation was accelerated after the beginning of TKI treatment demonstrated PD soon. The other 28 patients with RCC whose FDG accumulation was suppressed by TKI showed longer PFS (3.6 months vs 6.5 months, $P = 0.0026$), but this suppression in most cases (96%) was temporary and FDG accumulation was accelerated when tumor demonstrated PD. Interestingly, the FDG accumulation at PD was higher than that before VEGFr-TKI treatment in half of the cases. This study suggested that FDG PET/CT had potential as an assessment method monitoring not only the initial response but also following status of RCC during VEGFr-TKI treatment. Additionally, these results suggested that the acceleration of glucose uptake in RCC could be one of the mechanisms by which RCC acquires resistance to VEGFr-TKI treatment.

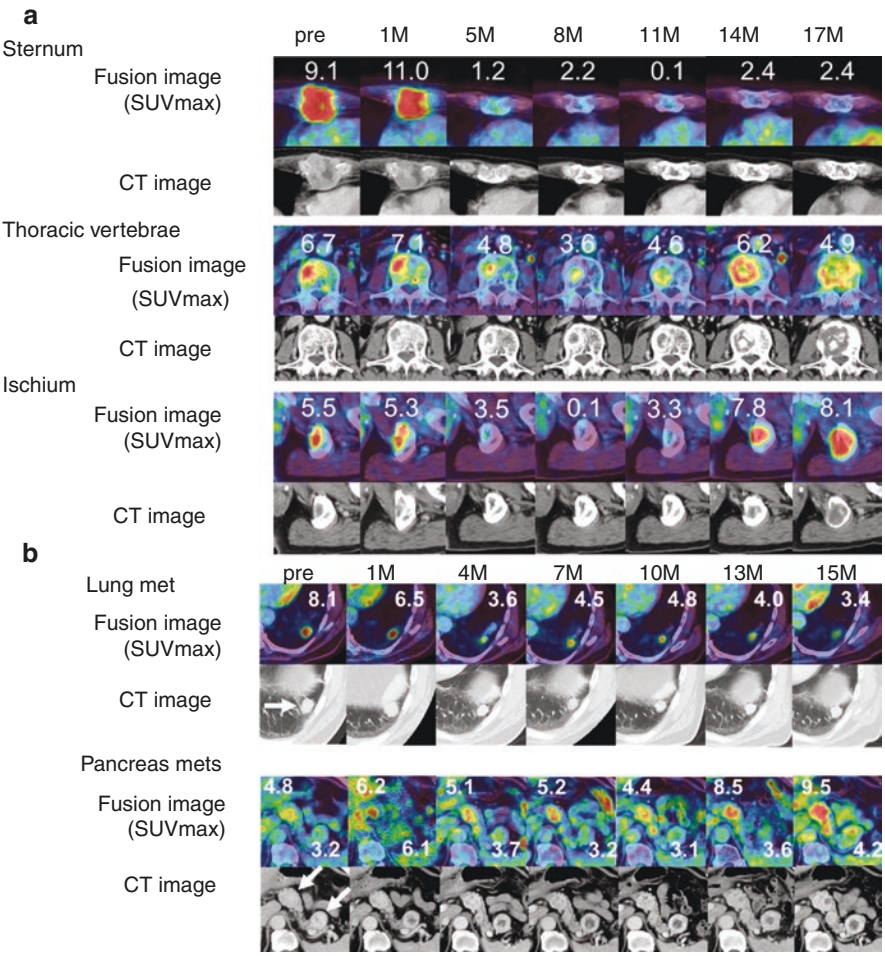

Fig. 6.3 Sequential Assessment of RCC by FDG PET/CT during VEGFr-TKI treatment. (**a**) A patient with multiple bone metastases treated by VEGFr-TKI. The SUVmax of all bone metastases decreased temporally and increased before tumor was judged as PD at the 17th month. Fusion images were upper lanes. The number means SUVmax of each lesion. CT images were lower lanes. "Pre" refers to pretreatment evaluation; "M" refers to month after TKI treatment started [26]. (**b**) A patient with lung and pancreas (head and tail) metastases treated by VEGFr-TKI. The SUVmax of lung metastasis had suppressed during treatment, but the SUVmax of pancreas head metastasis increased before tumor was judged as PD at the 15th month. Fusion images were upper lanes. The number means SUVmax of each lesion. CT images were lower lanes. "Pre" refers to pretreatment evaluation; "M" refers to the number of month after TKI treatment started [26]

6.6 mTOR Inhibitor and FDG PET/CT

Everolimus (EVL) is an oral inhibitor of mammalian target of rapamycin (mTOR), which is downstream in the PI3K/AKT signaling pathway and regulates protein synthesis, metabolism, autophagy, and other various mechanisms associated with cancer survival and progression [27, 28]. The phase III trial demonstrated that EVL prolonged PFS of the patients with metastatic RCC who were failed by prior VEGFr-TKI treatment [29]. However, only 1% of patients who received EVL had confirmed objective tumor responses according to RECIST criteria.

Chen et al. evaluated 63 patients with RCC treated by EVL by FDG PET/CT at baseline and 2 weeks and investigated prospectively the association of the assessment of FDG PET/CT and the change in tumor burden evaluated by CT scan at 8 weeks. They reported that the change in average SUVmax at 2 weeks was the best predictor of change in tumor burden ($P = 0.01$). Baseline average SUVmax was correlated with OS and PFS ($P = 0.023$; 0.020), but not with change in tumor burden [30].

We retrospectively reviewed 30 patients who were treated with EVL and evaluated by FDG PET/CT before and 1 month after starting treatment (Fig. 6.4a, b) [31]. Enrolled patients were divided into two groups by max SUVmax prior to EVL (median = 7.6) and at 1 month after EVL treatment (median = 5.7). PFS were significantly shorter in higher max SUVmax prior to EVL (<7.6, PFS 7.8 months vs 3.5 months, log-rank $P = 0.017$) and at 1 month after EVL (<5.7, PFS 10.6 months vs 2.7 months, log-rank $P = 0.002$) than lower max SUVmax. OS were also significantly shorter in higher max SUVmax prior to EVL (<7.6, OS 18.1 months vs 7.5 months, log-rank $P = 0.010$) and at 1 month after EVL (<5.7, OS 17.2 months vs 7.5 months, log-rank $P = 0.009$) than lower max SUVmax. Multivariate Cox hazard regression analysis indicated that max SUVmax at 1 month after EVL is independent predictor of both PFS and OS although univariate regression analysis showed max SUVmax before EVL is possible predictor.

6.7 Immune Checkpoint Inhibitor and FDG PET/CT

Nivolumab, which is anti-programmed death 1 (anti-PD1) monoclonal antibody, is the novel attractive treatment for metastatic RCC. It was thought to improve the capability of cytotoxic T-lymphocytes under the immunosuppressive conditions induced by malignancies to mount an effective response [32]. In 2015, a phase III randomized study demonstrated the superior effectiveness of nivolumab compared to everolimus for patients with metastatic clear cell RCC who had received previous antiangiogenic treatment [33]. Following this study, nivolumab was recommended as second-line therapy for metastatic RCC treated by VEGFr-TKI.

We investigated the association of FDG PET/CT assessment and the antitumor effect of nivolumab, based on the hypothesis that FDG PET/CT could evaluate the

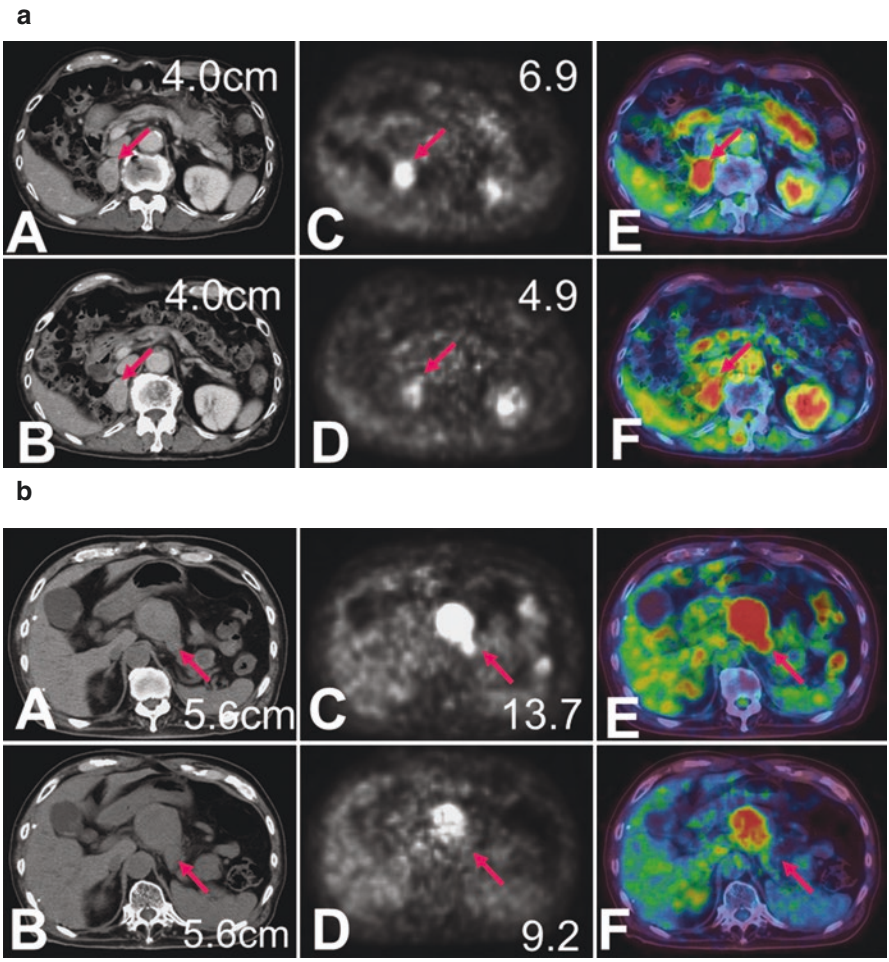

Fig. 6.4 Early assessment by FDG PET/CT of patients with advanced RCC treated with mTOR inhibitor and progression-free survival. (**a**) A patient with adrenal metastasis. The max SUVmax before treatment and 1 month after mTOR inhibitor started were 6.9 and 4.9, respectively. His progression-free survival was 24.6 months. Upper lane: assessment before treatment. Lower lane: assessment at 1 month after VEGFr-TKI treatment started. (A, B) CT images (C, D) PET images (E, F) fusion images [31]. (**b**) A patient with pancreas metastasis. The max SUVmax before treatment and 1 month after mTOR inhibitor started were 13.7 and 9.2, respectively. His progression-free survival was 5.0 months. Upper lane: assessment before treatment. Lower lane: assessment at 1 month after VEGFr-TKI treatment started. (A, B) CT images (C, D) PET images (E, F) fusion images [31]

reactivation of cytotoxic T-lymphocytes (Fig 6.5a, b) [34]. We evaluated 30 lesions in 9 patients with metastatic RCC who were treated by nivolumab. All patients underwent FDG PET/CT at baseline and 1 month as a first response assessment and contrast-enhanced or non-contrast-enhanced CT scan at 4 month as a second response assessment. RCC lesions whose diameter decreased ≥30% at second

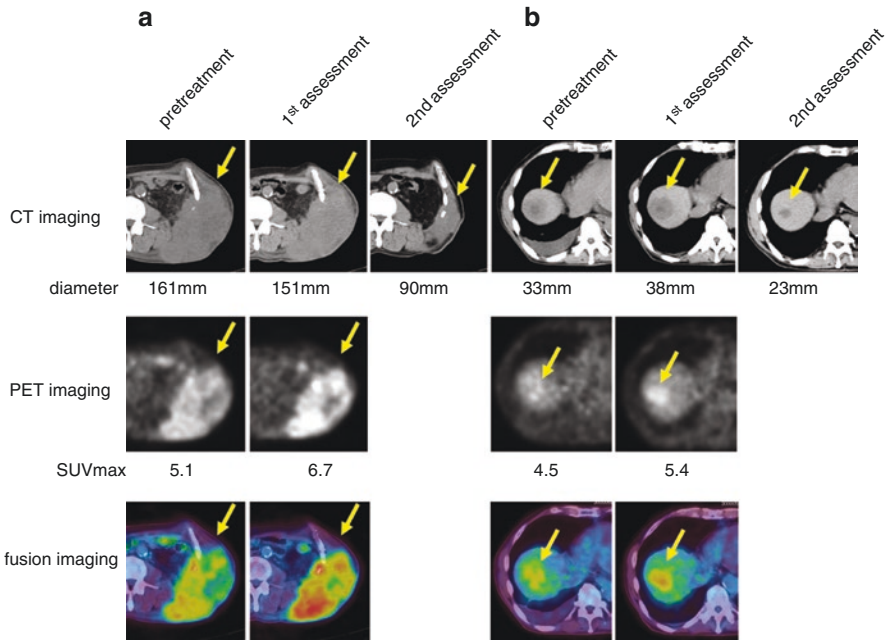

Fig. 6.5 The acceleration of FDG uptake in RCC treated with nivolumab predicts the following tumor shrinkage. A patient with subcutaneous metastasis and hepatic metastasis. The SUVmax of subcutaneous metastasis (**a**) and hepatic metastasis (**b**) increased 31% and 20% at 1 month after nivolumab started, and the diameters decreased 44% and 30% at fourth month, respectively [34]

assessment were defined as responding and lesions whose diameter did not decrease ≥30% were defined as non-responding. There were 18 responding lesions and 12 non-responding lesions. We compared change in diameter and SUVmax at first assessment with FDG PET/CT, respectively. All lesions with decreased diameter and elevated SUVmax at first assessment with FDG PET/CT showed responding at second assessment by CT scan, while most lesions with increased diameter and declined SUVmax at first assessment showed non-responding at second assessment. The multivariate logistic regression analyses revealed that only the elevation of SUVmax at 1 month was an independent predictor ($P = 0.025$, OR: 13.087, 95% CI: 1.373–124.716). Our findings suggest that the early assessment using FDG PET/CT can be effective to predict the response of RCC to nivolumab.

6.8 Other Urological Cancer

6.8.1 Testicular Tumor

Testicular tumor (TT) is the most common malignancy among men aged 15–44 years old [35]. The standard treatment for localized TT is surgical resection, but approximately 70% of patients are diagnosed with metastases [36]. TT shows high

sensitivity to combination chemotherapy using cisplatinum and the cure rates are high even among patients with poor risk and the evaluation of residual viable tumor after chemotherapy is clinically very important [37].

FDG PET/CT is used for the initial staging, the relapse diagnosis, and the confirmation of the residual viable tumor after systematic treatment in actual clinical practice. Ambrosini et al. investigated the usefulness of FDG as the assessment tool for initial staging targeting 51 patients with seminoma and 70 patients with non-seminoma retrospectively [38]. They reported that the sensitivity and the specificity of FDG PET/CT for seminoma was 92% and 84%, and that for non-seminoma was 77% and 95%, respectively. They recommended the FDG PET/CT assessment for initial staging because FDG PET/CT had an impact on deciding the treatment strategy in 92% of patients with seminoma and 84% of patients with non-seminoma.

There is no clear evidence of superiority of FDG PET/CT to diagnose relapse sites of TT, but there were some reports suggesting the usefulness. Cook et al. reported that evaluated 15 cases rising tumor markers by FDG PET/CT when CT had been unable to determine a site of recurrence disease. Thirteen cases showed abnormal FDG accumulation and all cases were true positive, confirmed either by surgery or through progression on following CT assessment [39].

About evaluation of residual viable tumor after chemotherapy, many retrospective studies and some meta-analyses were reported. The meta-analysis focusing five studies with 130 patients demonstrated the superiority of FDG PET in predicting viable residual tumors compared with CT scan alone [40]. FDG PET and CT scan showed a specificity 92% vs 59%, a sensitivity 72% vs 63%, positive predictive value 70% vs 28%, and negative predictive value 93% vs 86%, respectively. The other meta-analysis focusing nine studies including 375 patients with seminoma demonstrated that a sensitivity, a specificity, positive predictive value, negative predictive value, and accuracy of FDG PET or FDG PET/CT were 78%, 86%, 58%, 94%, and 84%, respectively [41]. This study suggested that the patients with negative FDG PET/CT findings warranted follow-up and could avoid inappropriate additional treatment. On the other hand, the prospective trial with 121 patients with non-seminoma demonstrated that FDG-PET is unable to give a clear additional clinical benefit to the standard diagnostic procedures, CT and serum tumor marker, in the prediction of tumor viability in residual masses [42]. Prediction of tumor viability with FDG-PET was correct in 56%, and was not better than the accuracy of CT (55%) or serum tumor marker (56%).

Based on these studies, FDG PET/CT is widely used in various situation during treatment for testicular tumor. Especially, the FDG PET/CT assessment is critical when the size of metastatic lesions evaluated by CT did not change during subsequent chemotherapy.

6.8.2 Bladder Cancer and Upper Urinary Tract Cancer

Bladder cancer (BC) is the ninth most common cancer worldwide [43]. The patients with non-muscle-invasive (superficial) BC who occupy 70% of all patients were treated by transurethral resection. They tend to recur but are generally not

life-threatening. Remaining 30% of patients presented muscle-invasive tumor. The case without distant metastasis was treated by cystectomy with or without chemotherapy and the case with metastatic disease were treated by chemotherapy, but associated with a high risk of death [44]. The conventional imaging for BC are CT, MRI, and bone scans. MRI is suitable for the diagnosis of local muscle invasion.

FDG PET/CT is not generally applied for diagnosis of BC, because the excreted radiotracer masks the tracer accumulation in BC. In order to improve the diagnosability of FDG PET/CT, forced diuresis using furosemide with or without oral hydration, or delayed pelvic imaging after spontaneous emptying of the bladder were effective. Lodde et al. evaluated 44 patients with muscle-invasive BC before radical cystectomy by FDG PET/CT with forced diuresis and delayed imaging. They reported that the sensitivity of FDG PET/CT was slightly higher than that of CT (85% vs 77%), but the specificity was low (25% vs 50%) [45]. A recent meta-analysis focus in 6 studies with 175 patients evaluated the diagnostic accuracy of FDG PET/CT for bladder lesions. The sensitivity and specificity of PET or PET/CT for the detection of BC was 80.0% and 84.0%, respectively [46].

Mertens et al. compared the staging by FDG PET/CT with the conventional staging with contrast-enhanced CT prospectively targeting 96 patients with muscle-invasive BC [47]. Upstaging by FDG PET/CT was detected in 19.8% of patients and downstaging by FDG PET/CT was in 2.1%. Clinical management changed for 13.5% of patients as a result of FDG PET/CT upstaging. In eight patients, FDG PET/CT detected second primary tumors. They concluded that FDG PET/CT provides important additional staging information which influence the treatment and recommended the initial staging of muscle-invasive BC. Apolo et al. evaluated 57 patients with BC by FDG PET/CT and suggested the impact on clinical decision of FDG PET/CT assessment [48]. The sensitivity and specificity were 87% and 88%. Additional malignant lesions were detected by FDG PET/CT in 40% of patients and clinicians changed their planned management in 68% of patients.

FDG PET/CT can be applied for the assessment of antitumor effect of chemotherapy. Giannatempo et al. evaluated 31 patients with metastatic BC treated by the modified combination of methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) by FDG PET after 2 cycles. The median PFS of 23 patients whose SUVmax defined as the highest value of SUV within a region of interest decreased >20% after 2 cycles was 8.0 months and that of other 8 patients was 3.0 months. There was a statistic difference [49]. Neoadjuvant chemotherapy (NAC) for muscle-invasive BC before cystectomy is standard treatment. Soubra et al. evaluated 37 patients with muscle-invasive BC who underwent MVAC or the combination of gemcitabine and cisplatin (GC) as NAC by FDG PET/CT before cystectomy. FDG PET/CT had 75% sensitivity and 90% specificity in identifying those with complete pathologic response with a 100% change in SUV_{max} [50].

Upper urinary tract cancer (UUTC) including renal pelvic cancer and ureter cancer are rare and typically urothelial carcinoma as BC. Asai et al. reported that 83% of 48 patients with UUTC had positive results from FDG PET/CT examination with only oral hydration. The positive predictive value was 95% [51]. Tanaka et al. evaluated 142 metastatic lesions from UUTC and the sensitivity of FDG PET/CT was significantly better than that of CT (85% vs 50%) [52].

6.8.3 Prostate Cancer

Prostate cancer (PCa) is the second most common cancer in men worldwide [53]. The localized PCa were treated by prostatectomy or radiation therapy, and metastatic PCa were treated by hormonal therapy and following chemotherapies. The conventional imaging for PCa are CT, Magnetic resonance imaging (MRI), and bone scans. Some investigators evaluated the usefulness of FDG PET/CT as the assessment of prostate cancer. But most study demonstrated low sensitivity and low specificity [54–56]. But, several studies about the effective use of FDG PET/CT for limited objects were reported. Oyama et al. evaluated 42 patients with PCa before surgery or endocrine therapy and reported the SUV assessed by FDG PET could be used as a prognostic marker [57]. Shreve et al. evaluated 22 patients with metastatic PCa and reported that FDG PET can help identify osseous and soft-tissue metastases of prostate cancer with a high positive predictive value but is less sensitive than bone scintigraphy in the identification of osseous metastases [58].

Jadver suggested that the causes were the low glucose uptake in well-differentiated PCa, masking by the urinary excreted tracer, and the difficulties in the differential diagnosis with the acute or chronic prostatitis and benign prostatic hyperplasia elevated FDG uptake. Therefore, he suggested that FDG PET was only limited in the restaging of selected PCa patients with high-grade hormone-resistant disease and poorly differentiated lesions, those were speculated to increase FDG uptake [59].

Summary and Key Points

In this chapter, we reviewed the current role of FDG PET/CT in the management of urological cancer and clinical studies suggesting the novel potencies of FDG PET/CT as the assessment tool of urological cancer.

The following are key points to understand the contents of this review.

- FDG PET/CT has potencies as a predictive biomarker for advanced renal cell carcinoma. The advanced renal cell carcinoma with high FDG accumulation showed poor response to molecular targeted therapy and short overall survival.
- One-month assessment using FDG PET/CT can predict the long-term response of advanced renal cell carcinoma to molecular targeted therapy and immune checkpoint inhibitor.
- FDG PET/CT is used for the initial staging, the relapse diagnosis, and the confirmation of the residual viable tumor after systematic treatment in the management of testicular tumor.
- When bladder cancer is assessed by FDG PET/CT, forced diuresis using furosemide, hydration, and delayed imaging after urination improve the diagnosability.
- In the management of prostate cancer, the advantage of FDG PET/CT is limited.

Although FDG PET/CT is supposed to be unsuitable for urological cancer due to the low FDG accumulation or masking by excreted tracer, FDG PET/CT which expresses the biological activity is a useful imaging biomarker in various situation during the management of urological malignancies.

References

1. Chen Z, Liu M, Li L, Chen L. Involvement of the Warburg effect in non-tumor diseases processes. J Cell Physiol. 2018;233(4):2839–49.
2. Chow WH, Devesa SS, Warren JL, Fraumeni JF Jr. Rising incidence of renal cell cancer in the United States. JAMA. 1999;281(17):1628–31.
3. Linehan WM, Walther MM, Alexander RB, Rosenberg SA. Adoptive immunotherapy of renal cell carcinoma: studies from the surgery branch, National Cancer Institute. Semin Urol. 1993;11(1):41–3.
4. Han KR, Bleumer I, Pantuck AJ, Kim HL, Dorey FJ, Janzen NK, Zisman A, Dinney CP, Wood CG, Swanson DA, Said JW, Figlin RA, Mulders PF, Belldegrun AS. Validation of an integrated staging system toward improved prognostication of patients with localized renal cell carcinoma in an international population. J Urol. 2003;170:2221–4.
5. Aide N, Cappele O, Bottet P, Bensadoun H, Regeasse A, Comoz F, Sobrio F, Bouvard G, Agostini D. Efficiency of [(18)F]FDG PET in characterising renal cancer and detecting distant metastases: a comparison with CT. Eur J Nucl Med Mol Imaging. 2003;30(9):1236–45.
6. Kang DE, White RL Jr, Zuger JH, Sasser HC, Teigland CM. Clinical use of fluorodeoxyglucose F 18 positron emission tomography for detection of renal cell carcinoma. J Urol. 2004;171(5):1806–9.
7. Majhail NS, Urbain JL, Albani JM, Kanvinde MH, Rice TW, Novick AC, Mekhail TM, Olencki TE, Elson P, Bukowski RM. F-18 fluorodeoxyglucose positron emission tomography in the evaluation of distant metastases from renal cell carcinoma. J Clin Oncol. 2003;21(21):3995–4000.
8. Namura K, Minamimoto R, Yao M, Makiyama K, Murakami T, Sano F, Hayashi N, Tateishi U, Ishigaki H, Kishida T, Miura T, Kobayashi K, Noguchi S, Inoue T, Kubota Y, Nakaigawa N. Impact of maximum standardized uptake value (SUVmax) evaluated by 18-Fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (18F-FDG-PET/CT) on survival for patients with advanced renal cell carcinoma: a preliminary report. BMC Cancer. 2010;10:667.
9. Heng DY, Xie W, Regan MM, Warren MA, Golshayan AR, Sahi C, Eigl BJ, Ruether JD, Cheng T, North S, Venner P, Knox JJ, Chi KN, Kollmannsberger C, McDermott DF, Oh WK, Atkins MB, Bukowski RM, Rini BI, Choueiri TK. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study. J Clin Oncol. 2009;27(34):5794–9.
10. Nakaigawa N, Kondo K, Tateishi U, Minamimoto R, Kaneta T, Namura K, Ueno D, Kobayashi K, Kishida T, Ikeda I, Hasumi H, Makiyama K, Kubota Y, Inoue T, Yao M. FDG PET/CT as a prognostic biomarker in the era of molecular-targeting therapies: max SUVmax predicts survival of patients with advanced renal cell carcinoma. BMC Cancer. 2016;16:67.
11. Komek H, Altindag S. Can C, Aguloglu N, Morcali H, Tuzun a, Kavak S. the prognostic value of preoperative PET/CT evaluation of maximum standardized uptake value in renal cell carcinomas. Ann Ital Chir. 2017;88:48–54.
12. Nakajima R, Matsuo Y, Kondo T, Abe K, Sakai S. Prognostic value of metabolic tumor volume and total lesion glycolysis on preoperative 18F-FDG PET/CT in patients with renal cell carcinoma. Clin Nucl Med. 2017;42(4):e177–82.
13. Alongi P, Picchio M, Zattoni F, Spallino M, Gianolli L, Saladini G, Evangelista L. Recurrent renal cell carcinoma: clinical and prognostic value of FDG PET/CT. Eur J Nucl Med Mol Imaging. 2016;43(3):464–73.
14. Hwang SH, Cho A, Yun M, Choi YD, Rha SY, Kang WJ. Prognostic value of pretreatment metabolic tumor volume and Total lesion glycolysis using 18F-FDG PET/CT in patients with metastatic renal cell carcinoma treated with anti-vascular endothelial growth factor-targeted agents. Clin Nucl Med. 2017;42(5):e235–41.
15. Nakaigawa N, Kondo K, Kaneta T, Tateishi U, Minamimoto R, Namura K, Ueno D, Kobayashi K, Kishida T, Ikeda I, Hasumi H, Makiyama K, Hayashi N, Osaka K, Muraoka K, Izumi K,

Kawahara T, Teranishi JI, Miyoshi Y, Yumura Y, Uemura H, Inoue T, Yao M. FDG PET/CT after first molecular targeted therapy predicts survival of patients with renal cell carcinoma. Cancer Chemother Pharmacol. 2018;81(4):739–44.
16. Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Rixe O, Oudard S, Negrier S, Szczylik C, Kim ST, Chen I, Bycott PW, Baum CM, Figlin RA. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med. 2007;356(2):115–24.
17. Escudier B, Eisen T, Stadler WM, Szczylik C, Oudard S, Siebels M, Negrier S, Chevreau C, Solska E, Desai AA, Rolland F, Demkow T, Hutson TE, Gore M, Freeman S, Schwartz B, Shan M, Simantov R, Bukowski RM, TARGET study Group. Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med. 2007;356(2):125–34.
18. Rini BI, Escudier B, Tomczak P, Kaprin A, Szczylik C, Hutson TE, Michaelson MD, Gorbunova VA, Gore ME, Rusakov IG, Negrier S, Ou YC, Castellano D, Lim HY, Uemura H, Tarazi J, Cella D, Chen C, Rosbrook B, Kim S, Motzer RJ. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. Lancet. 2011;378(9807):1931–9.
19. Motzer RJ, Hutson TE, Cella D, Reeves J, Hawkins R, Guo J, Nathan P, Staehler M, de Souza P, Merchan JR, Boleti E, Fife K, Jin J, Jones R, Uemura H, De Giorgi U, Harmenberg U, Wang J, Sternberg CN, Deen K, McCann L, Hackshaw MD, Crescenzo R, Pandite LN, Choueiri TK. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. N Engl J Med. 2013;369:722–31.
20. Ueno D, Yao M, Tateishi U, Minamimoto R, Makiyama K, Hayashi N, Sano F, Murakami T, Kishida T, Miura T, Kobayashi K, Noguchi S, Ikeda I, Ohgo Y, Inoue T, Kubota Y, Nakaigawa N. Early assessment by FDG-PET/CT of patients with advanced renal cell carcinoma treated with tyrosine kinase inhibitors is predictive of disease course. BMC Cancer. 2012;12:162.
21. Kakizoe M, Yao M, Tateishi U, Minamimoto R, Ueno D, Namura K, Makiyama K, Hayashi N, Sano F, Kishida T, Kobayashi K, Noguchi S, Ikeda I, Ohgo Y, Taguri M, Morita S, Inoue T, Kubota Y, Nakaigawa N. The early response of renal cell carcinoma to tyrosine kinase inhibitors evaluated by FDG PET/CT was not influenced by metastatic organ. BMC Cancer. 2014;14:390.
22. Lyrdal D, Boijsen M, Suurküla M, Lundstam S, Stierner U. Evaluation of sorafenib treatment in metastatic renal cell carcinoma with 2-fluoro-2-deoxyglucose positron emission tomography and computed tomography. Nucl Med Commun. 2009;30(7):519–24.
23. Khandani AH, Cowey CL, Moore DT, Gohil H, Rathmell WK. Primary renal cell carcinoma: relationship between 18F-FDG uptake and response to neoadjuvant sorafenib. Nucl Med Commun. 2012;33(9):967–73.
24. Kayani I, Avril N, Bomanji J, Chowdhury S, Rockall A, Sahdev A, Nathan P, Wilson P, Shamash J, Sharpe K, Lim L, Dickson J, Ell P, Reynolds A, Powles T. Sequential FDG-PET/CT as a biomarker of response to Sunitinib in metastatic clear cell renal cancer. Clin Cancer Res. 2011;17(18):6021–8.
25. Farnebo J, Grybäck P, Harmenberg U, Laurell A, Wersäll P, Blomqvist LK, Ullén A, Sandström P. Volumetric FDG-PET predicts overall and progression-free survival after 14 days of targeted therapy in metastatic renal cell carcinoma. BMC Cancer. 2014;14:408.
26. Nakaigawa N, Kondo K, Ueno D, Namura K, Makiyama K, Kobayashi K, Shioi K, Ikeda I, Kishida T, Kaneta T, Minamimoto R, Tateishi U, Inoue T, Yao M. The acceleration of glucose accumulation in renal cell carcinoma assessed by FDG PET/CT demonstrated acquisition of resistance to tyrosine kinase inhibitor therapy. BMC Cancer. 2017;17(1)
27. Laplante M, Sabatini DM. mTOR signaling in growth control and disease. Cell. 2012;149(2):274–93.
28. Sengupta S, Peterson TR, Sabatini DM. Regulation of the mTOR complex 1 pathway by nutrients, growth factors, and stress. Mol Cell. 2010;40(2):310–22.
29. Motzer RJ, Escudier B, Oudard S, Hutson TE, Porta C, Bracarda S, Grünwald V, Thompson JA, Figlin RA, Hollaender N, Urbanowitz G, Berg WJ, Kay A, Lebwohl D. Ravaud a;

RECORD-1 study group. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. Lancet. 2008;372(9637):449–56.
30. Chen JL, Appelbaum DE, Kocherginsky M, Cowey CL, Rathmell WK, McDermott DF, Stadler WM. FDG-PET as a predictive biomarker for therapy with everolimus in metastatic renal cell cancer. Cancer Med. 2013;2(4):545–52.
31. Ito H, Kondo K, Kawahara T, Kaneta T, Tateishi U, Ueno D, Namura K, Kobayashi K, Miyoshi Y, Yumura Y, Makiyama K, Hayashi N, Hasumi H, Osaka K, Yokomizo Y, Teranishi JI, Hattori Y, Inoue T, Uemura H, Yao M, Nakaigawa N. One-month assessment of renal cell carcinoma treated by everolimus using FDG PET/CT predicts progression-free and overall survival. Cancer Chemother Pharmacol. 2017;79(5):855–61.
32. Hamid O, Carvajal RD. Anti-programmed death-1 and anti-programmed death-ligand 1 antibodies in cancer therapy. Expert Opin Biol Ther. 2013;13(6):847–61.
33. Motzer RJ, Escudier B, McDermott DF, George S, Hammers HJ, Srinivas S, Tykodi SS, Sosman JA, Procopio G, Plimack ER, Castellano D, Choueiri TK, Gurney H, Donskov F, Bono P, Wagstaff J, Gauler TC, Ueda T, Tomita Y, Schutz FA, Kollmannsberger C, Larkin J, Ravaud A, Simon JS, Xu LA, Waxman IM, Sharma P, CheckMate 025 Investigators. Nivolumab versus Everolimus in advanced renal-cell carcinoma. N Engl J Med. 2015;373(19):1803–13.
34. Tabei T, Nakaigawa N, Kaneta T, Ikeda I, Kondo K, Makiyama K, Hasumi H, Hayashi N, Kawahara T, Izumi K, Osaka K, Muraoka K, Teranishi JI, Miyoshi Y, Yumura Y, Uemura H, Kobayashi K, Inoue T, Yao M. Early assessment with ^{18}F-2-fluoro-2-deoxyglucose positron emission tomography/computed tomography to predict short-term outcome in clear cell renal carcinoma treated with nivolumab. BMC Cancer. 2019;19(1):298.
35. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin. 2018;68(1):7–30.
36. Woldu SL, Bagrodia A. Update on epidemiologic considerations and treatment trends in testicular cancer. Curr Opin Urol. 2018;28(5):440–7.
37. Heidenreich A, Paffenholz P, Nestler T, Pfister D. European Association of Urology guidelines on testis cancer: important take home messages. Eur Urol Focus. 2019;5:742.
38. Ambrosini V, Zucchini G, Nicolini S, Berselli A, Nanni C, Allegri V, Martoni A, Rubello D, Cricca A, Fanti S. 18F-FDG PET/CT impact on testicular tumours clinical management. Eur J Nucl Med Mol Imaging. 2014;41(4):668–73.
39. Cook GJ, Sohaib A, Huddart RA, Dearnaley DP, Horwich A, Chua S. The role of 18F-FDG PET/CT in the management of testicular cancers. Nucl Med Commun. 2015;36(7):702–8.
40. Müller J, Schrader AJ, Jentzmik F, Schrader M. Assessment of residual tumours after systemic treatment of metastatic seminoma: ^{18}F-2-fluoro-2-deoxy-D-glucose positron emission tomography - meta-analysis of diagnostic value. Urologe A. 2011;50(3):322–7.
41. Treglia G, Sadeghi R, Annunziata S, Caldarella C, Bertagna F, Giovanella L. Diagnostic performance of fluorine-18-fluorodeoxyglucose positron emission tomography in the postchemotherapy management of patients with seminoma: systematic review and meta-analysis. Biomed Res Int. 2014;2014:852681.
42. Oechsle K, Hartmann M, Brenner W, Venz S, Weissbach L, Franzius C, Kliesch S, Mueller S, Krege S, Heicappell R, Bares R, Bokemeyer C, de Wit M, German Multicenter Positron Emission Tomography Study Group. [18F]Fluorodeoxyglucose positron emission tomography in nonseminomatous germ cell tumors after chemotherapy: the German multicenter positron emission tomography study group. J Clin Oncol. 2008;26(36):5930–5.
43. Antoni S, Ferlay J, Soerjomataram I, Znaor A, Jemal A, Bray F. Bladder Cancer incidence and mortality: a global overview and recent trends. Eur Urol. 2017;71(1):96–108.
44. Kaufman DS, Shipley WU, Feldman AS. Bladder cancer. Lancet. 2009;374(9685):239–49.
45. Lodde M, Lacombe L, Friede J, Morin F, Saourine A, Fradet Y. Evaluation of fluorodeoxyglucose positron-emission tomography with computed tomography for staging of urothelial carcinoma. BJU Int. 2010;106(5):658–63.
46. Wang N, Jiang P, Lu Y. Is fluorine-18 fluorodeoxyglucose positron emission tomography useful for detecting bladder lesions? A meta-analysis of the literature. Urol Int. 2014;92(2):143–9.

47. Mertens LS, Fioole-Bruining A, Vegt E, Vogel WV, van Rhijn BW, Horenblas S. Impact of (18) F-fluorodeoxyglucose (FDG)-positron-emission tomography/computed tomography (PET/CT) on management of patients with carcinoma invading bladder muscle. BJU Int. 2013;112(6):729–34.
48. Apolo AB, Riches J, Schöder H, Akin O, Trout A, Milowsky MI, Bajorin DF. Clinical value of fluorine-18 2-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography in bladder cancer. J Clin Oncol. 2010;28(25):3973–8.
49. Giannatempo P, Alessi A, Miceli R, Raggi D, Farè E, Nicolai N, Serafini G, Padovano B, Piva L, Biasoni D, Torelli T, Catanzaro M, Stagni S, Maffezzini M, Mariani L, Gianni AM, Sonpavde G, Salvioni R, Necchi A, Crippa F. Interim fluorine-18 fluorodeoxyglucose positron emission tomography for early metabolic assessment of therapeutic response to chemotherapy for metastatic transitional cell carcinoma. Clin Genitourin Cancer. 2014;12(6):433–9.
50. Soubra A, Gencturk M, Froelich J, Balaji P, Gupta S, Jha G, Konety BR. FDG-PET/CT for assessing the response to Neoadjuvant chemotherapy in bladder cancer patients. Clin Genitourin Cancer. 2018;16(5):360–4.
51. Asai S, Fukumoto T, Tanji N, Miura N, Miyagawa M, Nishimura K, Yanagihara Y, Shirato A, Miyauchi Y, Kikugawa T, Yokoyama M. Fluorodeoxyglucose positron emission tomography/computed tomography for diagnosis of upper urinary tract urothelial carcinoma. Int J Clin Oncol. 2015;20(5):1042–7.
52. Tanaka H, Yoshida S, Komai Y, Sakai Y, Urakami S, Yuasa T, Yamamoto S, Masuda H, Koizumi M, Kohno A, Fukui I, Yonese J, Fujii Y, Kihara K. Clinical value of 18F-fluorodeoxyglucose positron emission tomography/computed tomography in upper tract urothelial carcinoma: impact on detection of metastases and patient management. Urol Int. 2016;96(1):65–72.
53. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424.
54. Liu IJ, Zafar MB, Lai YH, Segall GM, Terris MK. Fluorodeoxyglucose positron emission tomography studies in diagnosis and staging of clinically organ-confined prostate cancer. Urology. 2001;57(1):108–11.
55. Picchio M, Messa C, Landoni C, Gianolli L, Sironi S, Brioschi M, Matarrese M, Matei DV, De Cobelli F, Del Maschio A, Rocco F, Rigatti P, Fazio F. Value of [11C]choline-positron emission tomography for re-staging prostate cancer: a comparison with [18F]fluorodeoxyglucose-positron emission tomography. J Urol. 2003;169(4):1337–40.
56. Watanabe H, Kanematsu M, Kondo H, Kako N, Yamamoto N, Yamada T, Goshima S, Hoshi H, Bae KT. Preoperative detection of prostate cancer: a comparison with 11C-choline PET, 18F-fluorodeoxyglucose PET and MR imaging. J Magn Reson Imaging. 2010;31(5):1151–6.
57. Oyama N, Akino H, Suzuki Y, Kanamaru H, Miwa Y, Tsuka H, Sadato N, Yonekura Y, Okada K. Prognostic value of 2-deoxy-2-[F-18]fluoro-D-glucose positron emission tomography imaging for patients with prostate cancer. Mol Imaging Biol. 2002;4(1):99–104.
58. Shreve PD, Grossman HB, Gross MD, Wahl RL. Metastatic prostate cancer: initial findings of PET with 2-deoxy-2-[F-18]fluoro-D-glucose. Radiology. 1996;199(3):751–6.
59. Jadvar H. Is there use for FDG-PET in prostate Cancer? Semin Nucl Med. 2016;46(6):502–6.

Chapter 7
Bone and Soft-Tissue Tumors

Hitoshi Yamada

7.1 Bone and Soft-Tissue Tumors

Bone and soft-tissue tumors are categorized into the following three classes: benign, intermediate, and malignant. Several tumor types are present in each class. Malignant bone and soft-tissue tumors are known as sarcomas; they are extremely rare and comprise approximately 1% of all malignant tumors [1]. Accurate diagnosis of malignant bone and soft-tissue tumors is challenging owing to their rarity and variety. F-18 FDG PET scanning is useful to diagnose bone and soft-tissue tumors. A patient with chondrosarcoma of the right pelvic bone showed F-18 FDG accumulation, and the tumor was located at the P1–2 level [2]. The external iliac artery was intact, and hip transposition was performed after tumor removal (Fig. 7.1) using temporary external fixation [3]. The patient was able to walk with complete weight-bearing using two crutches 35 days postoperatively. Furthermore, another patient having alveolar soft part sarcoma with femur invasion showed F-18 FDG accumulation on PET/MRI (Fig. 7.2). Another rare case of a high-grade malignant bone tumor arising from the proximal tibia was examined, wherein the lesion was a little painful. The lesion was suspected to be diaphyseal medullary stenosis [4] and observed carefully. A malignant bone tumor developed during observation, and 1 year and 7 months later, it was observed via PET/MRI (Fig. 7.3a–d). This patient was treated with neoadjuvant chemotherapy for osteosarcoma. During surgery, the tibia with the tumor was elevated, and the pedicle was frozen using liquid nitrogen [5] before prosthetic replacement (Fig. 7.3e, f). F-18 FDG is absorbed into areas with inflammatory activity and into some benign or intermediate tumors, including

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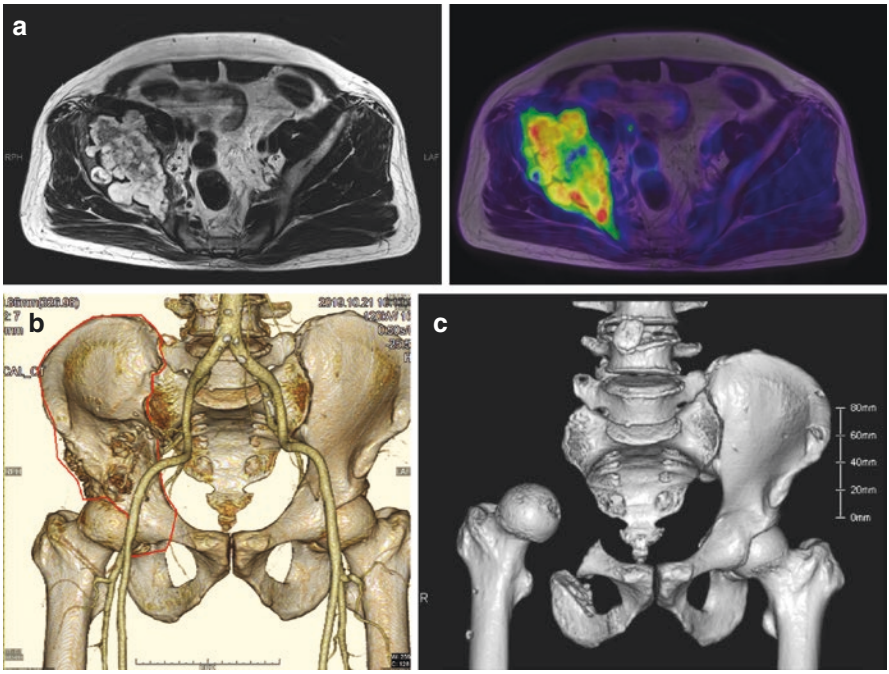


Fig. 7.1 Chondrosarcoma of the right pelvis. (**a**) T2-weighted MRI showing right pelvic bone tumor expanding with a lobulated structure. PET/MRI showing abnormal F-18 FDG accumulation in the tumor. (**b**) Three-dimensional CT angiography showing intact right external iliac artery and planned excision range. (**c**) Postoperative 3D-CT scans showing hip transposition where the tumor was removed

those of sarcoidosis [6] and schwannoma [7] as well as giant cell tumors [8, 9]. In a rare case of chronic expanding hematoma postinfection, PET/MRI revealed a lesion that mimicked a malignant tumor (Fig. 7.4), which was similar to an undifferentiated pleomorphic sarcoma (Fig. 7.5). A patient with sarcoidosis was referred to our hospital for scanning and treatment after the removal of a retroperitoneal leiomyosarcoma at another hospital. PET/CT scanning was performed to detect any recurrence or metastases. Swelling and abnormal F-18 FDG accumulation in the bilateral multiple hilar lymph nodes were observed (Fig. 7.6a). Biopsy confirmed the diagnosis of inflammatory granuloma rather than metastasis (Fig. 7.6b). In another case, F-18 FDG PET scanning revealed a phosphaturic mesenchymal tumor that caused osteomalacia (Fig. 7.7); thus, whole-body imaging should be performed for such patients [10]. In another patient with localized Castleman's disease in soft tissue, PET/MRI revealed F-18 FDG accumulation (Fig. 7.8). Localized Castleman's disease is a benign lymphoepithelial disorder, and its occurrence in soft tissue is quite rare [11]. However, F-18 FDG accumulation is suggestive of malignancy in many cases [12], and a biopsy should be performed to establish a pathological diagnosis and decide the line of treatment.

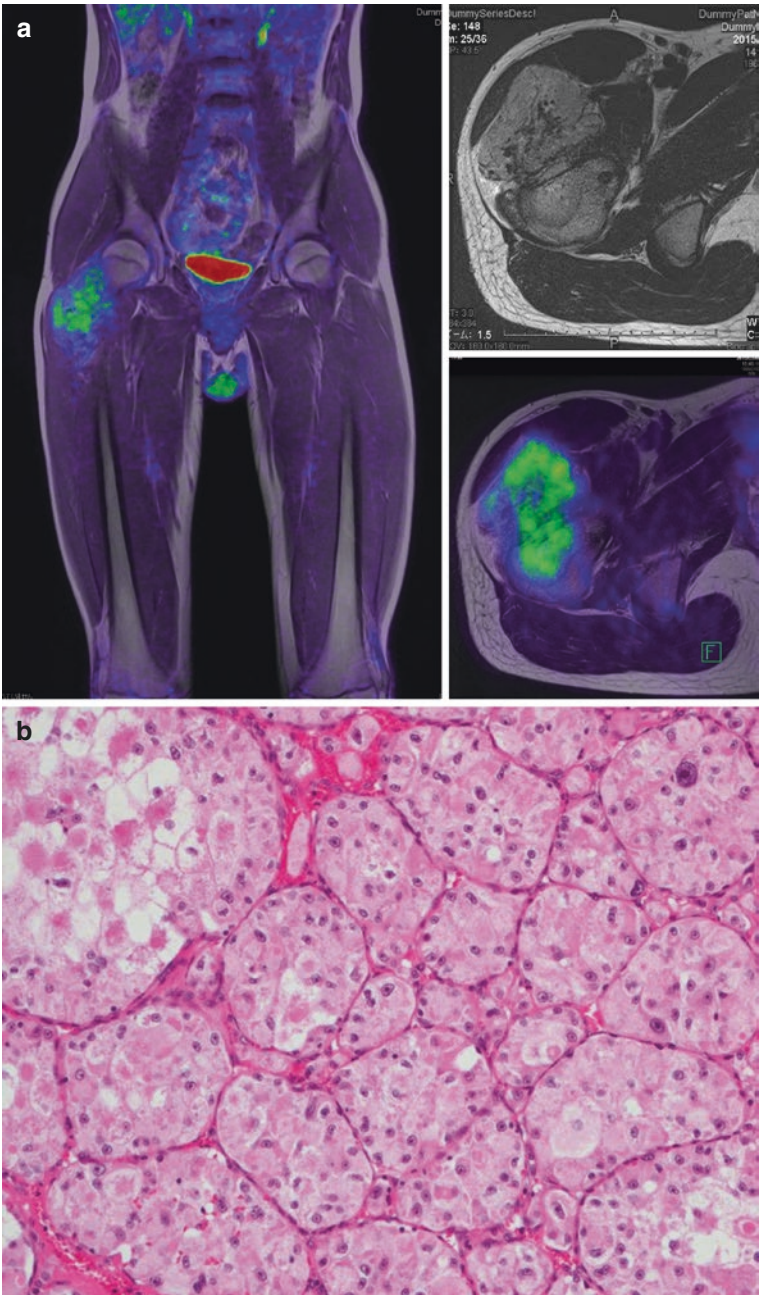


Fig. 7.2 Alveolar soft part sarcoma (ASPS) of the right hip. (**a**) T2-weighted MRI showing the tumor of right hip rich in vascularization (black spots in the tumor). PET/MRI showing abnormal F-18 FDG accumulation in the tumor and femoral invasion clearly. (**b**) Microscopy showing the typical organoid pattern of ASPS

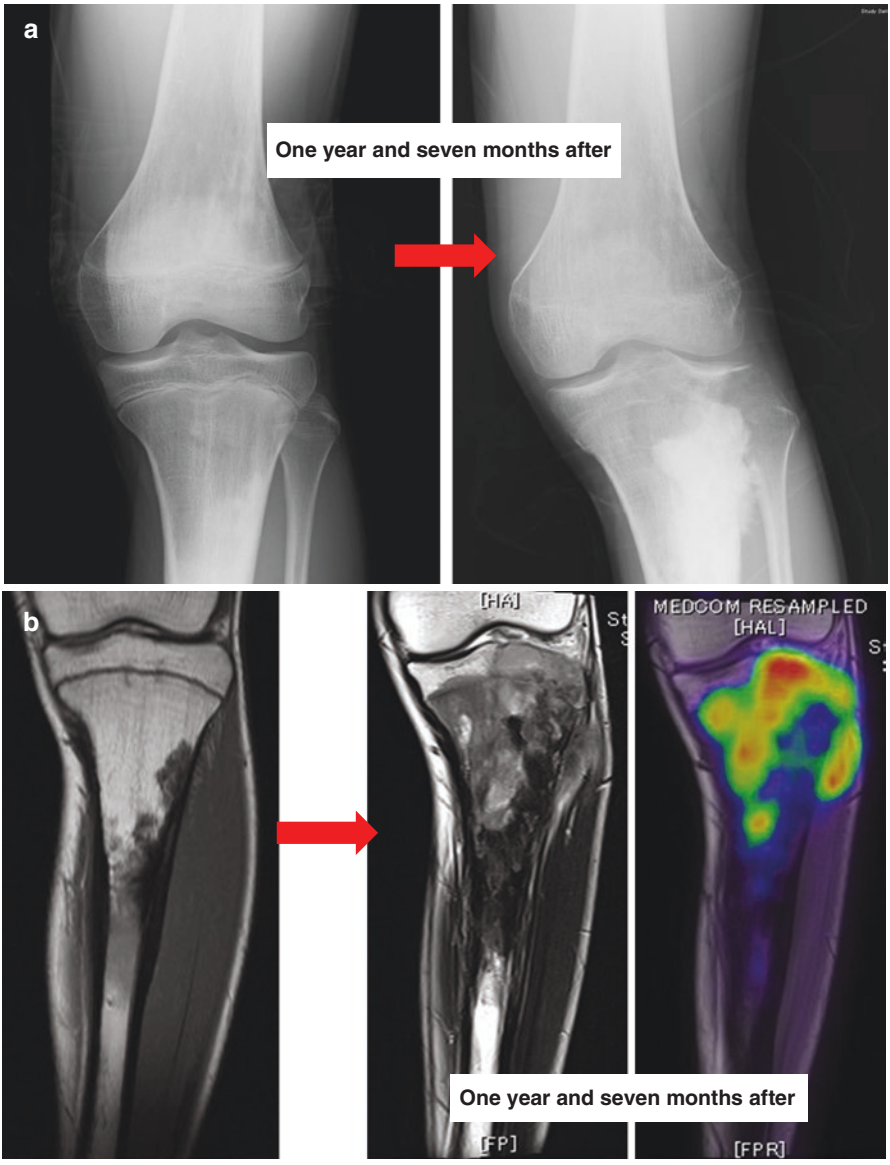
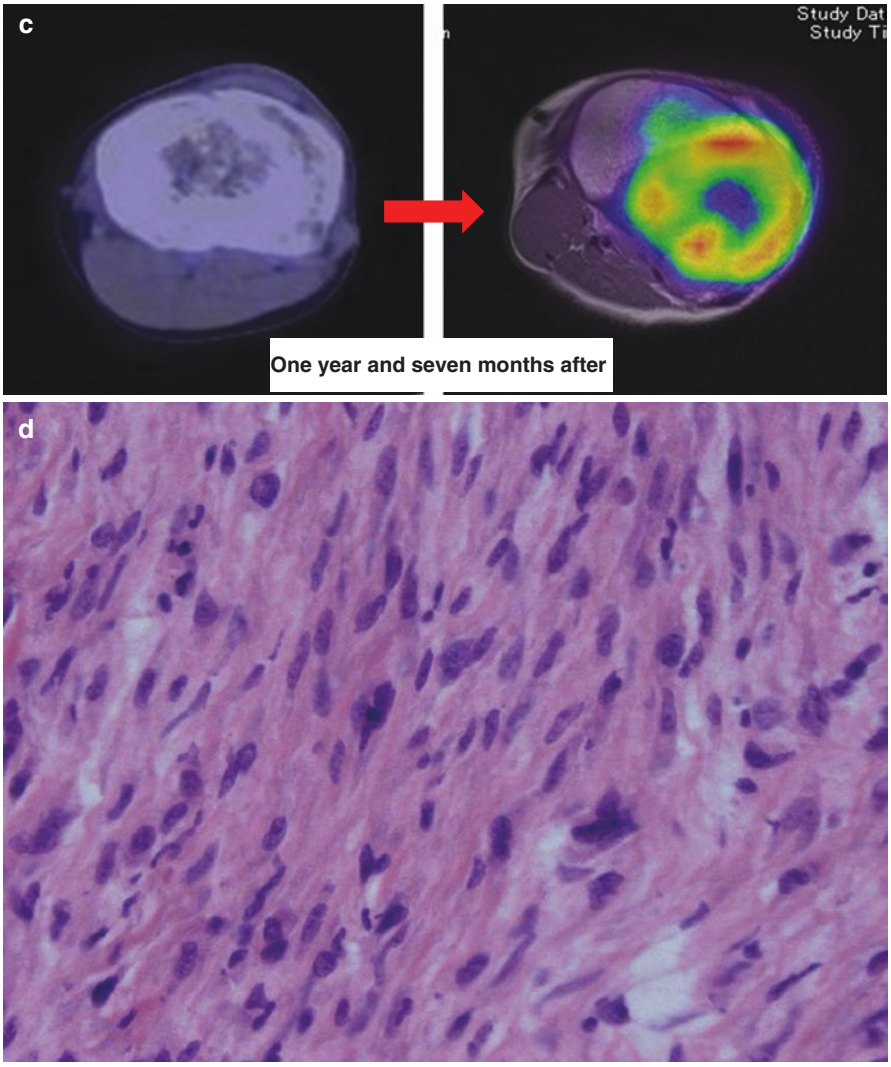


Fig. 7.3 High-grade malignant bone tumor arising at the left proximal tibia. (**a**) X-ray showing evolution of malignant bone tumor after 1 year and 7 months. (**b**) MRI and PET/MRI showing malignant bone tumor development, lesion enlargement, and abnormal F-18 FDG accumulation after 1 year and 7 months. (**c**) Abnormal F-18 FDG accumulation missing at the first imaging examination. (**d**) Biopsy specimen showing spindle cell tumor with pleomorphism but lacking osteoid. (**e**) The tibia was elevated to avoid exposing the tumor, and pedicle freezing procedure was performed using liquid nitrogen mounted as an intact body. (**f**) Composite grating was performed to replace the artificial knee joint surgery with the frozen bone



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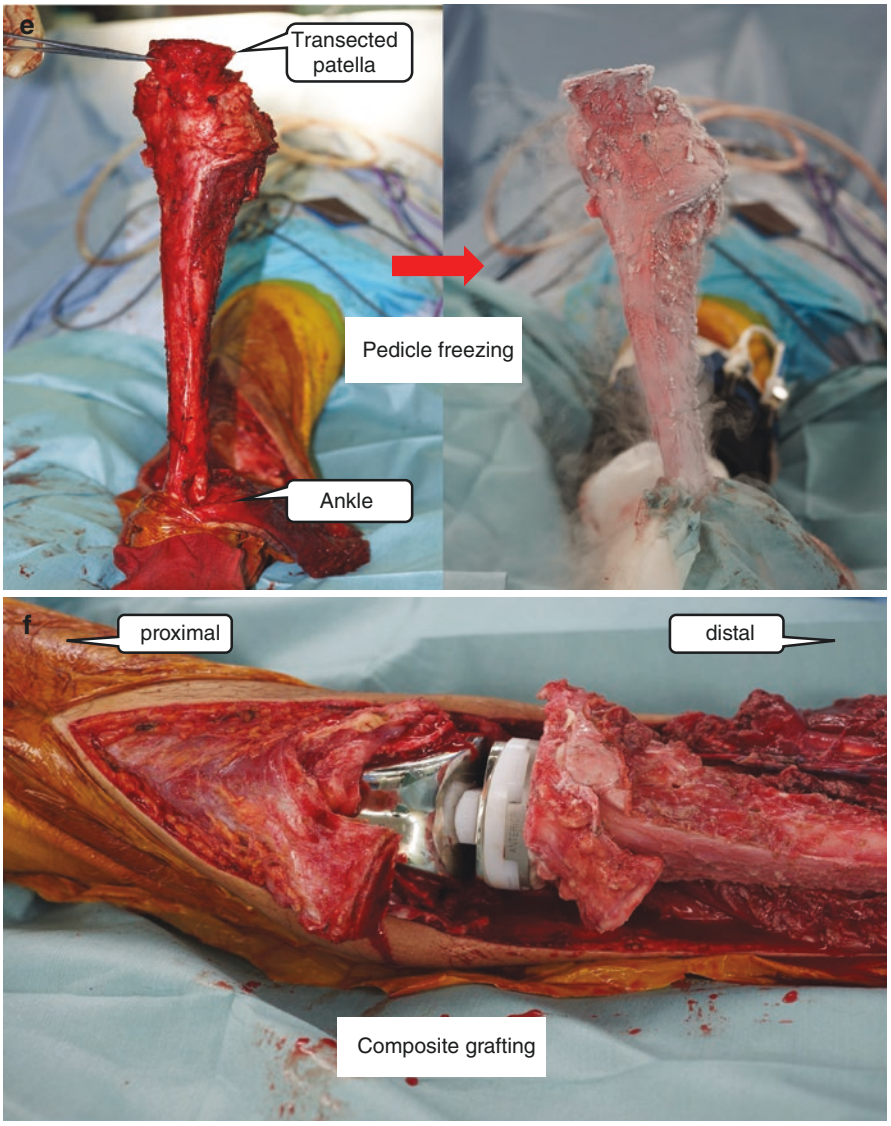

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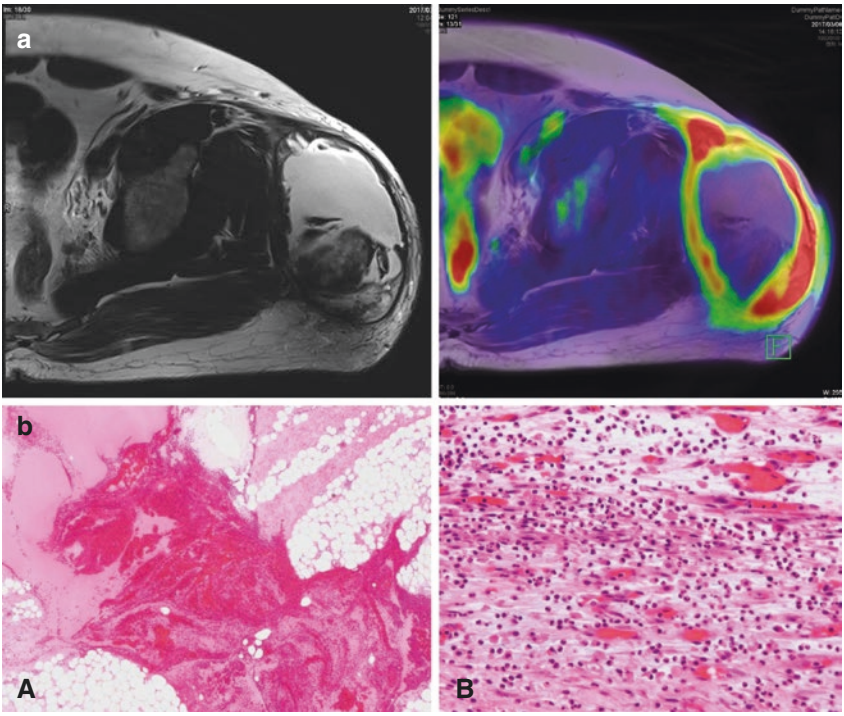


Fig. 7.4 Chronic expanding hematoma of the left hip. (**a**) T2-weighted MRI showing a large subcutaneous lesion with solid and liquid parts and abnormal F-18 FDG accumulation around the lesion. (**b**) Microscopic slides showing (A) hemorrhage and (B) inflammatory cellular infiltration without tumor cells

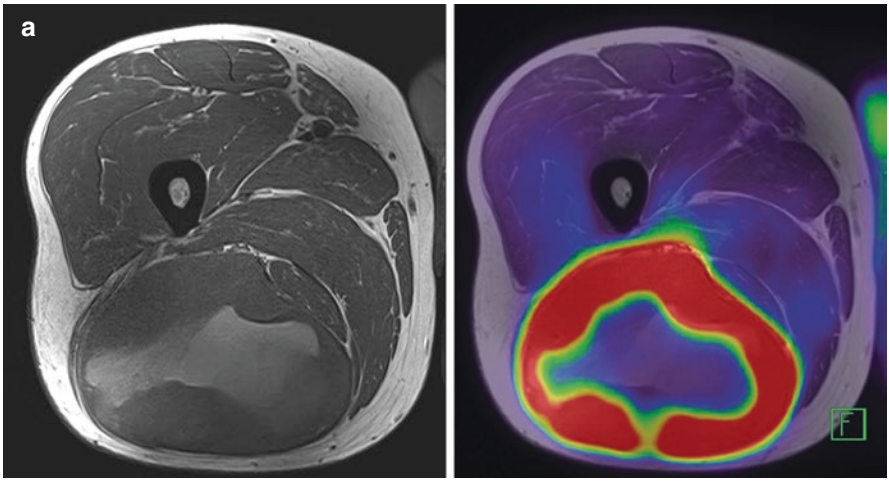
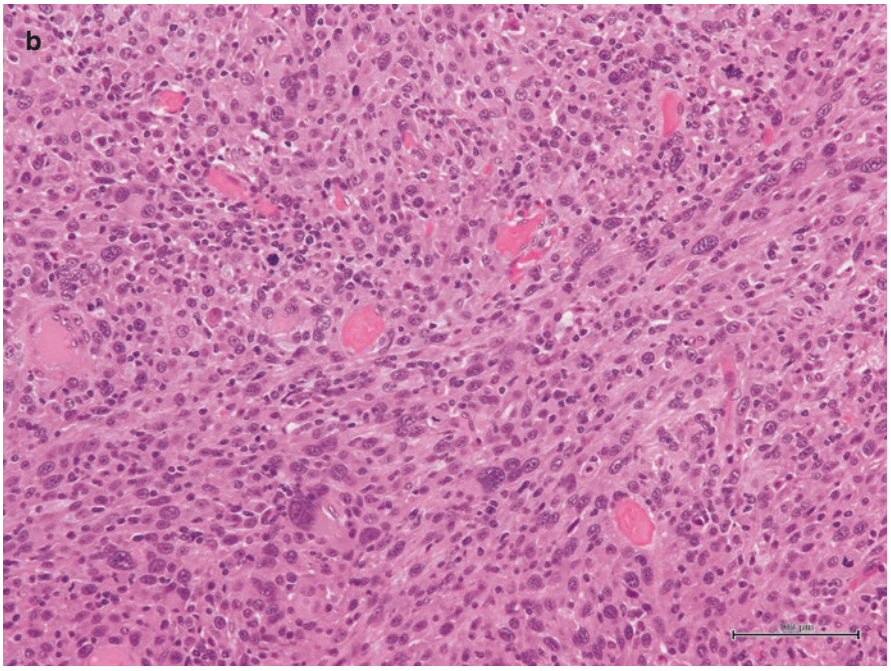


Fig. 7.5 Undifferentiated pleomorphic sarcoma of the right thigh. (**a**) T1-weighted MRI showing a large subfascial lesion with an area of high intensity owing to hemorrhagic necrosis and abnormal F-18 FDG accumulation without necrosis. (**b**) Microscopy showing high-grade pleomorphic malignancy with abnormal giant cells and mitosis



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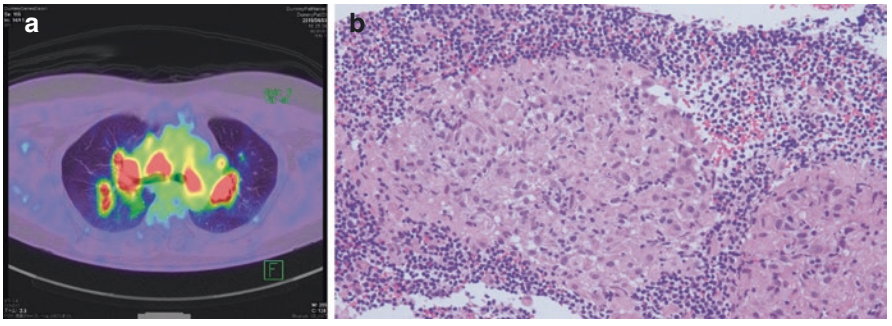


Fig. 7.6 Sarcoidosis. (**a**) PET/CT scans showing swelling and abnormal F-18 FDG accumulation in multiple bilateral hilar lymph nodes. (**b**) Biopsy specimen showing an inflammatory granuloma

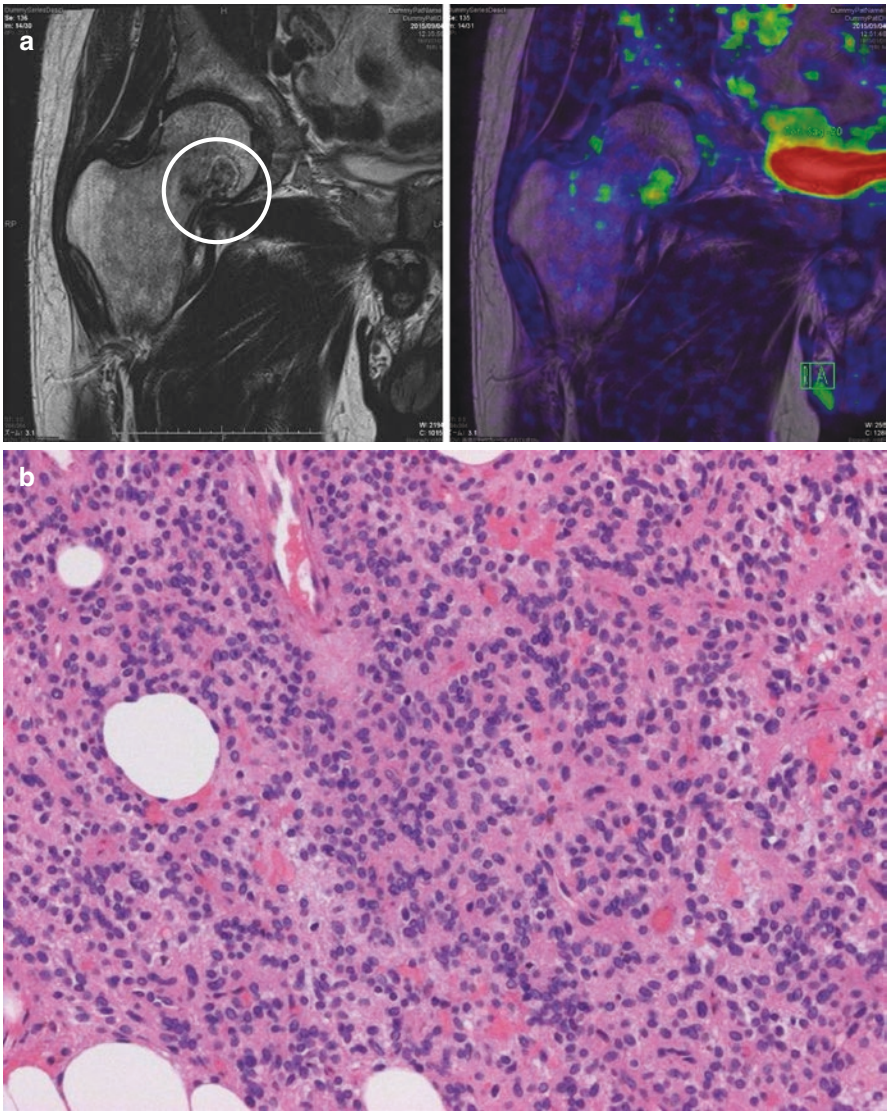


Fig. 7.7 Phosphaturic mesenchymal tumor of the right proximal femur. (**a**) T2-weighted MRI showing right proximal femur lesion in the circle. PET/MRI showing abnormal F-18 FDG accumulation. (**b**) Microscopy showing spindle cell proliferation without cytological atypia. (**c**) FGF23 expression detected by RT-PCR

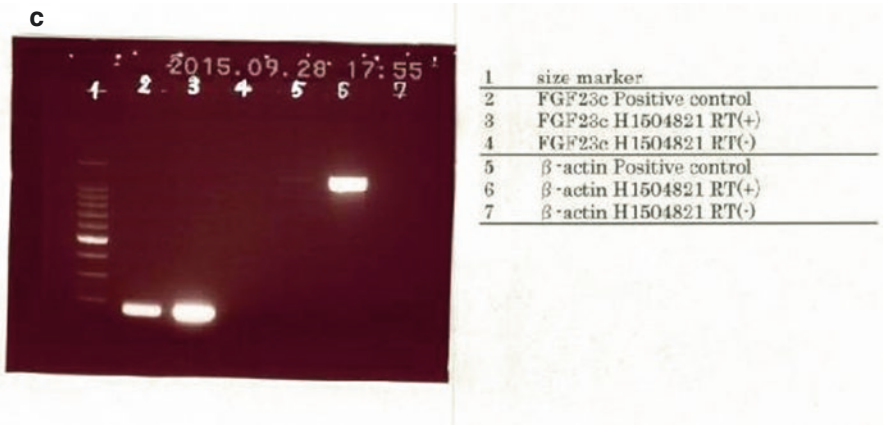


Fig. 7.7 (continued)

7.2 Determining a Location for Biopsy

Biopsy samples obtained from necrotic tissues cannot be used to make a pathological diagnosis. Viable and high-grade tumor specimens must be identified for accurate pathologic diagnoses. F-18 FDG accumulation in a tumor suggests the presence of a viable and high-grade lesion in a portion of the tumor [13]. In a patient with synovial sarcoma of the left groin, PET/MRI could clearly highlight viable and necrotic regions that could not be detected via plain MRI (Fig. 7.9). In a patient with dedifferentiated liposarcoma of the left hip, dedifferentiation in an atypical lipomatous tumor was clearly observed on PET/MRI (Fig. 7.10). Because tumors can disseminate intermuscularly, biopsies should be performed to identify viable and high-grade parts of the tumor and ought to avoid via intermuscular space.

7.3 Evaluation of Chemotherapy Clinical Outcomes

Chemotherapy is an important treatment option for osteosarcomas, Ewing sarcoma family of tumors, and other tumors. Chemotherapy outcomes need to be evaluated for determining whether to continue or change the regimen. Changes in pain intensity, tumor size, and F-18 FDG accumulation can help in evaluating these outcomes [13]. A patient with an osteosarcoma of the right humeral bone was treated with neoadjuvant chemotherapy; PET/MRI performed after five rounds of chemotherapy revealed reduced F-18 FDG accumulation and tumor regression, suggesting a good

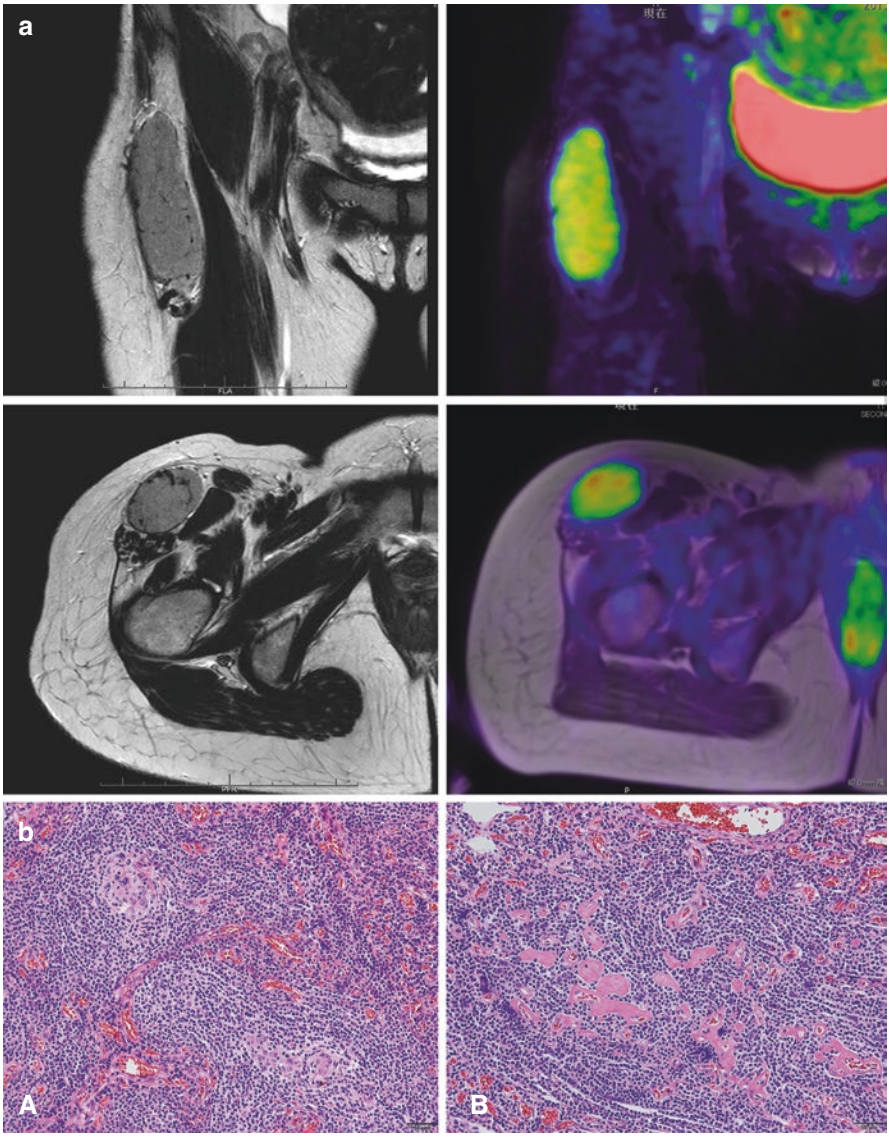


Fig. 7.8 Localized Castleman's disease of the right thigh. (**a**) Coronal and axial views of T2-weighted MRI showing a subfascial lesion similar to a malignant lymphoma with vascularization (black spots in the tumor). The same view via PET/MRI revealed F-18 FDG accumulation in the tumor. (**b**) Microscopic slides showing (A) atrophy of germinal centers and (B) hyaline vessels

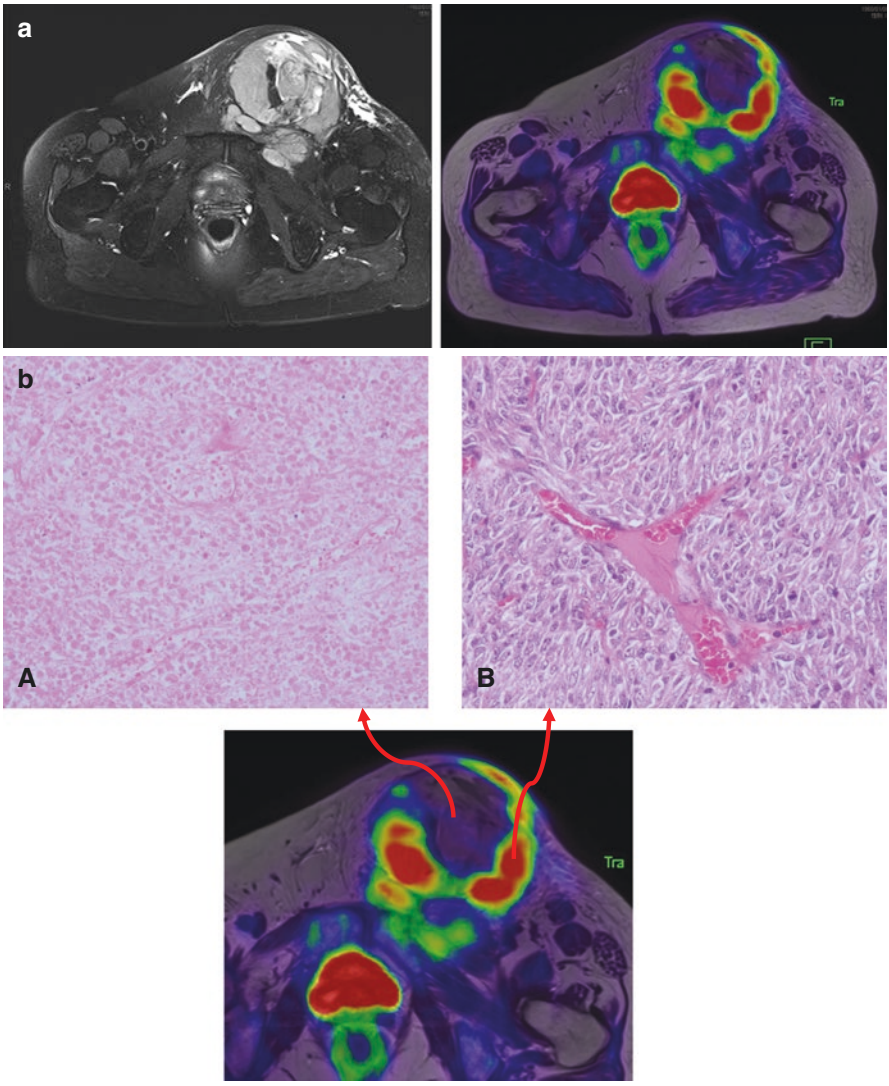


Fig. 7.9 Synovial sarcoma of the left groin. (**a**) PET/MRI showing partial F-18 FDG accumulation in the tumor. STIR MRI cannot distinguish between viable and necrotic regions. (**b**) (A) Specimen from the non-accumulation area showing necrosis. (B) Specimen from the F-18 FDG accumulation area showing a synovial sarcoma

response to chemotherapy (Fig. 7.11). In addition, a patient with Ewing sarcoma of the left scapula was evaluated via PET/CT scanning to assess the effectiveness of preoperative chemotherapy (Fig. 7.12). This patient underwent tumor removal and reconstruction using pasteurized bone [14]. Another patient with a poorly differentiated synovial sarcoma of the left chest with supraclavicular lymph node metastasis provided a complete response to chemotherapy, as assessed via PET/MRI (Fig. 7.13).

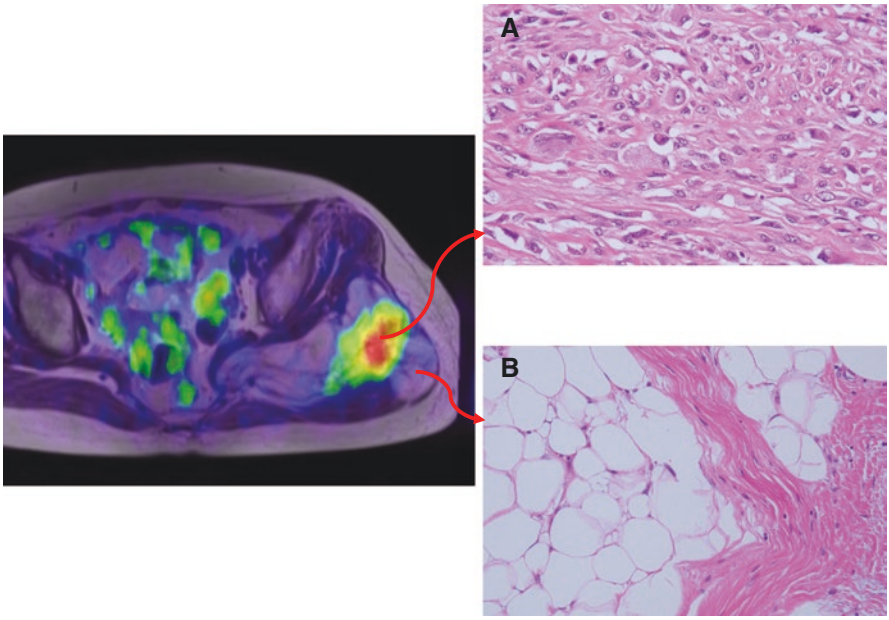


Fig. 7.10 Dedifferentiated liposarcoma of the left hip. PET/MRI showing isolated F-18 FDG accumulation in the lipomatous tumor. (A) Specimen from the F-18 FDG accumulation area showing a high-grade sarcoma. (B) Specimen from the non-accumulation area showing an atypical lipomatous tumor

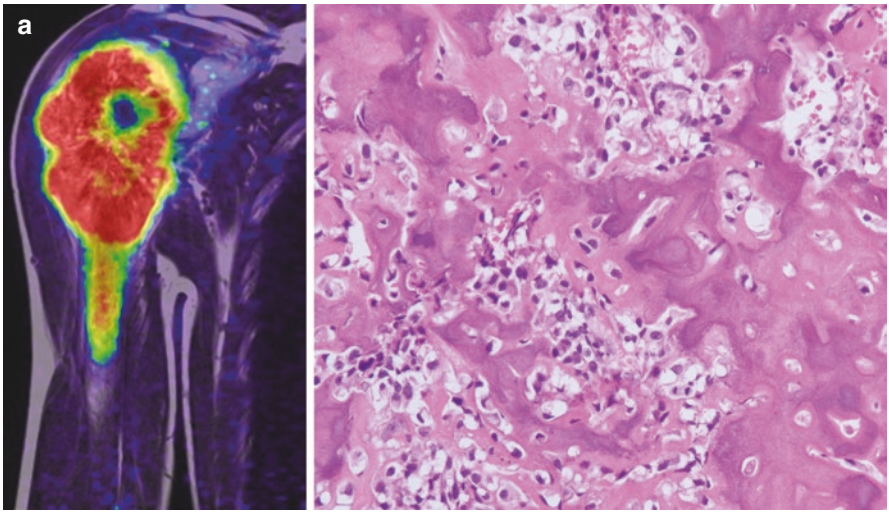
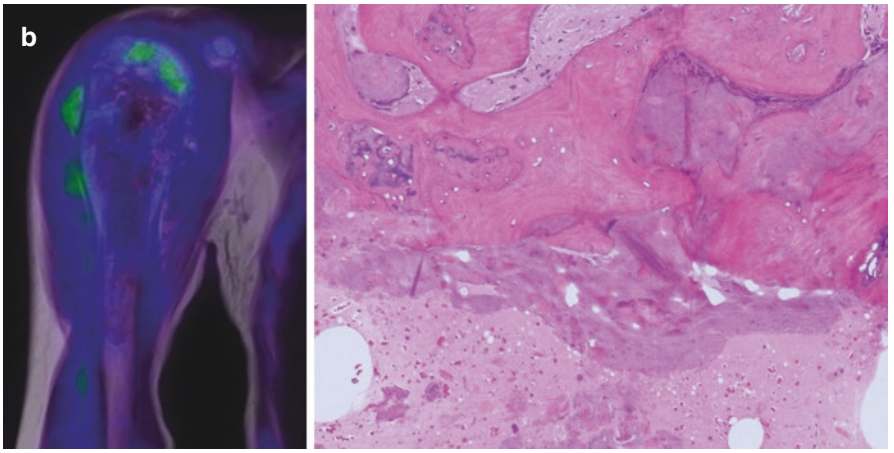


Fig. 7.11 Osteosarcoma of the right proximal humerus. (**a**) PET/MRI showing a growing tumor with the destruction of bone and high F-18 FDG accumulation. A biopsy specimen showing conventional osteosarcoma. (**b**) Effective preoperative chemotherapy. Decreased accumulation of FDG on PET/MRI. Microscopy showing bone differentiation and tumor necrosis



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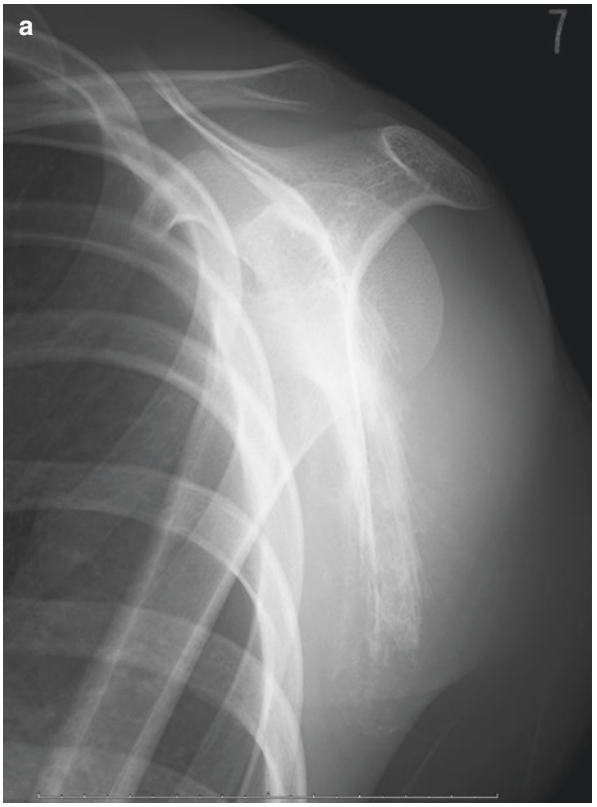
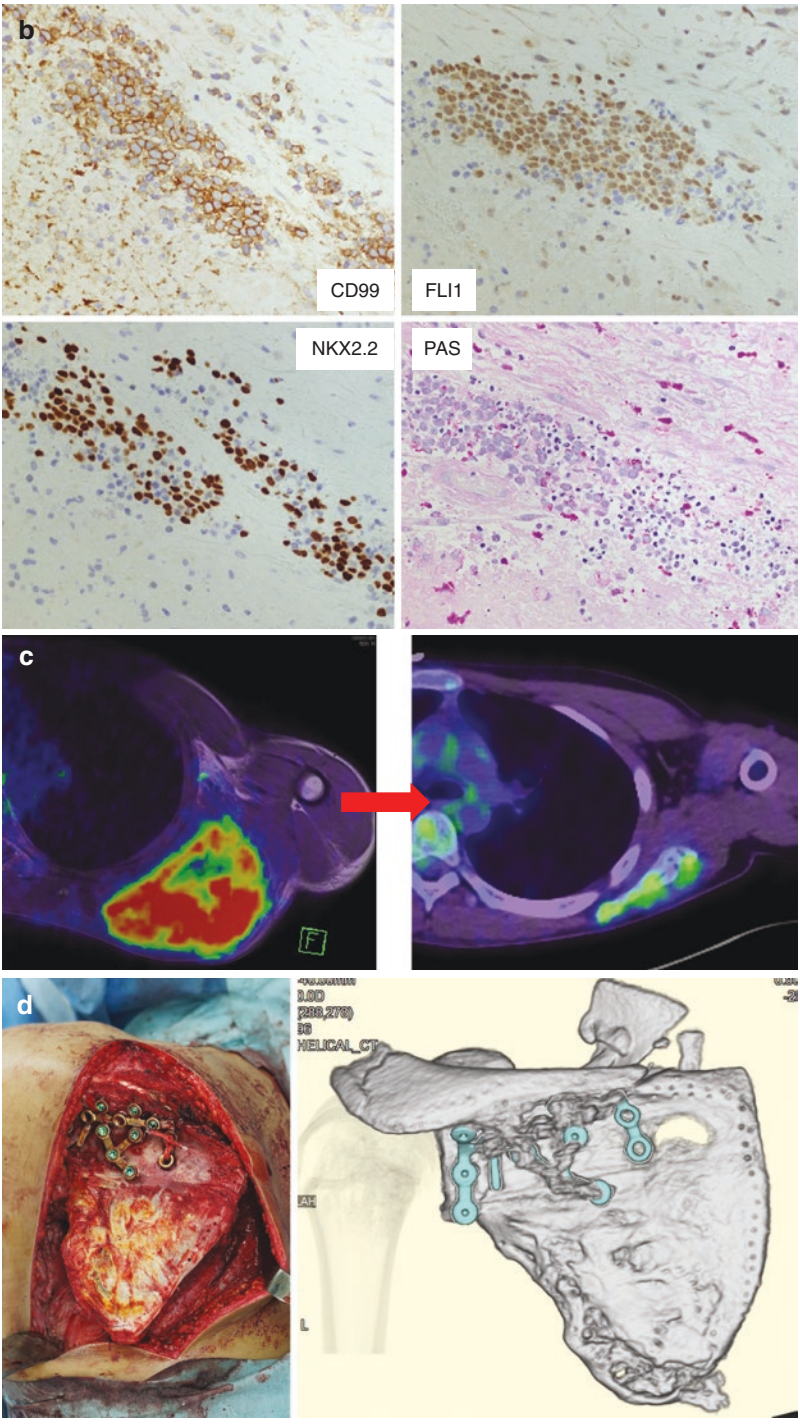


Fig. 7.12 Ewing sarcoma of the left scapula. (**a**) X-ray showing bone destruction and periosteal reaction. (**b**) Biopsy specimen showing a small round cell tumor with necrosis. PAS and immunoreactive staining showing Ewing sarcoma. (**c**) Despite the difference between PET/MR and PET/CT scans, preoperative chemotherapy was effective owing to a decrease in the tumor size and F-18 FDG accumulation. (**d**) Photograph and 3D-CT scans showing reconstruction with pasteurized bone after tumor removal



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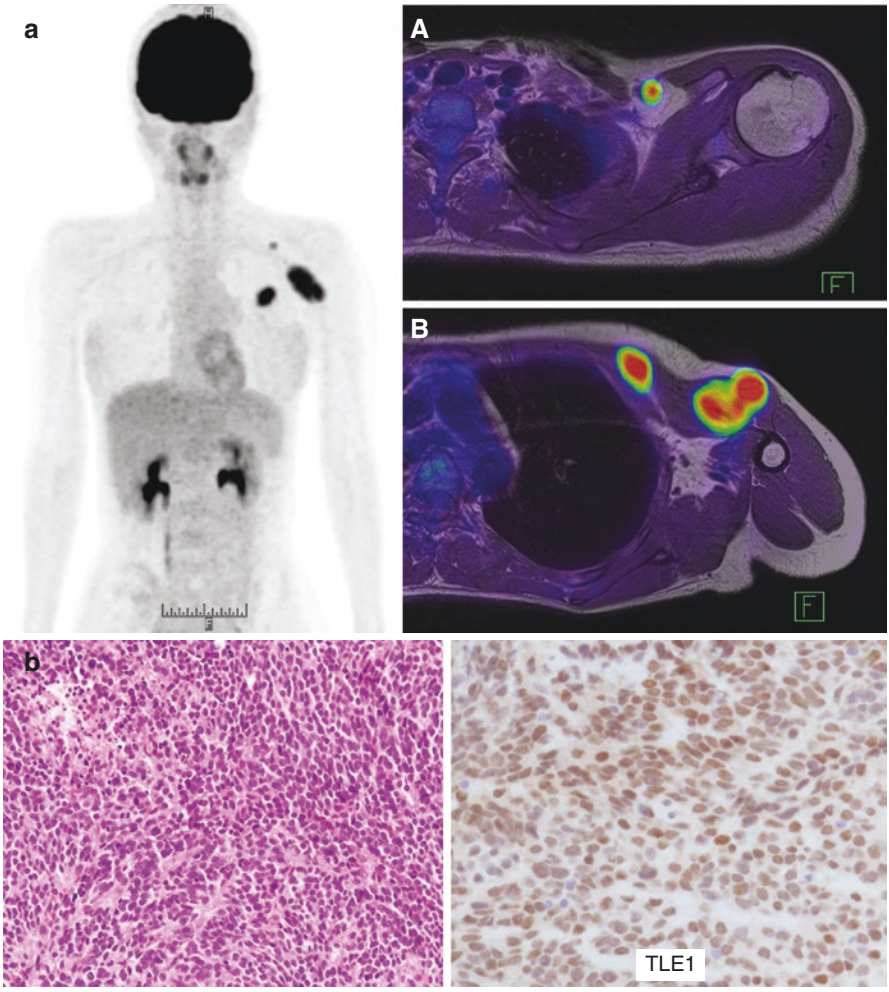

Fig. 7.13 Poorly differentiated synovial sarcoma of the left chest. (**a**) PET/MRI showing a clear tumor location, (A) supraclavicular lymph node metastasis, (B) Two lesions in the left greater pectoral muscle. (**b**) Biopsy specimen showing poorly differentiated synovial sarcoma positive for TLE1 by immunohistochemical staining. (**c**) Rare PET showing complete response to chemotherapy

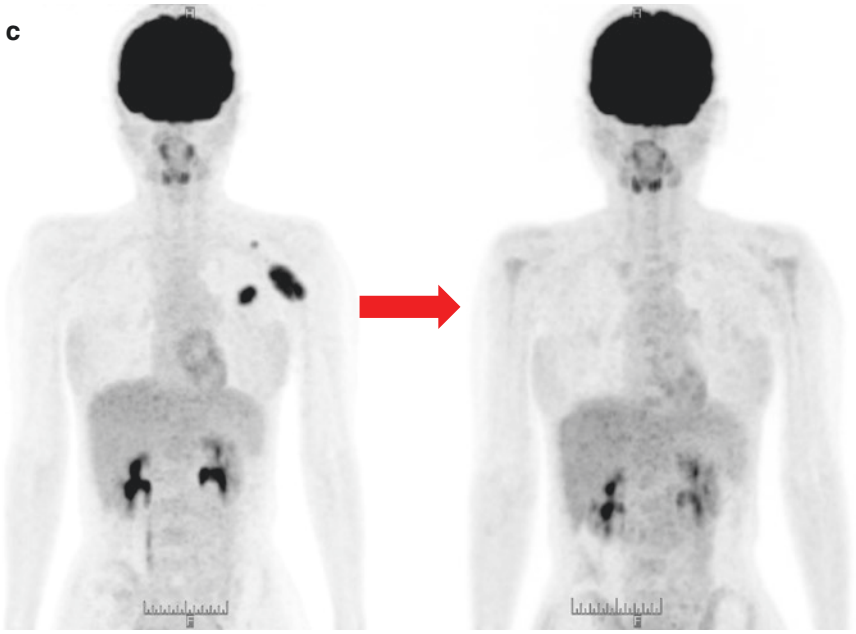

Fig. 7.13 (continued)

7.4 Surgical Planning

The first-line therapy for soft-tissue sarcomas is surgical removal. This procedure is important for treating bone sarcomas. Surgery for bone and soft-tissue sarcomas involves a wide resection [15], with a focus on salvaging the limb and reconstruction function. Surgical planning is based on MRI findings; however, planning for invasive sarcomas such as myxofibrosarcomas is challenging [16]. F-18 FDG PET scanning is performed for diagnosing tumor invasions [17] that are difficult or impossible to evaluate. In a patient with angiosarcoma of the right leg, MRI revealed tumor invasion to the subcutaneous, tibia, and tibialis anterior muscles (Fig. 7.14). In another patient with myxofibrosarcoma of the left calf, MRI revealed the tail sign, which is the reaction layer extending along the fascia in the subcutaneous tissue (Fig. 7.15). F-18 FDG accumulation was unclear in the reaction layer in these two abovementioned cases. The tumor, including the reaction layer, was removed according to the presurgical plan; however, histopathological examination revealed that the margin was marginal in the patient with angiosarcoma, and it was positive in the patient with myxofibrosarcoma.

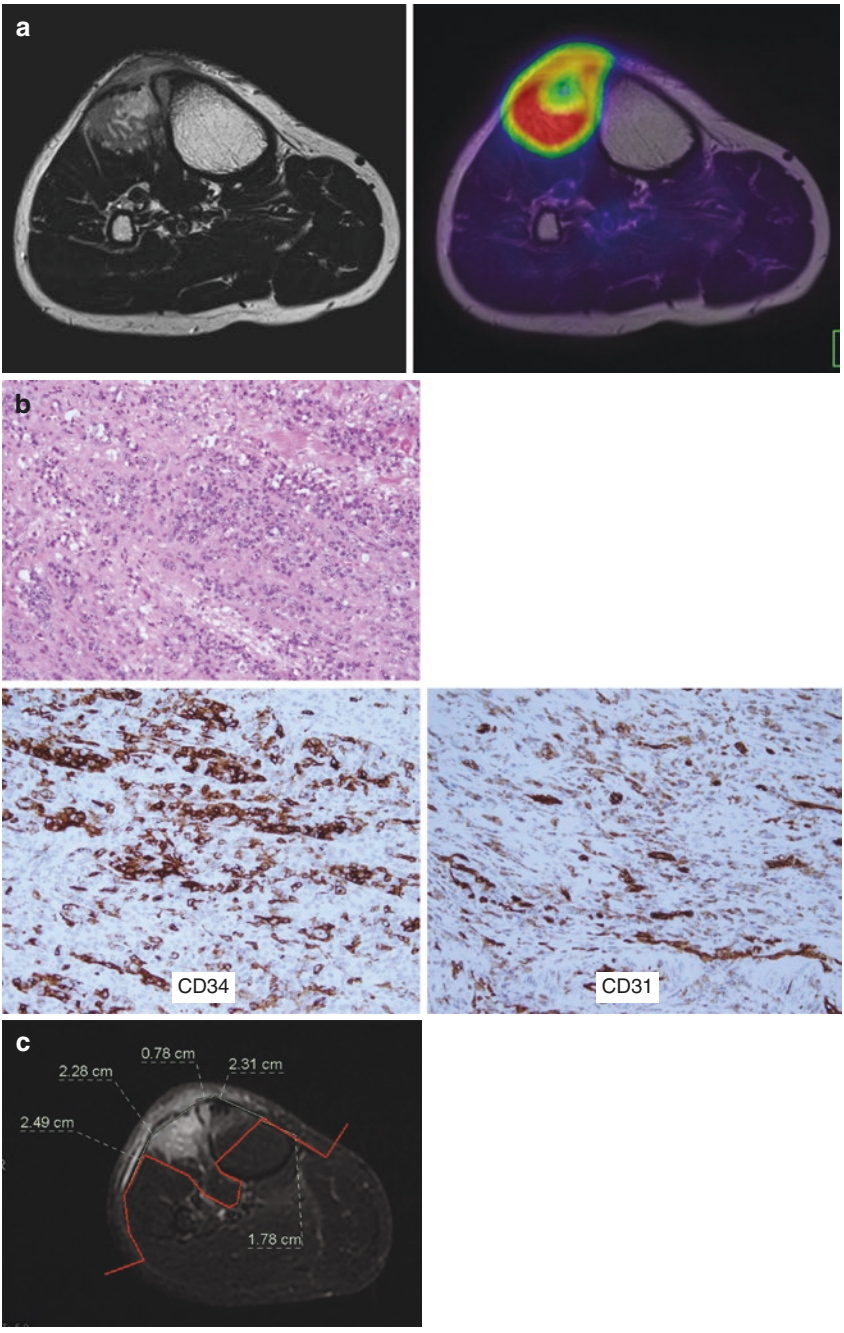

Fig. 7.14 Angiosarcoma of the right leg. (**a**) T2-weighted MRI and PET/MRI showing invasive tumor. (**b**) Microscopy showing CD34- and CD31-positive angiosarcoma by immunohistochemical staining. (**c**) Presurgical planning was performed via STIR MRI because the reaction layer was noted on STIR but was unclear on PET/MRI

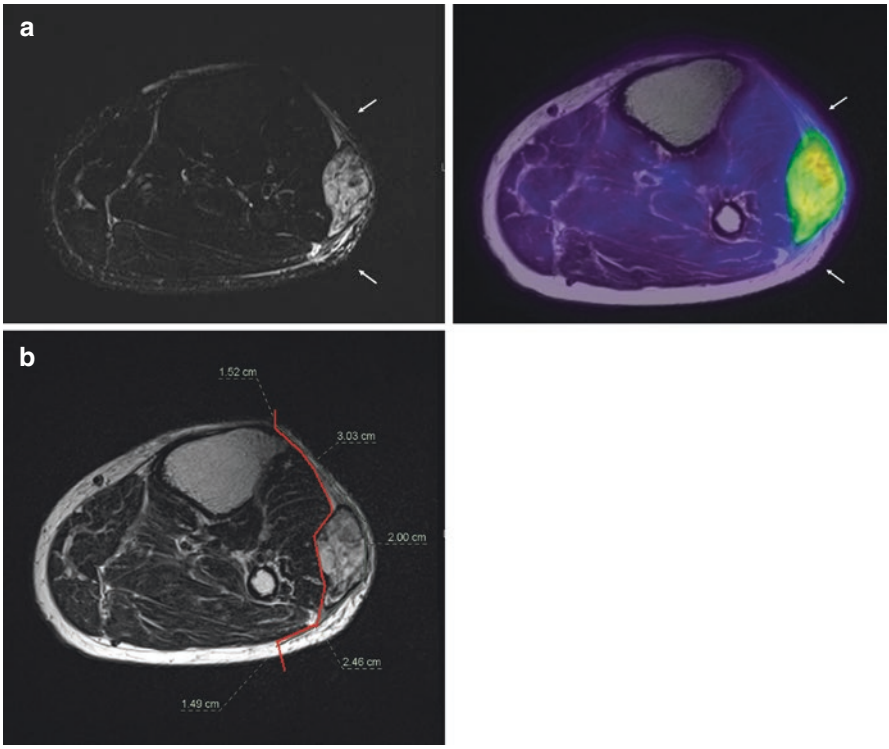

Fig. 7.15 Myxofibrosarcoma of the left calf. (**a**) MRI showing the tail sign, which is the reaction layer extending along the fascia in the subcutaneous tissue. PET/MRI showing unclear F-18 FDG accumulation in the reaction layer. (**b**) Presurgical planning was based on PET/MRI findings, but tumor invasion assessment was too optimistic in this case

7.5 Comparing PET/MRI and PET/CT

MRI is superior to CT scanning owing to its higher contrast. PET/MRI, which combines F-18 FDG PET and MRI, reveals abnormal structural changes in greater detail than PET/CT [18]. However, MRI requires a longer imaging time than CT. Thus, PET/CT scanning is better than PET/MRI for identifying lesions present in the internal organs and also for patients experiencing severe pain. Via PET/CT scanning, local recurrences in the periphery of an implant (Fig. 7.16) and some types of metastasis that cannot be detected via plain CT scanning can be detected. In a patient with a leiomyosarcoma of the right knee (Fig. 7.17a–c), multiple bone metastases were noted on PET/CT scanning 8 months postoperatively. These lesions were not painful and could not be detected via plain CT scanning (Fig. 7.17d).

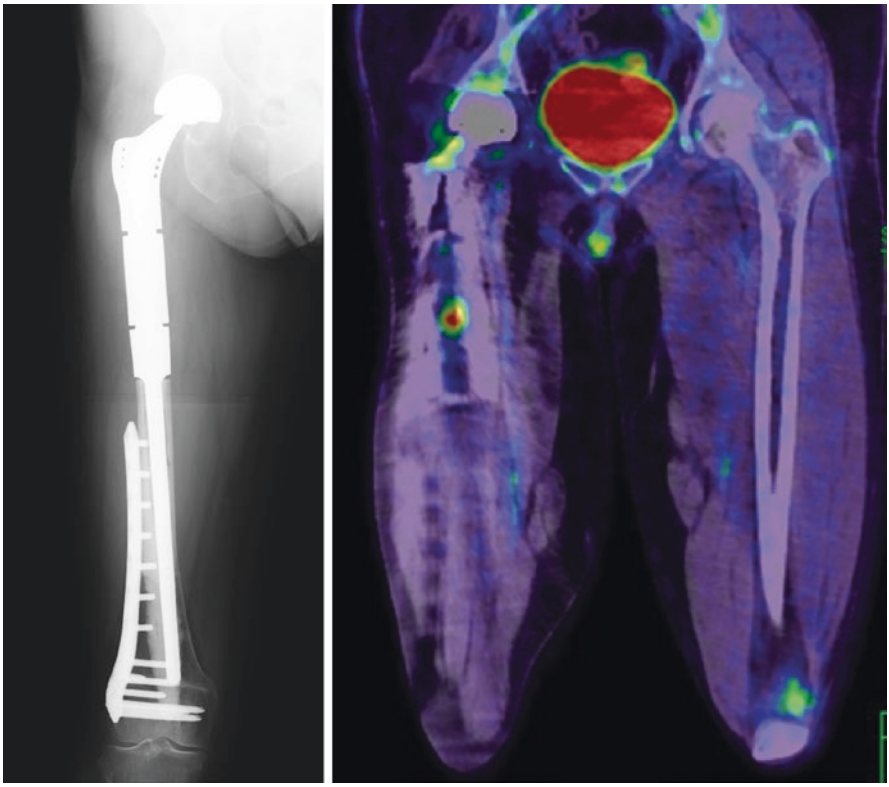

Fig. 7.16 Dedifferentiated chondrosarcoma of the right femur. X-ray of the removed recurrent tumor and reconstruction of pasteurized bone and implants. Local recurrence in the periphery of an implant can be detected via PET/CT

Thus, PET/MRI and PET/CT scanning are useful in diagnosing bone and soft-tissue tumors by understanding the nature of F-18 FDG accumulation.

Summary and Key Points

In this chapter, the usefulness and the limitations of FDG PET in diagnosing bone and soft-tissue tumors were shown in various cases.

The following are key points to understand the contents of this review.

- Diagnosis of malignant bone and soft-tissue tumors is difficult because of their rarity and variety.
- FDG is absorbed not only into malignant tumors but also areas with inflammatory activity and into some benign or intermediate tumors.

- FDG PET is useful in determining a location for biopsy because FDG accumulation in a tumor suggests the presence of a viable and high-grade lesion in a portion of the tumor.
- FDG accumulation can help in evaluating the effect of chemotherapy; however, Japanese public health insurance does not cover at this time.
- Evaluating tumor invasion for surgical planning is crucial and can be difficult or even impossible, even if PET/MRI is performed.

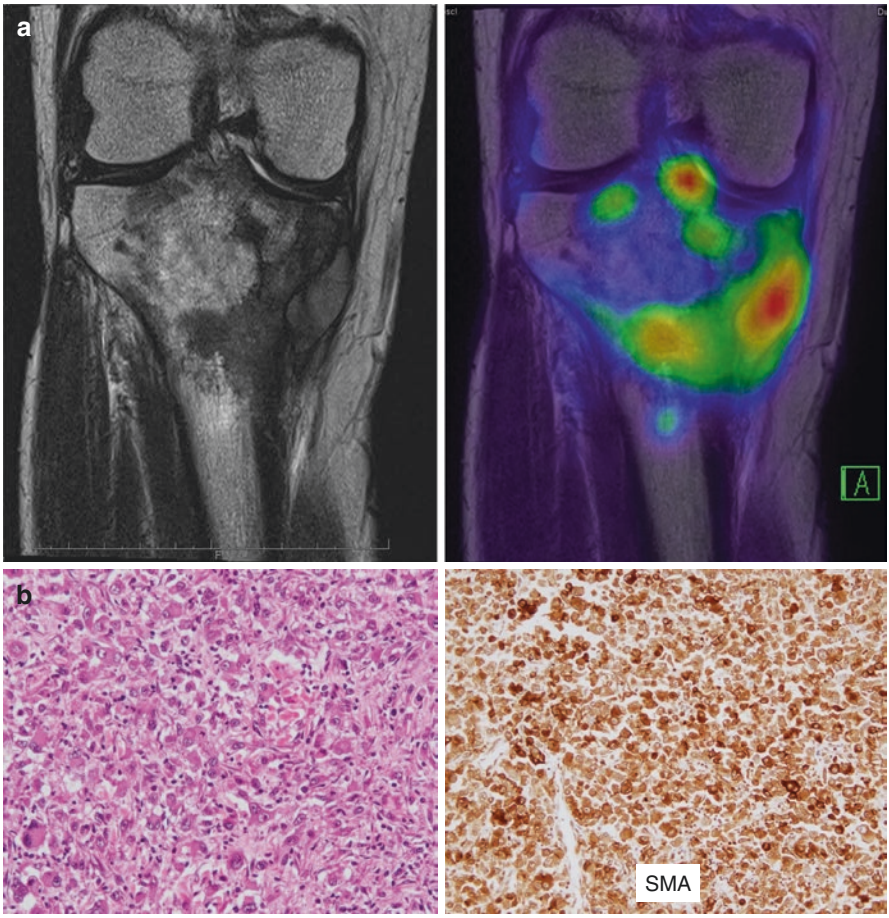

Fig. 7.17 Leiomyosarcoma of the right knee. (**a**) MRI and PET/MRI showing extensive soft-tissue tumor invasion in the proximal tibia. (**b**) Microscopy showing immunohistochemical staining of SMA-positive leiomyosarcoma. (**c**) Artificial knee joint surgery replacement performed after wide tumor resection. (**d**) Metastases of the sacrum and right iliac bone, which are unclear on plain CT, can be detected via PET/CT

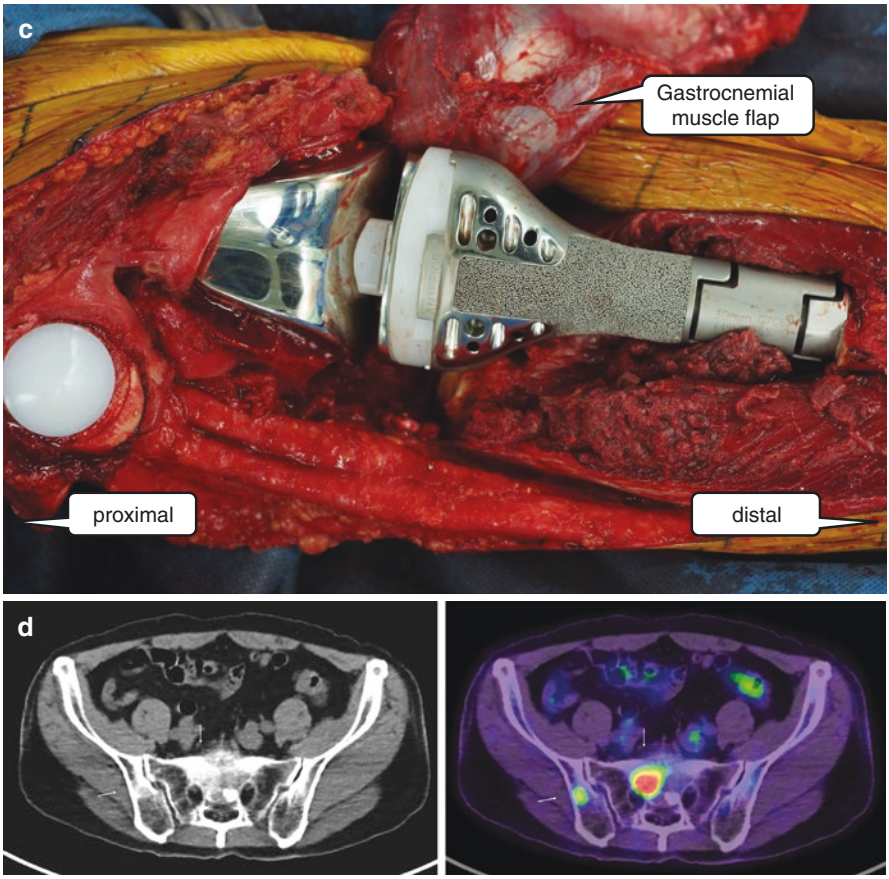

Fig. 7.17 (continued)

References

1. Fletcher DMC, Bridge JA, Hogendoorn CWP, Mertens F, editors. WHO classification of tumours of soft tissue and bone. 4th ed. IARC: Lyon; 2013.
2. Enneking WF, Dunham WK. Resection and reconstruction for primary neoplasms involving the innominate bone. J Bone Joint Surg Am. 1978;60(6):731–46.
3. Kunisada T, Fujiwara T, Hasei J, et al. Temporary external fixation can stabilize hip transposition arthroplasty after resection of malignant periacetabular bone tumors. Clin Orthop Relat Res. 2019;477(8):1892–901. https://doi.org/10.1097/CORR.0000000000000764.
4. Hardcastle P, Nade S, Arnold WJ. Hereditary bone dysplasia with malignant change. Report of three families. J Bone Joint Surg Am. 1986;68(7):1079–89.
5. Tsuchiya H, Wan SL, Sakayama K, et al. Reconstruction using an autograft containing tumour treated by liquid nitrogen. J Bone Joint Surg Br. 2005;87(2):218–25. https://doi.org/10.1302/0301-620x.87b2.15325.

6. Maeda J, Ohta M, Hirabayashi H, et al. False positive accumulation in 18F fluorodeoxyglucose positron emission tomography scan due to sarcoid reaction following induction chemotherapy for lung cancer. Jpn J Thorac Cardiovasc Surg. 2005;53(4):196–8. https://doi.org/10.1007/s11748-005-0104-9.
7. Boré P, Descourt R, Ollivier L, et al. False positive 18F-FDG positron emission tomography findings in schwannoma-a caution for reporting physicians. Front Med (Lausanne). 2018;5:275. https://doi.org/10.3389/fmed.2018.00275.
8. Hakozaki M, Tajino T, Yamada H, et al. Radiological and pathological characteristics of giant cell tumor of bone treated with denosumab. Diagn Pathol. 2014;9:111. https://doi.org/10.1186/1746-1596-9-111.
9. Tang K, Zheng X, Lin J, et al. Diffuse-type tenosynovial giant cell tumor of the shoulder evaluated by FDG PET/CT. Clin Nucl Med. 2019;44(4):310–2. https://doi.org/10.1097/RLU.0000000000002451.
10. Kaneuchi Y, Hakozaki M, Yamada H, et al. Missed causative tumors in diagnosing tumor-induced osteomalacia with (18)F-FDG PET/CT: a potential pitfall of standard-field imaging. Hell J Nucl Med. 2016;19(1):46–8. https://doi.org/10.1967/s002449910337.
11. Hakozaki M, Tajino T, Yamada H, et al. Intramuscular Castleman's disease of the deltoid: a case report and review of the literature. Skelet Radiol. 2010;39(7):715–9. https://doi.org/10.1007/s00256-010-0895-3.
12. Tateishi U, Yamaguchi U, Seki K, et al. Bone and soft-tissue sarcoma: preoperative staging with fluorine 18 fluorodeoxyglucose PET/CT and conventional imaging. Radiology. 2007;245(3):839–47. https://doi.org/10.1148/radiol.2453061538.
13. Kandathil A, Subramaniam RM. PET/computed tomography and precision medicine: musculoskeletal sarcoma. PET Clin. 2017;12(4):475–88. https://doi.org/10.1016/j.cpet.2017.05.005.
14. Manabe J, Ahmed AR, Kawaguchi N, et al. Pasteurized autologous bone graft in surgery for bone and soft tissue sarcoma. Clin Orthop Relat Res. 2004;419(419):258–66. https://doi.org/10.1097/00003086-200402000-00042.
15. Enneking WF, Spanier SS, Goodman MA. A system for the surgical staging of musculoskeletal sarcoma. Clin Orthop Relat Res. 1980;153(153):106–20.
16. Lefkowitz RA, Landa J, Hwang S, et al. Myxofibrosarcoma: prevalence and diagnostic value of the "tail sign" on magnetic resonance imaging. Skelet Radiol. 2013;42(6):809–18. https://doi.org/10.1007/s00256-012-1563-6.
17. Loft A, Jensen KE, Löfgren J, et al. PET/MRI for preoperative planning in patients with soft tissue sarcoma: a technical report of two patients. Case Rep Med. 2013;2013:791078. https://doi.org/10.1155/2013/791078.
18. Buchbender C, Heusner TA, Lauenstein TC, et al. Oncologic PET/MRI, part 2: bone tumors, soft-tissue tumors, melanoma, and lymphoma. J Nucl Med. 2012;53(8):1244–52. https://doi.org/10.2967/jnumed.112.109306.

Chapter 8
F-18 FDG PET Tests in Skin Cancer Including Malignant Melanoma

Ryota Tanaka and Yasuhiro Fujisawa

8.1 Introduction

^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) provides morphologic information on tumor metabolic activity, which has the potential to detect recurrences and metastases resulting from various kinds of malignancies, including skin malignancies [1–3].

The aim of this review is to elucidate the clinical utility of ^{18}F-FDG PET or ^{18}F-FDG PET-computed tomography (^{18}F-FDG PET-CT) in skin malignancies and the potential effect on patient management. In particular, epithelial malignancies and cutaneous soft tissue sarcomas were the focus in the present review. Furthermore, epithelial malignancies were divided into malignant melanomas and nonmelanoma skin cancers.

8.2 Epithelial Malignancies

8.2.1 Malignant Melanoma

Malignant melanoma, arising from the melanocytes in the basal layer of the epidermis, comprise of only 4% of skin cancers. However, melanoma is the most lethal form of epithelial skin malignancy, which accounts for 75% of skin cancer-related mortality [4, 5]. Increased primary tumor thickness and metastasis to the draining lymph node (sentinel lymph node) correlate with poor prognosis [6].

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Therefore, early diagnosis and treatment are important to improve the prognosis of melanoma patients [7, 8].

8.2.1.1 Preoperative Assessment

Since ^{18}F-FDG PET-CT was proven useful in detecting metastasis of melanomas with sensitivity and specificity of 83% and 85%, respectively, in a comprehensive review based on 28 studies [2], such imaging modalities have commonly been used for melanoma staging and assessment of therapeutic response [6] in patients in advanced stages (stages III and IV). However, due to low diagnostic accuracy and potential false-positive results [6, 8–10], routine use of such radiological tests for early-stage melanomas is not recommended [11] because most of the stages (American Joint Committee on Cancer Stage I and II) are potentially curable by surgical resection, which yields a 5-year survival rate of 90% [7, 8]. Meanwhile, as patients with >pT3a tumors have the potential to develop metastasis, radiological tests could be used for staging (Fig. 8.1) [12].

As for melanoma staging on ^{18}F-FDG PET-CT, a systemic review of 17 diagnostic studies reported sensitivity ranging from 68% to 87% and specificity ranging from 92% to 98% for stage III and IV melanomas compared to sensitivity ranging from 0% to 67% and specificity ranging from 77% to 100% for stage I and II melanomas [13]. In addition, Cha et al. reported that the maximum standardized uptake value (SUV_{max}) of over 2.4 showed high sensitivity (91%) and accuracy (89%) in detecting lymph node metastasis sized >10 mm, while an SUV_{max} of less than 1.4 detected benign tumors with lymph nodes sized <10 mm [14], suggesting that combining the ^{18}F-FDG parameters, such as SUV_{max}, on ^{18}F-FDG PET-CT shows a higher diagnostic value than the conventional anatomical images alone. However, prospective randomized studies are required to confirm these results.

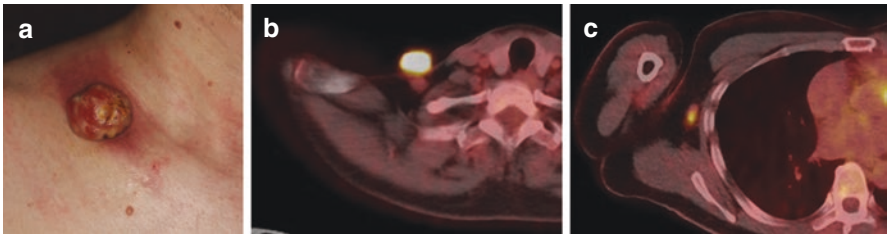

Fig. 8.1 *A typical case of melanoma in which the patient underwent ^{18}F-FDG PET-CT for staging (>pT3).* A 48-year-old man developed amelanotic tumor with some pigmented areas on the edge at the right supraclavicular fossa (**a**). ^{18}F-FDG PET-CT detected a tumor measuring 25 × 16 × 20 mm with SUV_{max} of 20.9 and SUV_{peak} of 15.3 (**b**). In addition, a lymph node with SUV_{max} of 8.27 was also detected in the right axilla (**c**), suggesting the presence of metastasis. Indeed, the lymph node had both S-100 and HMB45-positive melanoma cell infiltration (T4bN1M0 Stage)

8.2.2 Recurrence or Distant Metastasis Assessment

Although ^{18}F-FDG PET-CT is superior in melanoma staging before the therapy [2, 6, 8, 9], its role in the regular follow-up of asymptomatic melanoma patients remains unclear. In a review by Xing et al., ^{18}F-FDG PET-CT appears to be useful in detecting tumor relapses with a high positive predictive value (92%) and tumor-free patients with a high negative predictive value (95%) [10]. Considering higher radiation exposure in ^{18}F-FDG PET-CT compared to conventional CT [15], further investigations are required to establish an optimal follow-up protocol, as the evidence of its role in the routine follow-up of asymptomatic melanoma patients is yet to be established.

In patients with metastatic disease, ^{18}F-FDG PET-CT is the most sensitive and accurate, thereby making it the first-line modality to identify distant metastases [16–18]. A large meta-analysis concluded that ^{18}F-FDG PET-CT was superior to ^{18}F-FDG PET or CT alone to detect distant metastasis, in which the sensitivity of ^{18}F-FDG PET-CT (86%) was better than that of ^{18}F-FDG PET or CT alone (82% and 63%, respectively) [10]. To detect skin metastases, such as in-transit or satellite lesions, both magnetic resonance imaging (MRI) and ^{18}F-FDG PET-CT are considered superior to CT [17, 19]. However, whole-body MRI appears to be more accurate than ^{18}F-FDG PET-CT owing to physiological uptake and infective inflammatory conditions in ^{18}F-FDG PET-CT, resulting in higher false-positive findings [8].

8.2.3 Response to Therapy Assessment

Although ^{18}F-FDG PET-CT has been well validated to assess the response to therapy and predict prognosis in patients with lymphoma [20], it is not well established for patients with metastatic melanoma. Usually, the assessment of therapeutic response is evaluated by size criteria from the Response Evaluation Criteria in Solid Tumors (RECIST) [21]. On the other hand, the use of ^{18}F-FDG uptake on ^{18}F-FDG PET-CT, which could be evaluated by SUV to assess the tumor response, has been reported to be a useful method for detecting metastases, since melanomas are ^{18}F-FDG-avid and ^{18}F-FDG PET-CT would be more sensitive than CT or MRI [6, 10].

Recent developments of effective therapies such as BRAF inhibitors and immune checkpoint inhibitors (ICI) have revolutionized the treatment of advanced-stage melanoma [22, 23]. With the advent of these therapies, evidence of the utility of ^{18}F-FDG PET-CT in monitoring response and outcome with therapy is in great demand.

8.2.4 Assessing Response to Molecular Targeted Kinase Inhibitors

To date, small molecule drugs that target the MAPK pathway for the treatment of advanced-stage melanoma, including BRAF inhibitors, MEK inhibitors, and combination BRAF and MEK inhibitor regimens have been approved in Japan. Several reports showed that the response to BRAF and MEK inhibitors can be effectively monitored by ^{18}F-FDG PET-CT [24–26]. A decrease in ^{18}F-FDG uptake was correlated with longer progression-free survival [25], which in turn allows an early identification of non-responders or resistant lesions [26]. McArthur et al. found that patients who received vemurafenib showed an early metabolic response in ^{18}F-FDG on day 15 [25], which may be caused by an effective downregulation of extracellular signal-regulated kinase (ERK), the terminal gene of the MAPK pathway, suppressing glycolysis via a network of transcriptional regulators of glycolysis [27]. Moreover, Wong et al. found a lack of reduction of ^{18}F-FDG uptake in rare variant BRAF mutations refractory to MAPK pathway inhibition, suggesting that persistence or reactivation of ^{18}F-FDG uptake is a feature of resistance [26].

8.2.5 Assessing Response to Immune Checkpoint Inhibitor Therapy

To date, there are two different types of approved ICI for the treatment of advanced-stage melanoma in Japan, anti-PD-1 (nivolumab and pembrolizumab), anti-CTLA-4 (ipilimumab), and combination anti-PD-1/CTLA-4 regimens (nivolumab–ipilimumab). Although time to treatment response takes longer in patients treated with ICI than those with BRAF inhibitors, durable response in patients who responded to the treatment has been reported, which is a unique characteristic of ICI [22]. Tumor response assessment for immunotherapy using ^{18}F-FDG PET-CT is currently under investigation since most of the published studies contained preliminary results and are difficult to interpret.

One of the issues with long and durable response to ICI is whether treatment can be stopped for long-term responders because ICI can cause autoimmune adverse events and some of which are life-threatening [28, 29]. A cohort study that investigated the outcome of 185 advanced melanoma patients treated with anti-PD-1 antibody reported that those who achieved complete response (CR) over 6 months of treatment showed a significant lower risk of relapse after discontinuing therapy when compared to those with partial response (PR) ($P = 0.002$; HR 2.99, 95% CI 1.45–6.16) or maintaining stable disease (SD) ($P < 0.001$; HR 5.15, 95% CI 2.19–12.09) as best tumor response [30]. On the other hand, the results from early clinical trials suggest that patients who achieved CR, and those with long-term PR or stable disease (SD) also showed that discontinuation of therapy after 2 years had a low risk of subsequent progression for melanoma [31, 32]. These results suggest that, unlike with cytotoxic chemotherapy or targeted therapies, evaluation of

response to ICI therapy by conventional CT response criteria alone would be insufficient for identifying long-lasting responders other than those with CR.

To predict long-term outcomes which may lead to discontinuation of ICI therapy, combined use of ^{18}F-FDG PET assessment and conventional CT response criteria could be helpful [33]. A retrospective study which analyzed 104 metastatic melanoma patients treated with anti-PD-1 antibody-based immunotherapy suggested a potential benefit of ^{18}F-FDG PET scan use. In this study, they measured using ^{18}F-FDG PET the standardized uptake value (SUV_{max}) of the top five most intense metastatic lesions at baseline and after 1 year of treatment. Responses by ^{18}F-FDG PET assessment were coded as complete metabolic response (CMR), partial metabolic response, stable metabolic disease, or progressive metabolic disease, and were compared to response by contrast-enhanced CT images using RECIST 1.1 criteria (CR, PR, SD, and Progressive Disease) [6]. In this study, patients with PR who also achieved CMR (PR + CMR) showed improved PFS when compared to those without CMR (PR + non-CMR) (median not reached versus 12.8 months; HR 0.07 [95% CI 0.02–0.27]; $P < 0.01$). Moreover, among 78 patients who achieved CMR, 78% had discontinued treatment and 96% had ongoing response [33]. These data suggest that additional functional information by ^{18}F-FDG PET imaging would be helpful for identifying long-term responders and providing guidance for ICI therapy discontinuation. Importantly, however, the optimal protocol should be determined in a prospective study.

Meanwhile, whether an early ^{18}F-FDG PET-CT evaluation could predict response to ICI therapy in patients with advanced melanoma remains unclear. Some retrospective studies have shown that ^{18}F-FDG PET or ^{18}F-FDG PET-CT could identify responders by ICI therapy [34–36]. However, there are several potential limitations that should be clarified with further prospective studies: first, the evaluation protocol adopted in each study was different, requiring optimal timing of scans for the response evaluation detection. Second, immunotherapy may induce immune cell infiltration and tumor inflammation during the early treatment course, which might confound interpretation of early ^{18}F-FDG PET scans [33, 37]. Finally, several inflammatory reactions or side effects, such as sarcoid-like reactions are likely to manifest as new lesions (Fig. 8.2). This may lead to the lesions being misjudged as

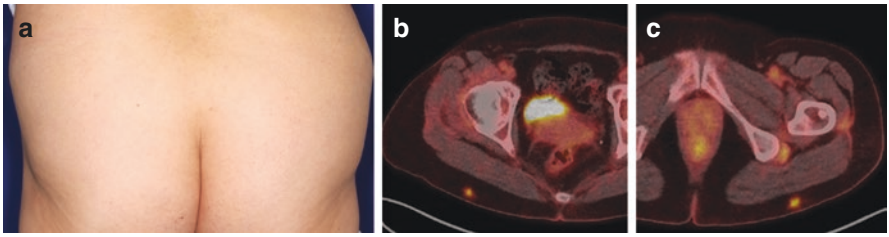

Fig. 8.2 *A case of melanoma in which the patient developed sarcoid reaction during treatment with nivolumab.* A 59-year-old woman with stage IV melanoma was treated with an anti-PD-1 antibody nivolumab. Four months later, occult subcutaneous nodules with high ^{18}F-FDG uptake were detected on the hips bilaterally (**a**–**c**). Although metastasis was considered as the most likely cause, the excised nodule was determined to be due to sarcoid reaction

disease progression; thus, a protocol that successfully excludes these inflammatory reactions is needed [38, 39].

8.2.6 Nonmelanoma Skin Cancers

Nonmelanoma skin cancers (NMSCs) primarily comprise basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). NMSCs are ^{18}F-FDG-avid lesions and reportedly ^{18}F-FDG PET-CT shows high diagnostic accuracy for the detection of these lesions [1]. Notably, most NMSCs are detected by skin biopsy and removed at an early stage. Therefore, further imaging modalities are not required in most NMSCs [40–42].

BCC is the most common type of skin cancer over the races [42, 43] and primarily affects elderly patients. It tends to grow slowly, spreads locally, and may invade deeper structures; however, it rarely metastasizes (<0.1% of cases) [42, 44]. Therefore, ^{18}F-FDG PET-CT shows limited utility in the detection of BCCs.

SCC is the second most common type of NMSC [42, 43], which also occurs primarily in elderly patients. SCCs commonly occur on the face, forearms, or hands and manifest as painless erythematous papules or nodules [41]. Chronic wounds including burn scars predispose to SCCs; therefore, SCCs should be suspected in patients presenting with an untreatable ulcer or skin injury at the site of a chronic wound or scar [41, 52]. Tumors with ill-defined borders and/or large ulceration indicate invasive and aggressive behavior with a higher risk of metastasis and fatality [45, 46]. Radiological imaging is considered most beneficial in patients with aggressive SCCs [47].

^{18}F-FDG PET-CT is considered superior to CT for visualization of small volume lymph nodes, subclinical recurrence, or metastases [1, 48]. Moreover, ^{18}F-FDG PET-CT is particularly preferred for postoperative surveillance of SCCs of the head and neck [48–50], because scar tissue that can distort normal anatomy may affect optimal visualization on CT alone [51]. However, the best imaging modality has not yet been established. Notably, ^{18}F-FDG PET-CT shows limited utility especially in cases with chronic ulcer with inflammation because ^{18}F-FDG PET detects increased glucose uptake, which could occur in a wide variety of lesions, and infection and inflammation are associated with high false-positive rates [52].

Merkel cell carcinoma (MCC) is a rare type of aggressive NMSC that occurs in elderly patients. MCC is known to originate from Markel neuroendocrine cells in the epidermis, which usually presents as a rapidly growing solitary nodule on sun-exposed areas of skin with a high propensity for lymph node and distant metastasis [53, 54]. Patients with metastasis show 5-year survival rates as low as 14% [55]; therefore, accurate pretreatment staging is mandatory. Imaging modalities such as CT, MRI, and ^{18}F-FDG PET-CT are useful for staging and posttreatment follow-up of MCC [56, 57].

MCCs are usually ^{18}F-FDG-avid tumors [57] and ^{18}F-FDG PET-CT is used for initial staging to detect an occult primary lesion or metastases [58–60]. A

meta-analysis of ^{18}F-FDG PET-CT reported high sensitivity (90%) and specificity (98%) in patients with MCC, which is superior to that of other imaging modalities for the detection of nodal and in-transit (metastatic lesions between the primary tumor and draining lymph nodes) metastases [56]. Additionally, it has been reported that ^{18}F-FDG PET-CT findings may lead to upstaging in >25% of patients and alter the treatment strategy in approximately 43% of patients [61, 62].

A prospective Trans Tasman Radiation Oncology Group 09.03 study investigated the utility of ^{8}F-FDG PET in the management of MCC. The study reported that ^{18}F-FDG PET showed a sensitivity of 95% [95% confidence interval (CI) 82–99.3] and a specificity of 88% (95% CI 63.56–98.54), a positive predictive value of 95% (95% CI 83–98.5), and a negative predictive value of 88% (95% CI 65.8–96.7). Pretreatment ^{18}F-FDG PET findings affected the treatment decision in 27.6% of cases, with 15 cases (25.9%) being upstaged without any downstaging. Although posttreatment ^{18}F-FDG PET was not of prognostic value, the authors concluded that staging ^{18}F-FDG PET significantly affected treatment decisions, and thus the pretreatment ^{18}F-FDG PET should be considered, particularly in patients with aggressive MCC [63].

Consequently, the MCC Clinical Practice Guidelines from the National Comprehensive Cancer Network® suggested that whole-body ^{8}F-FDG PET with fused axial imaging (CT or MR) is preferred in patients at a high risk of recurrence or in those with a high index of clinical suspicion for nodal or distant metastasis [64].

Extramammary Paget disease (EMPD) is another rare type of NMSC with a reported incidence of 2.4 patients per 100,000 person-years [65]. Although EMPD resembles mammary Paget disease with regard to pathological appearance and human epidermal growth factor receptor 2 overexpression [66–68], these conditions differ with regard to pathogenesis. Mammary Paget disease is necessarily associated with underlying breast carcinoma, whereas an association between EMPD and underlying malignancies is uncommon [69]. EMPD typically originates and persists as carcinoma in situ over several years with a favorable prognosis [69]. However, EMPD may metastasize to regional lymph nodes and distant sites if it transforms into an invasive tumor [70, 71] Reportedly, the incidence of such transformation is 34–61% of all cases of EMPDs [71–73]. Additionally, EMPD is associated with an underlying internal malignancy in nearly 20% of cases [74, 75]. Therefore, a thorough investigation is warranted for metastases and underlying malignancy before initiation of treatment for EMPD.

To date, the role of ^{18}F-FDG PET-CT in EMPD has only been described by a few case reports [76–78]. Clinical lymphadenopathy is a significant indicator of lymph node metastasis, which is also associated with low survival rates [70, 72]. However, lymph node enlargement may occasionally be caused by secondary inflammation in EMPD (Fig. 8.3). Therefore, it is challenging to accurately determine whether lymph node enlargement observed on ^{18}F-FDG PET-CT is due to metastasis or inflammation. In summary, the utility of ^{18}F-FDG PET-CT for EMPD remains unclear.

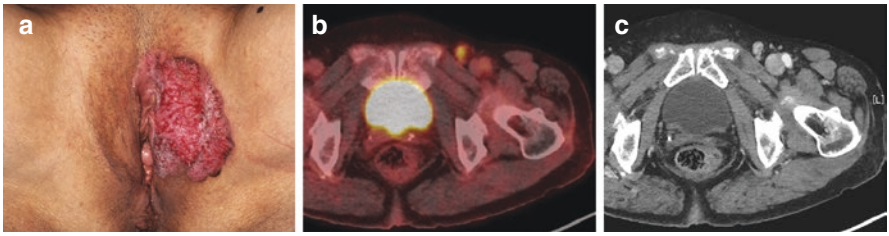

Fig. 8.3 *EMPD case with a false-positive result on ^{18}F-FDG PET-CT.* A 66-year-old woman developed erythema in her genital area (vulva) and was pathologically diagnosed with extramammary Paget disease (**a**). An asymmetrically enlarged regional lymph node in the left groin (SUV_{max}, 6.45; SUV_{peak}, 2.77) was identified on ^{18}F-FDG PET-CT, which suggested lymph node metastasis (**b**, **c**). However, metastasis was not detected in the excised lymph node

8.3 Cutaneous Soft Tissue Sarcomas

Cutaneous soft tissue sarcomas are rare heterogeneous mesenchymal neoplasms, which represent <1% of malignant tumors [79].

Dermatofibrosarcoma protuberans (DFSP) is a slow-growing rare mesenchymal malignancy of fibroblastic origin typically involving middle-aged adults [80]. Primary DFSP usually presents clinically as a solitary round or oval non-tender cutaneous and subcutaneous mass, usually smaller than 5 cm in diameter, with a well-defined margin [80]. DFSP arises from the dermis, most commonly in the trunk, and involves the underlying subcutaneous tissue, thereby making preoperative imaging such as CT and MRI useful for evaluating the size and shape to determine the adequate wide radical excision of the tumor [80–82]. Usually, ^{18}F-FDG PET-CT is considered to be superior to CT and MRI by detecting small volume lymph nodes, subclinical recurrence, or metastases [1, 9, 56]. However, regional nodal and distant metastases are uncommon for patients with DFSP [83], and thus CT and MRI are suffice for evaluating the extent of DFSP.

Angiosarcoma is a rare tumor accounting for 1–2% of all soft tissue sarcomas [79, 84] and less than 0.1% of all head and neck cancers [85]. Angiosarcomas arise from vascular or lymphatic endothelial cells and the skin is one of the locations where this highly malignant tumor with dismal prognosis develops (Fig. 8.4). Although most cutaneous angiosarcomas (CAS) develop in the head and neck region, some patients with chronic lymphedema may also develop angiosarcoma, known in this case as Stewart-Treves syndrome (STS) [79, 85, 86]. Cutaneous angiosarcomas have high rates of recurrence and metastasis, most commonly in the lung, followed by lymph nodes, bone, and liver [87, 88]. Multimodality treatment (radiotherapy/chemotherapy) is usually employed and has been shown to be beneficial [89]. However, even with multimodality treatment, the risk of recurrence is still high and the optimal treatment is yet to be determined [88, 90, 91].

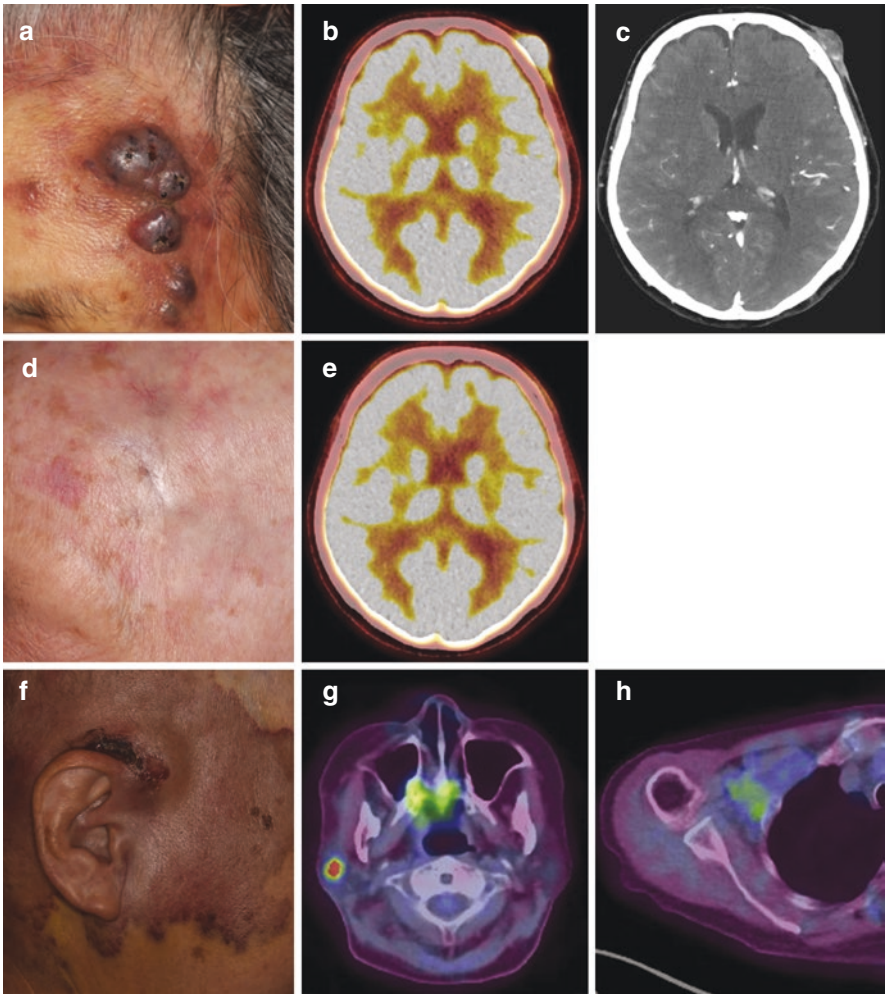

Fig. 8.4 *A case of angiosarcoma on the scalp.* A 66-year-old woman developed purpura and nodules on the left side of her forehead (**a**). She was diagnosed with angiosarcoma on biopsy. ^{18}F-FDG PET-CT revealed a tumor measuring 26 × 32 × 14 mm on the left frontal aspect, with an SUV_{max} of 21.2 and SUV_{peak} of 13.6 (**b**, **c**). The tumor responded well to weekly combination therapy comprising paclitaxel and radiotherapy, which helped in achieving complete remission (**d**, **e**). However, local recurrence occurred 24 months after treatment initiation. Although chemotherapy was restarted, the disease progressed (**f**), and the most recent ^{18}F-FDG PET-CT revealed a ^{18}F-FDG-avid lesion in the cervical (SUV_{max}, 12.73) (**g**) and axillary lymph nodes (SUV_{max}, 3.95) (**h**), which indicated a high likelihood of metastasis

There are several reports suggesting the use of ^{18}F-FDG PET-CT as a promising imaging tool in angiosarcomas, as it enables the detection of disease extension and multiple tumor foci in a single session, and could also detect recurrent disease [92–94]. In addition, Kajihara et al. reported that ^{18}F-FDG PET-CT evaluation possibly determines response to therapy [95]; in their retrospective study analyzing data from 18 patients, those with high SUV_{max} of the primary tumor had significantly unfavorable prognosis than those with low SUV_{max}, suggesting SUV_{max} of primary lesions could potentially predict patient survival [96]. Meanwhile, in terms of distant metastasis detection, some metastatic pulmonary lesions such as thin-walled pulmonary cystic lesions are reported to present as a negative study or misinterpreted as benign lesions due to the lack of ^{18}F-FDG uptake [97, 98]. Therefore, we have to be aware of cystic lesions that can be ^{18}F-FDG PET-negative even though pulmonary metastases of CAS have a variety of morphologic patterns on imaging [99, 100] and some of which could be ^{18}F-FDG-avid.

In STS, the incidence of which is more rare than CAS, Dawlatly et al. showed the efficacy of ^{18}F-FDG PET-CT in demonstrating the extent of the subcutaneous spread of tumors [101]. ^{18}F-FDG PET-CT was able to demonstrate recurrent disease in another report, indicating that ^{18}F-FDG PET-CT can be used for detecting local recurrence in STS [94]. The literature is sparse; however, these reports suggest that ^{18}F-FDG PET-CT could be superior to MRI, as it enables detecting disease extension in a single session.

8.4 Conclusion

Focal ^{18}F-FDG uptake of the cutaneous or subcutaneous lesions is a common incidental finding on ^{18}F-FDG PET. The present study focused on the potential benefit of ^{18}F-FDG PET or ^{18}F-FDG PET-CT in skin malignancies. As for some patients, ^{18}F-FDG PET-CT scan is considered to be the best modality, being the most sensitive for accurate diagnosis. However, we should be aware of the fact that ^{18}F-FDG uptake is not specific for malignant neoplasms, and might be due to inflammation, infection, or a benign tumor. Continuous investigation for detecting the optimal protocol is required.

Summary and Key Points

The aim of the current chapter was to elucidate the potential benefit and clinical utility of ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) or ^{18}F-FDG PET-computed tomography (^{18}F-FDG PET-CT) in skin malignancies, both carcinomas and sarcomas. Their importance in malignant melanomas was covered in the first half and their role in nonmelanoma skin cancers and cutaneous soft tissue sarcomas in the latter half.

The following are the key points of this review:

- Skin malignancies are reported to be ^{18}F-FDG-avid.
- ^{18}F-FDG PET-CT is considered the most sensitive and accurate diagnostic tool for patients with >pT3a malignant melanoma, as it is useful in detecting metas-

tasis of advanced melanomas (stages III and IV) with a sensitivity of 68–87% and specificity of 92–98%. However, its routine use for early-stage melanomas and follow-up of asymptomatic melanomas is not recommended.

- ^{18}F-FDG PET-CT has not been validated for the assessment of response to therapy in any type of skin malignancy. For melanoma, the possibility of using ^{18}F-FDG PET-CT to monitor response and predict long-term outcomes of recent therapies, such as BRAF inhibitors and immune checkpoint inhibitors, is under investigation.
- The utility of ^{18}F-FDG PET-CT for nonmelanoma skin cancers and cutaneous sarcomas remains unclear, except in aggressive Merkel cell carcinoma (MCC). Pretreatment ^{18}F-FDG PET should be considered in patients with aggressive MCC. In addition, whole-body ^{18}F-FDG PET with fused axial imaging (CT or magnetic resonance imaging) is preferred in patients with a high risk of recurrence or in those with a greater index of suspicion for nodal or distant metastasis.

References

1. Mogensen M, Jemec GB. Diagnosis of nonmelanoma skin cancer/keratinocyte carcinoma: a review of diagnostic accuracy of nonmelanoma skin cancer diagnostic tests and technologies. Dermatol Surg. 2007;33(10):1158–74.
2. Krug B, Crott R, Lonneux M, Baurain J-F, Pirson A-S, Vander BT. Role of PET in the initial staging of cutaneous malignant melanoma: systematic review. Radiology. 2008;249(3):836–44.
3. Perng P, Marcus C, Subramaniam RM. 18F-FDG PET/CT and melanoma: staging, immune modulation and mutation-targeted therapy assessment, and prognosis. Am J Roentgenol. 2015;205(2):259–70.
4. Lee CC, Faries MB, Wanek LA, Morton DL. Improved survival after lymphadenectomy for nodal metastasis from an unknown primary melanoma. J Clin Oncol. 2008;26(4):535–41.
5. Li Q, Yang J. Role of imaging methods in metastatic melanoma. Oncol Res Treatment. 2012;35(9):522–6.
6. Patnana M, Bronstein Y, Szklaruk J, Bedi DG, Hwu W-J, Gershenwald JE, et al. Multimethod imaging, staging, and spectrum of manifestations of metastatic melanoma. Clin Radiol. 2011;66(3):224–36.
7. Balch CM, Soong S-J, Gershenwald JE, Thompson JF, Reintgen DS, Cascinelli N, et al. Prognostic factors analysis of 17,600 melanoma patients: validation of the American joint committee on Cancer melanoma staging system. J Clin Oncol. 2001;19(16):3622–34.
8. Kumar R, Mavi A, Bural G, Alavi A. Fluorodeoxyglucose-PET in the management of malignant melanoma. Radiol Clin. 2005;43(1):23–33.
9. Veit-Haibach P, Vogt FM, Jablonka R, Kuehl H, Bockisch A, Beyer T, et al. Diagnostic accuracy of contrast-enhanced FDG-PET/CT in primary staging of cutaneous malignant melanoma. Eur J Nucl Med Mol Imaging. 2009;36(6):910.
10. Xing Y, Bronstein Y, Ross MI, Askew RL, Lee JE, Gershenwald JE, et al. Contemporary diagnostic imaging modalities for the staging and surveillance of melanoma patients: a meta-analysis. J Natl Cancer Inst. 2011;103(2):129–42.
11. Coit DG, Thompson JA, Albertini MR, Barker C, Carson WE, Contreras C, et al. Cutaneous melanoma, version 2.2019, NCCN clinical practice guidelines in oncology. J Natl Compr Cancer Netw. 2019;17(4):367–402.
12. Dummer R, Hauschild A, Lindenblatt N, Pentheroudakis G, Keilholz U. Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26(suppl_5):v126–v32.

13. Schröer-Günther MA, Wolff RF, Westwood ME, Scheibler FJ, Schürmann C, Baumert BG, et al. F-18-fluoro-2-deoxyglucose positron emission tomography (PET) and PET/computed tomography imaging in primary staging of patients with malignant melanoma: a systematic review. Syst Rev. 2012;1(1):62.
14. Cha J, Kim S, Wang J, Yun M, Cho A. Evaluation of 18 F-FDG PET/CT parameters for detection of lymph node metastasis in cutaneous melanoma. Nucl Med Mol Imaging. 2018;52(1):39–45.
15. Brix G, Lechel U, Glatting G, Ziegler SI, Münzing W, Müller SP, et al. Radiation exposure of patients undergoing whole-body dual-modality 18F-FDG PET/CT examinations. J Nucl Med. 2005;46(4):608–13.
16. Mohr P, Eggermont A, Hauschild A, Buzaid A. Staging of cutaneous melanoma. Ann Oncol. 2009;20(suppl_6):vi14–21.
17. Shon IAH, Chung DK, Saw RP, Thompson JF. Imaging in cutaneous melanoma. Nucl Med Commun. 2008;29(10):847–76.
18. Gao G, Gong B, Shen W. Meta-analysis of the additional value of integrated 18FDG PET–CT for tumor distant metastasis staging: comparison with 18FDG PET alone and CT alone. Surg Oncol. 2013;22(3):195–200.
19. Jouvet J, Thomas L, Thomson V, Yanes M, Journe C, Morelec I, et al. Whole-body MRI with diffusion-weighted sequences compared with 18 FDG PET-CT, CT and superficial lymph node ultrasonography in the staging of advanced cutaneous melanoma: a prospective study. J Eur Acad Dermatol Venereol. 2014;28(2):176–85.
20. Barrington SF, Kluge R. FDG PET for therapy monitoring in Hodgkin and non-Hodgkin lymphomas. Eur J Nucl Med Mol Imaging. 2017;44(1):97–110.
21. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228–47.
22. Callahan MK, Postow MA, Wolchok JD. Targeting T cell co-receptors for cancer therapy. Immunity. 2016;44(5):1069–78.
23. Kakadia S, Yarlagadda N, Awad R, Kundranda M, Niu J, Naraev B, et al. Mechanisms of resistance to BRAF and MEK inhibitors and clinical update of US Food and Drug Administration-approved targeted therapy in advanced melanoma. Onco Targets Ther. 2018;11:7095.
24. Kraeber-Bodéré F, Carlier T, Naegelen VM, Shochat E, Lumbroso J, Trampal C, et al. Differences in the biologic activity of 2 novel MEK inhibitors revealed by 18F-FDG PET: analysis of imaging data from 2 phase I trials. J Nucl Med. 2012;53(12):1836–46.
25. McArthur GA, Puzanov I, Amaravadi R, Ribas A, Chapman P, Kim KB, et al. Marked, homogeneous, and early [18F] fluorodeoxyglucose–positron emission tomography responses to vemurafenib in BRAF-mutant advanced melanoma. J Clin Oncol. 2012;30(14):1628.
26. Wong AN, McArthur GA, Hofman MS, Hicks RJ. The advantages and challenges of using FDG PET/CT for response assessment in melanoma in the era of targeted agents and immunotherapy. Eur J Nucl Med Mol Imaging. 2017;44(1):67–77.
27. Parmenter TJ, Kleinschmidt M, Kinross KM, Bond ST, Li J, Kaadige MR, et al. Response of BRAF-mutant melanoma to BRAF inhibition is mediated by a network of transcriptional regulators of glycolysis. Cancer Discov. 2014;4(4):423–33.
28. Tanaka R, Fujisawa Y, Sae I, Maruyama H, Ito S, Hasegawa N, et al. Severe hepatitis arising from ipilimumab administration, following melanoma treatment with nivolumab. Jpn J Clin Oncol. 2016;47(2):175–8.
29. Thompson JA, Schneider BJ, Brahmer J, Andrews S, Armand P, Bhatia S, et al. Management of immunotherapy-related toxicities, version 1.2019, NCCN clinical practice guidelines in oncology. J Natl Compr Cancer Netw. 2019;17(3):255–89.
30. Jansen Y, Rozeman E, Mason R, Goldinger S, Geukes Foppen M, Hoejberg L, et al. Discontinuation of anti-PD-1 antibody therapy in the absence of disease progression or treatment limiting toxicity: clinical outcomes in advanced melanoma. Ann Oncol. 2019;30:1154.
31. Robert C, Long GV, Schachter J, Arance A, Grob JJ, Mortier L, et al. Long-term outcomes in patients (pts) with ipilimumab (ipi)-naive advanced melanoma in the phase 3 KEYNOTE-006 study who completed pembrolizumab (pembro) treatment. Am Soc Clin Oncol J. 2017;35:9504.

32. Long GV, Schachter J, Ribas A, Arance AM, Grob J-J, Mortier L, et al. 4-year survival and outcomes after cessation of pembrolizumab (pembro) after 2-years in patients (pts) with ipilimumab (ipi)-naive advanced melanoma in KEYNOTE-006. Am Soc Clin Oncol J. 2018;36:9503.
33. Tan A, Emmett L, Lo S, Liu V, Kapoor R, Carlino M, et al. FDG-PET response and outcome from anti-PD-1 therapy in metastatic melanoma. Ann Oncol. 2018;29(10):2115–20.
34. Seith F, Forschner A, Schmidt H, Pfannenberg C, Gückel B, Nikolaou K, et al. 18F-FDG-PET detects complete response to PD1-therapy in melanoma patients two weeks after therapy start. Eur J Nucl Med Mol Imaging. 2018;45(1):95–101.
35. Sachpekidis C, Larribere L, Pan L, Haberkorn U, Dimitrakopoulou-Strauss A, Hassel JC. Predictive value of early 18 F-FDG PET/CT studies for treatment response evaluation to ipilimumab in metastatic melanoma: preliminary results of an ongoing study. Eur J Nucl Med Mol Imaging. 2015;42(3):386–96.
36. Cho SY, Lipson EJ, Im H-J, Rowe SP, Gonzalez EM, Blackford A, et al. Prediction of response to immune checkpoint inhibitor therapy using early-time-point 18F-FDG PET/CT imaging in patients with advanced melanoma. J Nucl Med. 2017;58(9):1421–8.
37. Vilain RE, Menzies AM, Wilmott JS, Kakavand H, Madore J, Guminski A, et al. Dynamic changes in PD-L1 expression and immune infiltrates early during treatment predict response to PD-1 blockade in melanoma. Clin Cancer Res. 2017;23(17):5024–33.
38. Ogawa T, Ishitsuka Y, Iwamoto K, Koguchi-Yoshioka H, Tanaka R, Watanabe R, et al. Programmed cell death 1 blockade-induced cutaneous sarcoid-like epithelioid granulomas in advanced melanoma: a case report. J Eur Acad Dermatol Venereol. 2018;32(7):e260–e1.
39. Dimitriou F, Frauchiger AL, Urosevic-Maiwald M, Naegeli MC, Goldinger SM, Barysch M, et al. Sarcoid-like reactions in patients receiving modern melanoma treatment. Melanoma Res. 2018;28(3):230.
40. Hong H, Sun J, Cai W. Anatomical and molecular imaging of skin cancer. Clin Cosmet Investig Dermatol. 2008;1:1.
41. Preston DS, Stern RS. Nonmelanoma cancers of the skin. New Engl J Med. 1992;327(23):1649–62.
42. Madan V, Lear JT, Szeimies R-M. Non-melanoma skin cancer. Lancet. 2010;375(9715):673–85.
43. Gloster HM Jr, Neal K. Skin cancer in skin of color. J Am Acad Dermatol. 2006;55(5):741–60.
44. Levell N, Igali L, Wright K, Greenberg D. Basal cell carcinoma epidemiology in the UK: the elephant in the room. Clin Exp Dermatol. 2013;38(4):367–9.
45. Cherpelis BS, Marcusen C, Lang PG. Prognostic factors for metastasis in squamous cell carcinoma of the skin. Dermatol Surg. 2002;28(3):268–73.
46. Johnson TM, Rowe DE, Nelson BR, Swanson NA. Squamous cell carcinoma of the skin (excluding lip and oral mucosa). J Am Acad Dermatol. 1992;26(3):467–84.
47. Ruiz ES, Karia PS, Morgan FC, Schmults CD. The positive impact of radiologic imaging on high-stage cutaneous squamous cell carcinoma management. J Am Acad Dermatol. 2017;76(2):217–25.
48. Duncan JR, Carr D, Kaffenberger BH. The utility of positron emission tomography with and without computed tomography in patients with nonmelanoma skin cancer. J Am Acad Dermatol. 2016;75(1):186–96.
49. Jeong HS, Baek CH, Son YI, Ki Chung M, Kyung Lee D, Young Choi J, et al. Use of integrated 18F-FDG PET/CT to improve the accuracy of initial cervical nodal evaluation in patients with head and neck squamous cell carcinoma. Head Neck. 2007;29(3):203–10.
50. Jennings L, Schmults CD. Management of high-risk cutaneous squamous cell carcinoma. J Clin Aesthet Dermatol. 2010;3(4):39.
51. MacFarlane D, Shah K, Wysong A, Wortsman X, Humphreys TR. The role of imaging in the management of patients with nonmelanoma skin cancer: diagnostic modalities and applications. J Am Acad Dermatol. 2017;76(4):579–88.
52. Rosenbaum SJ, Lind T, Antoch G, Bockisch A. False-positive FDG PET uptake—the role of PET/CT. Eur Radiol. 2006;16(5):1054–65.

53. Poulsen M. Merkel-cell carcinoma of the skin. Lancet Oncol. 2004;5(10):593–9.
54. Albores-Saavedra J, Batich K, Chable-Montero F, Sagy N, Schwartz AM, Henson DE. Merkel cell carcinoma demographics, morphology, and survival based on 3870 cases: a population based study. J Cutan Pathol. 2010;37(1):20–7.
55. Coggshall K, Tello TL, North JP, Siegrid SY. Merkel cell carcinoma: an update and review: pathogenesis, diagnosis, and staging. J Am Acad Dermatol. 2018;78(3):433–42.
56. Treglia G, Kakhki VRD, Giovanella L, Sadeghi R. Diagnostic performance of fluorine-18-fluorodeoxyglucose positron emission tomography in patients with Merkel cell carcinoma: a systematic review and meta-analysis. Am J Clin Dermatol. 2013;14(6):437–47.
57. Peloschek P, Novotny C, Mueller-Mang C, Weber M, Sailer J, Dawid M, et al. Diagnostic imaging in Merkel cell carcinoma: lessons to learn from 16 cases with correlation of sonography, CT, MRI and PET. Eur J Radiol. 2010;73(2):317–23.
58. Shintani SA, Foote RL, Lowe VJ, Brown PD, Garces YI, Kasperbauer JL. Utility of PET/CT imaging performed early after surgical resection in the adjuvant treatment planning for head and neck cancer. Int J Radiat Oncol Biol Phys. 2008;70(2):322–9.
59. Colgan M, Tarantola T, Weaver A. The predictive value of imaging studies in evaluating regional lymph node involvement in Merkel cell carcinoma. J Am Acad Dermatol. 2012;67:1250–6.
60. Foote M, Veness M, Zarate D, Poulsen M. Merkel cell carcinoma: the prognostic implications of an occult primary in stage IIIB (nodal) disease. J Am Acad Dermatol. 2012;67(3):395–9.
61. Ben-Haim S, Garkaby J, Primashvili N, Goshen E, Shapira R, Davidson T, et al. Metabolic assessment of Merkel cell carcinoma: the role of 18F-FDG PET/CT. Nucl Med Commun. 2016;37(8):865–73.
62. Concannon R, Larcos GS, Veness M. The impact of 18F-FDG PET-CT scanning for staging and management of Merkel cell carcinoma: results from Westmead hospital, Sydney, Australia. J Am Acad Dermatol. 2010;62(1):76–84.
63. Poulsen M, Macfarlane D, Veness M, Estall V, Hruby G, Kumar M, et al. Prospective analysis of the utility of 18-FDG PET in Merkel cell carcinoma of the skin: a trans Tasman radiation oncology group study, TROG 09: 03. J Med Imaging Radiat Oncol. 2018;62(3):412–9.
64. Bichakjian CK, Olencki T, Aasi SZ, Alam M, Andersen JS, Blitzblau R, et al. Merkel cell carcinoma, version 1.2018, NCCN clinical practice guidelines in oncology. J Natl Compr Cancer Netw. 2018;16(6):742–74.
65. Herrel LA, Weiss AD, Goodman M, Johnson TV, Osunkoya AO, Delman KA, et al. Extramammary Paget's disease in males: survival outcomes in 495 patients. Ann Surg Oncol. 2015;22(5):1625–30.
66. Tanaka R, Sasajima Y, Tsuda H, Namikawa K, Takahashi A, Tsutsumida A, et al. Concordance of the HER2 protein and gene status between primary and corresponding lymph node metastatic sites of extramammary Paget disease. Clin Exp Metastasis. 2016;33(7):687–97.
67. Tanaka R, Sasajima Y, Tsuda H, Namikawa K, Tsutsumida A, Otsuka F, et al. Human epidermal growth factor receptor 2 protein overexpression and gene amplification in extramammary Paget disease. Br J Dermatol. 2013;168(6):1259–66.
68. Lloyd J, Flanagan A. Mammary and extramammary Paget's disease. J Clin Pathol. 2000;53(10):742–9.
69. Kanitakis J. Mammary and extramammary Paget's disease. J Eur Acad Dermatol Venereol. 2007;21(5):581–90.
70. Ohara K, Fujisawa Y, Yoshino K, Kiyohara Y, Kadono T, Murata Y, et al. A proposal for a TNM staging system for extramammary Paget disease: retrospective analysis of 301 patients with invasive primary tumors. J Dermatol Sci. 2016;83(3):234–9.
71. Fujisawa Y, Yoshino K, Kiyohara Y, Kadono T, Murata Y, Uhara H, et al. The role of sentinel lymph node biopsy in the management of invasive extramammary Paget's disease: multicenter, retrospective study of 151 patients. J Dermatol Sci. 2015;79(1):38–42.
72. Hatta N, Yamada M, Hirano T, Fujimoto A, Morita R. Extramammary Paget's disease: treatment, prognostic factors and outcome in 76 patients. Br J Dermatol. 2008;158(2):313–8.

73. Dai B, Kong YY, Chang K, Qu YY, Ye DW, Zhang SL, et al. Primary invasive carcinoma associated with penoscrotal extramammary Paget's disease: a clinicopathological analysis of 56 cases. BJU Int. 2015;115(1):153–60.
74. Goldblum JR, Hart WR. Perianal Paget's disease: a histologic and immunohistochemical study of 11 cases with and without associated rectal adenocarcinoma. Am J Surg Pathol. 1998;22(2):170–9.
75. Wang Z, Lu M, Dong GQ, Jiang YQ, Lin MS, Cai ZK, et al. Penile and scrotal Paget's disease: 130 Chinese patients with long-term follow-up. BJU Int. 2008;102(4):485–8.
76. Aoyagi S, Sato-Matsumura KC, Shimizu H. Staging and assessment of lymph node involvement by18F-Fluorodeoxyglucose–positron emission tomography in invasive extramammary Paget's disease. Dermatol Surg. 2005;31(5):595–8.
77. Li Z-G, Qin X-J. Extensive invasive extramammary Paget disease evaluated by F-18 FDG PET/CT: a case report. Medicine. 2015;94(3):e371.
78. Cho SB, Yun M, Lee M-G, Chung KY. Variable patterns of positron emission tomography in the assessment of patients with extramammary Paget's disease. J Am Acad Dermatol. 2005;52(2):353–5.
79. Rouhani P, Fletcher CD, Devesa SS, Toro JR. Cutaneous soft tissue sarcoma incidence patterns in the US: an analysis of 12,114 cases. Cancer. 2008;113(3):616–27.
80. Juan Y-H, Saboo SS, Tirumani SH, Khandelwal A, Shinagare AB, Ramaiya N, et al. Malignant skin and subcutaneous neoplasms in adults: multimodality imaging with CT, MRI, and 18F-FDG PET/CT. Am J Roentgenol. 2014;202(5):W422–W38.
81. Korkolis D, Liapakis I, Vassilopoulos P. Dermatofibrosarcoma protuberans: clinicopathological aspects of an unusual cutaneous tumor. Anticancer Res. 2007;27(3B):1631–4.
82. Kransdorf MJ, Meis-Kindblom JM. Dermatofibrosarcoma protuberans: radiologic appearance. AJR Am J Roentgenol. 1994;163(2):391–4.
83. Bogucki B, Neuhaus I, Hurst EA. Dermatofibrosarcoma protuberans: a review of the literature. Dermatol Surg. 2012;38(4):537–51.
84. Brennan M, Alektiar K, Maki R, Vincent T, DeVita J, Hellman S, et al. Soft tissue sarcoma: table 39. 1–15. In: DeVita VT Jr, Lawrence TS, Rosenberg SA, Eds. Cancer: principles and practice of oncology. Wolters Klower: Alphen aan den Rijn; 2001.
85. Maddox JC, Evans HL. Angiosarcoma of skin and soft tissue: a study of forty-four cases. Cancer. 1981;48(8):1907–21.
86. Stewart FW, Treves N. Lymphangiosarcoma in postmastectomy lymphedema. A report of six cases in elephantiasis chirurgica. Cancer. 1948;1(1):64–81.
87. Weiss S, Lasota J, Miettinen M. Angiosarcoma of soft tissue. WHO classification tumours of soft tissue and bone. Lyon: IARC Press; 2002. p. 175–7.
88. Patel SH, Hayden RE, Hinni ML, Wong WW, Foote RL, Milani S, et al. Angiosarcoma of the scalp and face: the Mayo Clinic experience. JAMA. 2015;141(4):335–40.
89. Fujisawa Y, Yoshino K, Kadono T, Miyagawa T, Nakamura Y, Fujimoto M. Chemoradiotherapy with taxane is superior to conventional surgery and radiotherapy in the management of cutaneous angiosarcoma: a multicentre, retrospective study. Br J Dermatol. 2014;171(6):1493–500.
90. Fujisawa Y, Yoshino K, Fujimura T, Nakamura Y, Okiyama N, Ishitsuka Y, et al. Cutaneous angiosarcoma: the possibility of new treatment options especially for patients with large primary tumor. Front Oncol. 2018;8:46.
91. Lahat G, Dhuka A, Lahat S, Smith K, Pollock RE, Hunt KK, et al. Outcome of locally recurrent and metastatic angiosarcoma. Ann Surg Oncol. 2009;16(9):2502–9.
92. Vasanawala MS, Wang Y, Quon A, Gambhir SS. F-18 fluorodeoxyglucose PET/CT as an imaging tool for staging and restaging cutaneous angiosarcoma of the scalp. Clin Nucl Med. 2006;31(9):534–7.
93. Tokmak E, Özkan E, Yağcı S, Kır KM. F18-FDG PET/CT scanning in angiosarcoma: report of two cases. Mol Imaging Radionucl Ther. 2011;20(2):63.
94. Sharma P, Singh H, Singhal A, Bal C, Kumar R. Detection of recurrent cutaneous Angiosarcoma of lower extremity with 18F-Fluorodeoxyglucose positron emission tomography-computed tomography: report of three cases. Indian J Dermatol. 2013;58(3):242.

95. Kajihara I, Kanemaru H, Miyake T, Aoi J, Masuguchi S, Fukushima S, et al. Combination chemotherapy with S-1 and docetaxel for cutaneous angiosarcoma resistant to paclitaxel. Drug Discov Ther. 2015;9(1):75–7.
96. Umemura H, Yamasaki O, Kaji T, Hamada T, Otsuka M, Asagoe K, et al. Prognostic value of 18F-fluorodeoxyglucose positron emission tomography/computed tomography in patients with cutaneous angiosarcoma: a retrospective study of 18 cases. J Dermatol. 2017;44(9):1046–9.
97. Aryal S, Chu C, Morehead RS. An 83-year-old man with bilateral spontaneous pneumothoraces and multiple cysts. Chest. 2011;139(6):1536–9.
98. Andersen K, Albrecht-Beste E, Berthelsen A, Loft A. Angiosarcoma of the scalp: metastatic pulmonary cystic lesions initially misinterpreted as benign findings on 18F-FDG PET/CT. Diagnostics. 2016;6(1):1.
99. Kitagawa M, Tanaka I, Takemura T, Matsubara O, Kasuga T. Angiosarcoma of the scalp: report of two cases with fatal pulmonary complications and a review of Japanese autopsy registry data. Virchows Arch A Pathol Anat Histopathol. 1987;412(1):83–7.
100. Tateishi U, Hasegawa T, Kusumoto M, Yamazaki N, Iinuma G, Muramatsu Y, et al. Metastatic angiosarcoma of the lung: spectrum of CT findings. Am J Roentgenol. 2003;180(6):1671–4.
101. Dawlatly SL, Dramis A, Sumathi VP, Grimer RJ. Stewart–Treves syndrome and the use of positron emission tomographic scanning. Annals of Vasc Surg. 2011;25(5):699.e1–3.

Chapter 9
F-18 FDG PET Tests in Malignant Lymphoma

Norifumi Tsukamoto

9.1 Introduction

Malignant lymphomas, which are a heterogeneous group of diseases that arise from the cells of the immune system, are classified as Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). The HL group mainly involves the lymph node, and has been subdivided into nodular lymphocyte predominant HL and classic HL (cHL). The latter group has been further divided into four histological subtypes: (1) nodular sclerosis cHL, (2) lymphocyte-rich cHL, (3) mixed-cellularity cHL, and (4) lymphocyte depleted cHL [1]. In contrast, NHL often involves up to 40% extranodal sites, and based on the phenotype, is divided into the B cell lymphoma and NK/T cell lymphoma groups. Diffuse large B cell lymphoma (DLBCL) and follicular lymphoma (FL) are the common subtypes, with the former type being aggressive, while the latter is indicative of an indolent clinical course [1].

Accurate staging and post-therapy evaluation are essential for the improvement of lymphoma treatment. Imaging plays a key role in the management of lymphoma, as comparison of the images before and after treatment is objective and reproducible [2]. When the Cotswold classification [2], which is based on the Ann Arbor classifications [3, 4], is used for evaluation of computed tomography (CT) images, this makes it possible to visualize the lymph node and organs. The 1999 National Cancer Institute Working Group published an evaluation of lymphoma lesion by CT, which was also adopted for the staging and response criteria for NHL as well as HL [5]. These criteria involve complete (CR) and partial response (PR), stable, progressive, and relapsed disease (RD), and CR undetermined (CRu), in which the tumor mass persists with a size reduction following treatment due to tumor fibrosis rather than residual disease.

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Due to the high sensitivity of ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) in the detection of the disease, this methodology has become the standard procedure for the evaluation of lymphomas [6–8]. Furthermore, the 2007 International Working Group (IWG) also incorporated this technique into the revised response criteria due to both the superior sensitivity and specificity in HL and DLBCL, along with the elimination of the CRu [9]. The collection of sufficient additional information that supported the usefulness of PET/CT in other histologies, especially FL, subsequently led to the publication of the Lugano classification in 2014 [10, 11]. This classification recommended using PET/CT as the standard method for staging and response criteria in most of the FDG-avid lymphoma. In addition, this classification has also incorporated the Deauville 5-point scale method [12], which is a standardized criteria for the interpretation of scans. The recent introduction of immune checkpoint inhibitors has helped to elucidate a different clinical course named "pseudo-progression," which documents the presence of progressive disease despite the contrary evidence of clinical benefit [13, 14]. The provisional recommendation was introduced in 2016 in order to address this phenomenon in the guidelines [14].

9.2 Role of PET in Staging at the Time of Diagnosis

Staging is important not only for treatment decisions but also for predicting the lymphoma prognosis. This staging process is based on the Ann Arbor staging system, which differentiates the lymphoma lesion into four stages [3, 4]. Although CT scans and gallium scintigraphy were commonly used modalities for staging, PET/CT has proved to be a more sensitive and specific imaging method than a CT scan by itself. Moreover, the PET/CT methodology is advantageous as it can detect metabolic changes in the areas involved with lymphoma before the structural changes become visible. In the Lugano classification [10, 11], PET/CT was included as a way to evaluate the lymphoma lesions seen in most of the subtypes. These are recognized based on the increased FDG uptake in the lymph node, spleen, liver, and other extranodal sites, which includes the bone marrow (Table 9.1) (Fig. 9.1). Extension from a nodal lesion into extranodal tissues such as the lung, pericardium, and pleura, which may occur in stages I–III, does not cause the stage to develop into stage IV.

In the Ann Arbor classification, patients were subdivided according to the absence (A) or presence (B) of disease-related symptoms such as fever, weight loss, or sweating [3, 4]. However, these features do not confer unfavorable prognosis in NHL; the presence of disease-related symptoms correlates only in HL. Therefore, it is recommended that the description of the disease-related symptoms A or B are only needed in HL; it can be omitted in NHL [10].

In contrast, although FDG avidity is variable in small lymphocytic lymphoma, lymphoplasmacytic lymphoma, marginal zone lymphomas, and mycosis fungoides, CT scans can still be used for detection of lymphoma lesions [10].

Table 9.1 Staging system for lymphoma (the Lugano Classification)

Stage	Nodal Involvement	Extranodal Status
Limited		
I	One node or a group of adjacent nodes	Single extranodal lesions without nodal involvement
II	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited contiguous extranodal involvement
II bulky	II as above with "bulky" disease	Not applicable
Advanced		
III	Nodes on both sides of the diaphragm: Nodes above the diaphragm with spleen involvement	Not applicable
IV	Additional noncontiguous extralymphatic involvement	Not applicable

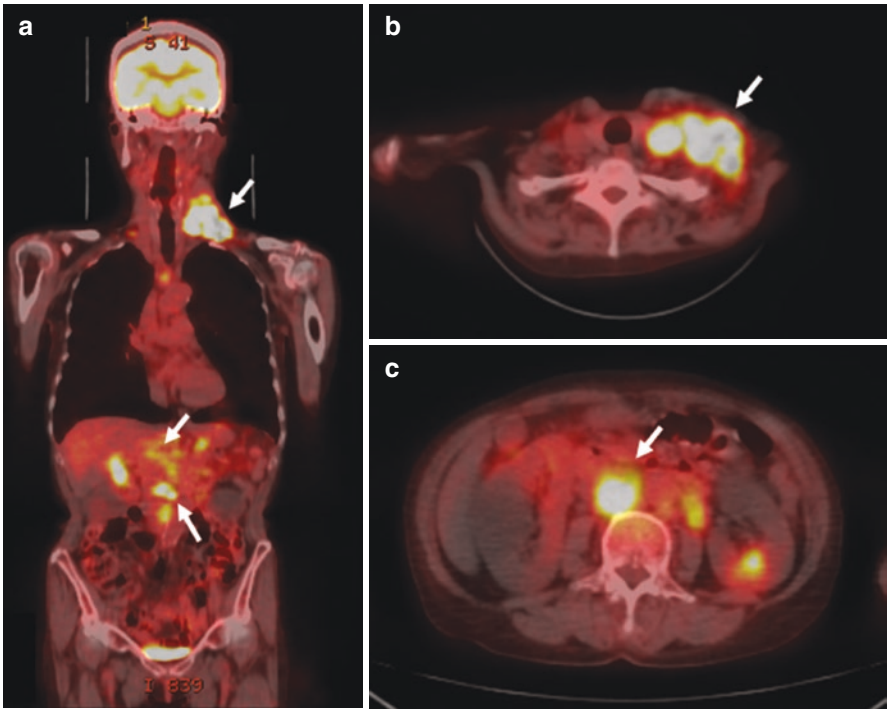

Fig. 9.1 Initial staging with ^{18}F-fluorodeoxyglucose (FDG) PET/CT in Hodgkin Lymphoma. (**a**) Coronal image shows accumulation of FDG in left cervical, mesenteric and para-aortic lymph nodes (arrows). Axial images of left cervical lymph node (**b**) and para-aortic lymph node (**c**) with SUVmax 12.5 and 10.5, respectively

PET/CT improves the accuracy of the lymphoma lesion detection, with mainly upstaging occurring in 10–30% of cases [10]. This can potentially help to avoid overtreatment as well as undertreatment. Upstaging has especially been reported to be more common in FL versus the other subtypes. However, since an enhanced CT scan can identify a nodal mass more clearly as compared to PET/CT, enhanced CT is considered to be suitable for accurately measuring the tumor size. When the size of the spleen exceeds 13 cm, this classification recommends that this condition be defined as splenomegaly. Furthermore, diffusely increased or focal uptake of FDG in the liver is recognized as liver involvement [10].

The presence of bulky disease is a negative prognostic factor in some lymphomas. In fact, the longest diameter of the largest lymphoma lesion is used as one of the factors in the FL International Prognostic Index 2 [15]. Although a variety of sizes have been proposed, such as 6 cm in FL, 6–10 cm in DLBCL, and 10 cm in HL, these sizes have yet to be definitively validated. The Lugano classification recommends recording of the longest measurement by CT in order to determine the presence of bulky disease [10].

The role of bone marrow biopsy has changed during the current PET/CT era. In HL and DLBCL, PET/CT sensitivity surpasses that for bone marrow biopsy when detecting bone marrow involvement [16, 17]. However, since the use of a bone marrow biopsy can still be important when evaluating hematopoietic function, performing a bone marrow biopsy prior to treatment is preferable in all cases.

The degree of the FDG uptake can be expressed quantitatively by the standardized uptake value (SUV). SUV is defined as the concentration of radioactivity in the tissue or lesion (MBq/mL) × patient body weight (g)/injected dose (MBq) [18], while the maximum uptake of ^{18}F-FDG in the tumor is represented by the SUVmax. SUVmax is correlated with the activity of the lymphoma lesion. HL and aggressive lymphoma such as DLBCL exhibited a higher FDG uptake as compared to indolent lymphoma [19, 20], with a SUVmax > 10 suggestive of aggressive lymphoma [19, 21]. These values can also potentially be used to identify the foci of the aggressive transformation in those patients who were initially diagnosed as indolent lymphoma.

Staging is an important component of a predictive model for newly diagnosed patients with lymphoma. For example, the five factors that affect the prognosis in aggressive lymphoma include age, serum lactate dehydrogenase (LDH), performance status (PS), stage, and extranodal involvement [22]. Likewise, the presence of an advanced stage (stages III–IV) is also an important risk factor for other lymphomas, such as the follicular lymphoma prognosis index (FLIPI) for FL [23], and the international prognosis score for advanced HL [24].

9.3 End of Treatment Evaluation

Since complete remission is a prerequisite for a cure, the major objective in patients with lymphoma is to achieve complete remission. The therapeutic response is assessed based on clinical manifestation, blood tests, and imaging. A decrease in the

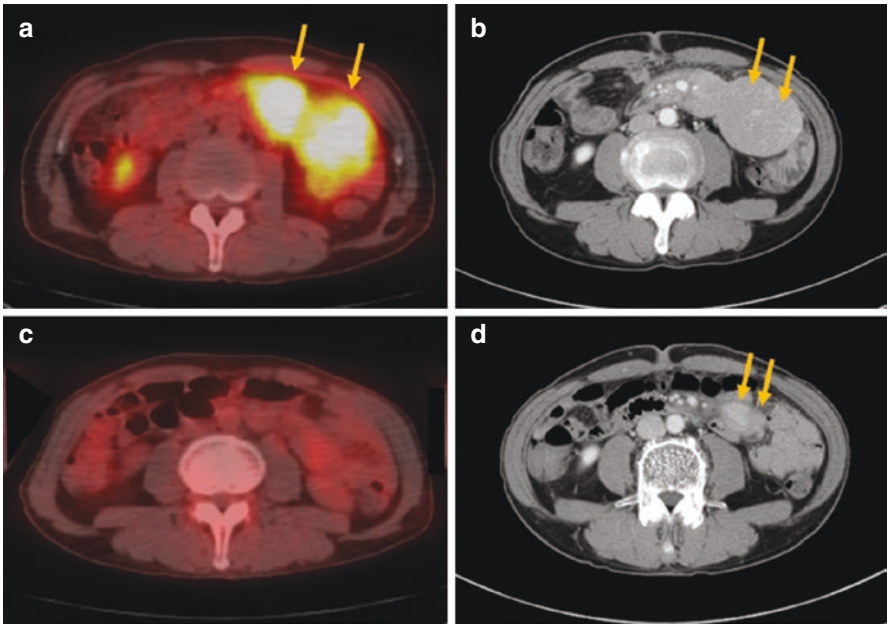

Fig. 9.2 Pretreatment and posttreatment images in a patient with follicular lymphoma. Pretreatment PET/CT (**a**) and CT scan (**b**) shows large mesenteric lymph nodes (arrows). Posttreatment PET/CT (**c**) demonstrates no uptake of FDG, but residual mass on CT scan (arrows) (**d**)

size of the tumor mass has been the cornerstone for a good therapeutic response in lymphoma. However, when CT finds a residual mass, this can be ambiguous, as it is not always metabolically active. Therefore, performing PET/CT at the end of treatment for lymphoma proved to be effective in discriminating residual active disease from fibrotic masses [10]. Thus, the value of PET/CT determined for the end of treatment assessments can be established for DLBCL, HL, FL, and other FDG-avid lymphomas (Fig. 9.2). In these subtypes, a positive PET/CT after treatment is strongly predictive of residual disease, whereas a negative PET is predictive of the absence of residual disease [10, 25, 26]. To minimize false-positive results, PET/CT needs to be performed at 6–8 weeks after the administration of chemotherapy, and at 8–12 weeks after completion of irradiation [27]. As PET/CT reflects glucose metabolism, evaluation of the CR indicates complete metabolic remission (CMR), whereas the PR indicates the partial metabolic response (PMR) [10].

For the 2007 IWG criteria, PET/CT evaluations were based on visual interpretations that used the mediastinal blood pool as the standard portion [9]. To assure reproducibility, a 5-point scale was recommended as the standard criteria for the scoring system used to assess the residual FDG uptake in the Lugano classification [10, 11]. The system is defined as follows [12]:

- Score 1: no uptake.
- Score 2: slight uptake, but below the mediastinum (blood pool).

- Score 3: uptake above the mediastinal, but below or equal to uptake in the liver.
- Score 4: uptake slightly to moderately higher than liver.
- Score 5: uptake markedly higher than liver and/or new lesions (on response evaluation).

The results of the PET/CT are interpreted as follows [10, 11] (Table 9.2):

- Complete response (CR): scores of 1, 2, or 3 together with the absence of any FDG-avid bone marrow lesion(s), irrespective of a persistent mass seen on CT.
- Partial response (PR): Deauville score of 4 or 5 with reduced uptake compared with baseline and residual mass(es) of any size.
- Stable disease (SD), also referred to as no response: Deauville score of 4 or 5 without any significant change in the FDG uptake from baseline.
- Progressive disease (PD): Deauville score of 4 to 5 with increasing intensity compared to baseline or any interim scan and/or new FDG-avid foci consistent with malignant lymphoma.

Score 3 should be interpreted according to the clinical context and the treatment, but in many patients indicates a good prognosis. A score of 4 or 5 indicates the presence of a residual lymphoma lesion even if the FDG uptake decreased from baseline [10].

In patients with relapsed or refractory HL or NHL, PET/CT can also determine prognostic information after salvage chemotherapy and high-dose chemotherapy followed by autologous stem cell transplantation. Three-year progression-free survival (PFS) in patients who were PET negative was more than 75%, which was superior to the 30–40% PFS in the PET positive patients. Thus, PET/CT findings may be useful in the final decision as to whether a patient should undergo high-dose chemotherapy followed by ASCT [11, 28, 29].

For the variable PET-avid subtypes, the assessment of the response needs to be done using a CT. CR is defined as follows: all of the target lesions, which includes up to six of the largest lesions at baseline, need to regress to a longest diameter of $\leq$1.5 cm after completion of the treatment. PR is defined as a decrease of more than 50% of the sum of the product of the long axis diameter and the short axis diameter for up to six of the target lesions. If the mass decreased in size but still persisted, it was defined as the best PR without the demonstration of the absence of lymphoma by biopsy [10, 11].

The results of the post chemotherapy evaluation by PET/CT is also part of the decision for the radiotherapy. Patients who were PET/CT negative had a far better PFS than that of patients who were PET/CT positive. In the posttreatment PET/CT positive patients, PFS of patients receiving radiotherapy was superior to those not receiving radiotherapy. Thus, the end of treatment PET/CT could potentially be used in the decision for using additional radiotherapy [30, 31]. With regard to radiotherapy planning, post-therapy PET/CT can more precisely determine the localization of the lymphoma lesion. In addition, PET/

Table 9.2 Response criteria for patients with FDG-avid lymphoma proposed in the 12th ICML Conference (Lugano 2013)

Response assessment	Evaluation by PET-CT	Lymph nodes and extralymphatic sites	Nonmeasured lesion	Organ enlargement	New lesion	Bone marrow
CR	Complete metabolic response (CMR)	Score 1, 2, or 3 with or without a residual mass on CT	NA	NA	None	No evidence of FDG-avid disease in marrow
PR	Partial metabolic response (PMR)	*Score 4 or 5 with reduced uptake compared with baseline and residual mass(es) of any size (but no new lesions)	NA	NA	None	Residual uptake higher than uptake in normal marrow but reduced compared with baseline
SD/NR	No metabolic response (NMR)	Score 4 or 5 with no significant change in FDG uptake from baseline	NA	NA	None	No change from baseline
PD	Progressive metabolic disease (PMD)	Score 4 or 5 with an increase in intensity of uptake from baseline and/or New FDG-avid foci consistent with lymphoma	None		New FDG-avid foci consistent with lymphoma rather than another etiology	New or recurrent FDG-avid foci
		*At end of treatment; residual disease, At interim; responding disease	NA: not applicable			

Table 9.3 Refinement of the Lugano classification lymphoma response criteria in the era of immunomodulatory therapy

Response assessment	Definition
CR	Disappearance of all lesions in 2 consecutive observations not less than 4 weeks apart
PR	≥50% decrease in tumor burden compared with baseline in 2 observations at least 4 weeks apart (as measured bidimensionally)
PD	≥25% increase in tumor burden compared with nadir (at any single time point) in 2 consecutive observations at least 4 weeks apart, where Tumor Burden = SPD index lesions + SPD new, measurable lesions

CT yields better consistency of the target volume delineation as compared to the CT scan [32–34].

Recently, immune checkpoint inhibitors have been added to lymphoma therapy. These agents are sometimes associated with the progression of the lymphoma lesion despite the evidence of clinical benefit. This is referred to as "pseudo-progression" and its occurrence is well-known in solid tumors [13, 14]. To address this issue, a workshop proposed the creation of provisional response criteria, which led to the concept of "indeterminate response." In order to confirm an evaluation, consecutive assessment for at least 4 weeks after the first documentation is required, after which either PD or pseudo-progression can be determined [14] (Table 9.3).

9.4 Interim PET (iPET)

In spite of the introduction of molecular target chemotherapy using agents such as rituximab or brentuximab vedotin, relapse is still the most important concern when treating the disease. In this respect, assessment of early response becomes an important factor. Since PET/CT makes it possible to perform early evaluation of metabolic changes during induction therapy, PET/CT is now recognized as a useful method for assessing the therapeutic response during the chemotherapy course. In most chemotherapy responders, the PET/CT becomes negative after 2 cycles of chemotherapy [35, 36]. In HL, iPET has proven to be a powerful predictor of treatment outcome. Patients who were PET/CT negative after 2–3 cycles of chemotherapy (ABVD) had a remarkably better PFS and overall survival (OS) than those who were PET/CT positive, while patients who were iPET positive had a poor prognosis [36–38]. Thus, it would be of interest to know whether an iPET-adaptive strategy based on early chemotherapy escalation could perhaps improve the prognosis in patients who are iPET positive. Gellamini et al. examined iPET positive patients after 2 cycles of ABVD and found that the PFS and OS improved after the administration of BEACOPP chemotherapy [39]. Besides achieving a cure for the disease, one of the other major goals of treatments is to reduce the toxicity. In early stage

HL, iPET negative patients were shown to be able to reduce the cycles of chemotherapy [40, 41]. Likewise, in advanced stage HL, patients who were iPET negative were able to omit bleomycin without any effect on the survival [42].

However, conflicting results have been reported for DLBCL. In the recent report by Burggraaff et al., a meta-analysis of 18 studies found there was a predictive value for iPET [43]. Likewise, Gouill et al. also reported iPET can assist the clinician in predicting patients' outcome [44]. On the contrary, Mamot et al. reported the results of a prospective trial in 138 patients with DLBCL who were treated with R-CHOP-14. In these patients, iPET was performed after two (PET-2), four (PET-4), and six (PET-6) cycles of R-CHOP with results revealing that PET-2 and PET-4 had a less predictive value than PET-6 (=end of treatment) [45]. Dührsen et al. also reported finding limited prognostic value in patients treated with R-CHOP. In their analysis, although they used a semi-quantitative method based on the SUVmax and SUVmax variation (ΔSUVmax) to improve the sensitivity, the prediction capability of prognosis was not high, and iPET-guided therapy did not improve outcome [46]. These data seem to suggest that iPET has a limited prognostic value for DLBCL. Furthermore, these findings showed that iPET-guided treatment did not improve the treatment outcome.

9.5 Post-Therapy Surveillance

In HL and DLBCL, approximately two-thirds of the patients are expected to achieve long-term remission with first-line chemotherapy. Among the patients achieving remission from first-line chemotherapy, relapse is commonly seen within 2 years [47]. Thus, surveillance imaging is conducted in order to detect relapse as early as possible, as salvage chemotherapy can be effective if the tumor burden is low. However, many studies have reported finding that a relapse was identified before the scheduled follow-up visit. As a result, surveillance imaging was only able to detect relapse before clinical manifestations in a minority of these patients. Furthermore, relapses detected by imaging, which included PET/CT were not associated with an improved survival even when the relapse was only in the early stage [11, 47, 48].

These studies suggest current imaging approaches such as PET/CT and CT are not able to detect most relapses prior to the presence of clinical signs and symptoms, and thus they do not contribute to an improved survival.

Summary and Key Points

In this chapter, we overviewed the important roles of PET/CT in staging at the time of diagnosis in the first half. In the latter half, we described the role of PET/CT in evaluation of post- and mid- therapy evaluation. PET/CT has high sensitivity in detecting lymphoma lesions compared to CT and it has become standard procedure for staging and end of treatment evaluation in most of the lymphoma subtypes. Whereas significance of Interim PET in predicting treatment outcome is limited.

The following are key points to understand the contents of this review.

- PET/CT has high sensitivity in detecting lymphoma lesion compared to CT scan. This methodology has become the standard procedure for the evaluation of lymphomas.
- In staging at the time of diagnosis, PET/CT is regarded as a standard method to evaluate the lymphoma lesions in most of FDG-avid subtypes. In contrast, in small lymphocytic lymphoma, lymphoplasmacytic lymphoma, marginal zone lymphomas, and mycosis fungoides, CT scans can still be used.
- The value of PET/CT determined for the end of treatment assessments is established for DLBCL, HL, FL, and other FDG-avid lymphomas.
- A 5-point scale is recommended as the standard criteria for the scoring system used to assess the residual FDG uptake.
- Interim PET (iPET) is a powerful predictor of treatment outcome in Hodgkin lymphoma, but its role in other subtypes is controversial. Furthermore, the value of iPET-guided therapy is not established.
- Surveillance imaging by PET/CT does not contribute to an improved survival.

References

1. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al. WHO classification of tumours of haematopoietic and lymphoid tissues (revised 4th edition). Lyon: IRAC; 2017.
2. Lister TA, Crowther D, Sutcliffe SB, Glatstein E, Canellos GP, Young RC, et al. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. J Clin Oncol. 1989;7:1630–6.
3. Rosenberg SA, Boiron M, VT DV Jr, Johnson RE, Lee BJ, Ultmann JE, et al. Report of the committee on Hodgkin's disease staging procedures. Cancer Res. 1971;31:1862–3.
4. Carbone PP, Kaplan HS, Musshoff K, Smithers DW, Tubiana M. Report of the Committee on Hodgkin's Disease Staging Classification. Cancer Res. 1971;31:1860–1.
5. Cheson BD, Horning SJ, Coiffier B, Shipp MA, Fisher RI, Connors JM, et al. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas: NCI Sponsored International Working Group. J Clin Oncol. 1999;17:1244–53.
6. Hicks RJ, Mac Manus MP, Seymour JF. Initial staging of lymphoma with positron emission tomography and computed tomography. Semin Nucl Med. 2005;31:165–329.
7. Freudenberg LS, Antoch G, Schutt P, Beyer T, Jenzen W, Muller SP, et al. FDG-PET/CT in re-staging of patients with lymphoma. Eur J Nucl Med Mol Imging. 2004;31:325–9.
8. Gallamini A, Borra A. Role of PET in lymphoma. Curr Treat Options Oncol. 2014;15:248–61.
9. Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, et al. Revised response criteria for malignant lymphoma. J Clin Oncol. 2007;25:579–86.
10. Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, et al. recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014;32:3059–68.
11. Barrington SF, Mikhaeel NG, Kostakoglu L, Meignan M, Hutchings M, Müeller SP, et al. Role of imaging in the staging and response assessment of lymphoma: consensus of the international conference on Malignant Lymphomas Imaging Working Group. J Clin Oncol. 2014;32:3048–58.

12. Meignan M, Gallamini A, Haioun C, Polliack A. Report on the second international workshop on interim positron emission tomography in lymphoma held in Menton, France, 8-9 April 2010. Leuk Lymphoma. 2010;51:2171–80.
13. Hodi FS, Hwu WJ, Kefford R, Weber JS, Daud A, Hamid O, et al. Evaluation of immune-related response criteria and RECIST v1.1 in patients with advanced melanoma treated with Pembrolizumab. J Clin Oncol. 2016;34:1510–7.
14. Cheson BD, Ansell S, Schwartz L, Gordon LI, Advani R, Jacene HA, et al. Refinement of the Lugano classification lymphoma response criteria in the era of immunomodulatory therapy. Blood. 2016;128:2489–96.
15. Federico M, Bellei M, Marcheselli L, Luminari S, Lopez-Guillermo A, Vitolo U, et al. Follicular lymphoma international prognostic index 2: a new prognostic index for follicular lymphoma developed by the international follicular lymphoma prognostic factor project. J Clin Oncol. 2009;27:4555–62.
16. El-Galaly TC, d'Amore F, Mylam KJ, de Nully Brown P, Bøgsted M, Bukh A, et al. Routine bone marrow biopsy has little or no therapeutic consequence for positron emission tomography/computed tomography-staged treatment-naive patients with Hodgkin lymphoma. J Clin Oncol. 2012;30:4508–14.
17. Berthet L, Cochet A, Kanoun S, Berriolo-Riedinger A, Humbert O, Toubeau M, et al. In newly diagnosed diffuse large B-cell lymphoma, determination of bone marrow involvement with 18F-FDG PET/CT provides better diagnostic performance and prognostic stratification than does biopsy. J Nucl Med. 2013;54:1244–50.
18. Tokue A, Higuchi T, Arisaka Y, Nakajima T, Tokue H, Tsushima Y. Role of F-18 FDG PET/CT in assessing IgG4-related disease with inflammation of head and neck glands. Ann Nucl Med. 2015;29:499–505.
19. Ngeow JY, Quek RH, Ng DC, Hee SW, Tao M, Lim LC, et al. High SUV uptake on FDG-PET/CT predicts for an aggressive B-cell lymphoma in a prospective study of primary FDG-PET/CT staging in lymphoma. Ann Oncol. 2009;20:1543–7.
20. Tsukamoto N, Kojima M, Hasegawa M, Oriuchi N, Matsushima T, Yokohama A, et al. The usefulness of (18)F-fluorodeoxyglucose positron emission tomography (18)F-FDG-PET with (67)gallium scintigraphy in the evaluation of lymphoma: relation to histologic subtypes based on the world health organization classification. Cancer. 2007;110:652–9.
21. Schöder H, Noy A, Gönen M, Weng L, Green D, Erdi YE, et al. Intensity of 18fluorodeoxyglucose uptake in positron emission tomography distinguishes between indolent and aggressive non-Hodgkin's lymphoma. J Clin Oncol. 2005;23:4643–51.
22. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for non-Hodgkin's lymphoma. N Engl J Med. 1993;329:987–94.
23. Solal-Céligny P, Roy P, Colombat P, White J, Armitage JO, Arranz-Saez R, et al. Follicular lymphoma international prognostic index. Blood. 2004;104:1258–65.
24. Hasenclever D, Diehl V, Armitage JO, Assouline D, Björkholm M, Brusamolino E, et al. A prognostic score for advanced Hodgkin's disease. International prognostic factors project on advanced Hodgkin's disease. N Engl J Med. 1998;339:1506–14.
25. Kobe C, Dietlein M, Hellwig D. PET/CT for lymphoma post-therapy response assessment in Hodgkin lymphoma and diffuse large B-cell lymphoma. Semin Nucl Med. 2018;48:28–36.
26. Karls S, Shah H, Jacene H. PET/CT for lymphoma post-therapy response assessment in other lymphomas, response assessment for autologous stem cell transplant, and lymphoma follow-up. Semin Nucl Med. 2018;48:37–49.
27. Juweid ME, Stroobants S, Hoekstra OS, Mottaghy FM, Dietlein M, Guermazi A, et al. Use of positron emission tomography for response assessment of lymphoma: consensus of the imaging Subcommittee of International Harmonization Project in lymphoma. J Clin Oncol. 2007;25:571–8.
28. Moskowitz AJ, Yahalom J, Kewalramani T, Maragulia JC, Vanak JM, Zelenetz AD, et al. Pretransplantation functional imaging predicts outcome following autologous stem cell transplantation for relapsed and refractory Hodgkin lymphoma. Blood. 2010;116:4934–7.

29. Dickinson M, Hoyt R, Roberts AW, Grigg A, Seymour JF, Prince HM, et al. Improved survival for relapsed diffuse large B cell lymphoma is predicted by a negative pre-transplant FDG-PET scan following salvage chemotherapy. Br J Haematol. 2010;150:39–45.
30. Terezakis SA, Hunt MA, Kowalski A, McCann P, Schmidtlein CR, Reiner A, et al. [^{18}F]FDG-positron emission tomography coregistration with computed tomography scans for radiation treatment planning of lymphoma and hematologic malignancies. Int J Radiat Oncol Biol Phys. 2011;81:615–22.
31. Girinsky T, Aupérin A, Ribrag V, Elleuch M, Fermé C, Bonniaud G, et al. Role of FDG-PET in the implementation of involved-node radiation therapy for Hodgkin lymphoma patients. Int J Radiat Oncol Biol Phys. 2014;89:1047–52.
32. Metwally H, Courbon F, David I, Filleron T, Blouet A, Rives M, et al. Coregistration of pre-chemotherapy PET-CT for planning pediatric Hodgkin's disease radiotherapy significantly diminishes interobserver variability of clinical target volume definition. Int J Radiat Oncol Biol Phys. 2011;80:793–9.
33. Terezakis SA, Schöder H, Kowalski A, McCann P, Lim R, Turlakov A, et al. A prospective study of ^{18}FDG-PET with CT coregistration for radiation treatment planning of lymphomas and other hematologic malignancies. Int J Radiat Oncol Biol Phys. 2014;89:376–83.
34. Girinsky T, van der Maazen R, Specht L, Aleman B, Poortmans P, Lievens Y, et al. Involved-node radiotherapy (INRT) in patients with early Hodgkin lymphoma: concepts and guidelines. Radiother Oncol. 2006;79:270–7.
35. Mikhaeel NG, Hutchings M, Fields PA, O'Doherty MJ, Timothy AR. FDG-PET after two to three cycles of chemotherapy predicts progression-free and overall survival in high-grade non-Hodgkin lymphoma. Ann Oncol. 2005;16:1514–23.
36. Hutchings M, Loft A, Hansen M, Pedersen LM, Buhl T, Jurlander J, et al. FDG-PET after two cycles of chemotherapy predicts treatment failure and progression-free survival in Hodgkin lymphoma. Blood. 2006;107:52–9.
37. Gallamini A, Barrington SF, Biggi A, Chauvie S, Kostakoglu L, Gregianin M, et al. The predictive role of interim positron emission tomography for Hodgkin lymphoma treatment outcome is confirmed using the interpretation criteria of the Deauville five-point scale. Haematologica. 2014;99:1107–13.
38. Biggi A, Gallamini A, Chauvie S, Hutchings M, Kostakoglu L, Gregianin M, et al. International validation study for interim PET in ABVD-treated, advanced-stage Hodgkin lymphoma: interpretation criteria and concordance rate among reviewers. J Nucl Med. 2013;54:683–90.
39. Gallamini A, Tarella C, Viviani S, Rossi A, Patti C, Mulé A, et al. A early chemotherapy intensification with escalated beacopp in patients with advanced-stage hodgkin lymphoma with a positive interim positron emission tomography/computed tomography scan after two ABVD cycles: long-term results of the GITIL/FIL HD 0607 trial. J Clin Oncol. 2018;36:454–62.
40. Pavlovsky A, Fernandez I, Kurgansky N, Prates V, Zoppegno L, Negri P, et al. PET-adapted therapy after three cycles of ABVD for all stages of Hodgkin lymphoma: results of the GATLA LH-05 trial. Br J Haematol. 2019;185:865–73.
41. Straus DJ, Jung SH, Pitcher B, Kostakoglu L, Grecula JC, Hsi ED, et al. CALGB 50604: risk-adapted treatment of nonbulky early-stage Hodgkin lymphoma based on interim PET. Blood. 2018;132:1013–21.
42. Johnson P, Federico M, Kirkwood A, Fosså A, Berkahn L, Carella A, et al. Adapted treatment guided by interim PET-CT scan in advanced Hodgkin's lymphoma. N Engl J Med. 2016;374:2419–29.
43. Burggraaff CN, de Jong A, Hoekstra OS, Hoetjes NJ, Nievelstein RAJ, Jansma EP, et al. Predictive value of interim positron emission tomography in diffuse large B-cell lymphoma: a systematic review and meta-analysis. Eur J Nucl Med Mol Imaging. 2019;46:65–79.
44. Le Gouill S, Casasnovas RO. Interim PET-driven strategy in de novo diffuse large B-cell lymphoma: do we trust the driver? Blood. 2017;129:3059–70.
45. Mamot C, Klingbiel D, Hitz F, Renner C, Pabst T, Driessen C, et al. Final results of a prospective evaluation of the predictive value of interim positron emission tomography in patients

with diffuse large B-cell lymphoma treated with R-CHOP-14 (SAKK 38/07). J Clin Oncol. 2015;33:2523–9.
46. Dührsen U, Müller S, Hertenstein B, Thomssen H, Kotzerke J, Mesters R, et al. Positron emission tomography-guided therapy of aggressive non-hodgkin lymphomas (PETAL): a multicenter, randomized phase III trial. J Clin Oncol. 2018;36:2024–34.
47. Thompson CA, Ghesquieres H, Maurer MJ, Cerhan JR, Biron P, Ansell SM, et al. Utility of routine post-therapy surveillance imaging in diffuse large B-cell lymphoma. J Clin Oncol. 2014;32:3506–12.
48. Zinzani PL, Stefoni V, Tani M, Fanti S, Musuraca G, Castellucci P, et al. Role of [18F]fluorodeoxyglucose positron emission tomography scan in the follow-up of lymphoma. J Clin Oncol. 2009;27:1781–7.