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Recommendations on the application of positron emission tomography in oncology

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ABSTRACT

Positron emission tomography (PET) is a modern functional imaging method with a proven value in diagnosing, staging, evaluating responses to anticancer therapy and detecting relapses in numerous neoplasms. The utility, sensitivity and specificity of PET has increased by its use in combination with computed tomography (CT) or magnetic resonance in the form of fusion PET-CT or PET-MR and the introduction of new radiotracers. This paper, based on scientific evidence by a multidisciplinary group of authors, presents the utility and clinical recommendations for the application of PET-CT in oncology.

PET-CT is particularly useful for:

— appropriate diagnosis and initial staging of patients with head and neck, lung, pancreatic and esophageal cancers, as well as lymphomas, advanced melanomas and tumors of unknown primary site;
— detection of relapses in patients with colorectal, thyroid, ovarian, head and neck, and breast cancers, as well as lymphomas;
— monitoring of response to treatment in patients with testicular and lung cancers, lymphomas and some types of sarcomas.

PET-MR is particulary useful in pediatrics.

Key words: positron emission tomography, oncology, diagnosis, staging, response to treatment, recommendations

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Introduction

Positron emission tomography (PET) is a modern, functional imaging method used to evaluate many biological processes. The introduction of hybrid techniques such as a combination of PET with computed tomography (CT) — PET-CT imaging and with the magnetic resonance imaging (MRI) — PET-MRI imaging has increased the applicability and sensitivity of PET. The simultaneous application of CT or MRI and PET with the subsequent fusion of both images allows for the correction of the phenomenon of the absorption of the radiation emitted by the radioisotope combined with a radiotracer and the precise positioning of the site of abnormal radiotracer accumulation. Another factor influencing the importance of PET imaging is the introduction of novel radiotracers, allowing one to evaluate a range of phenotypic changes characteristic for different neoplastic processes. ^{18}F-phosphatydyloclucose (^{18}F-FDG) is still a basic radiotracer in PET imaging. PET imaging with the use of this radiotracer allows the evaluation of glucose metabolic processes, as well as those responsible for the Warburg phenomenon. An increase in ^{18}F-FDG intake is observed not only in malignant neoplasms but also in many inflammatory changes (e.g. tuberculosis, ulcers, fungal infections, sarcoidosis). Despite the limitation mentioned above, this method has a confirmed clinical value in establishing the diagnosis, in the initial cancer staging, in the assessment of the response to anticancer therapy and in the relapse detection in the course of many cancers.

However, the introduction of the PET-MRI method has not changed the indications for performing PET-CT imaging. PET-MRI should be considered mostly in children, especially when repeated PET imaging will be necessary to control treatment results. PET-MTI imaging permits an important reduction of absorbed radiation dose and consequently decreases the risk of secondary neoplasms induced by ionizing radiation. PET-MRI has also been proven to be more effective in diagnosing central nervous system (CNS) neoplasms, breast cancer, head and neck and pelvic neoplasms.

The aim of this paper is to analyse the utility and to define clinical recommendations to use PET-CT imaging in oncology. The authors have considered and present both in descriptive form and in the tables (Table 1) current, detailed clinical indications for using PET-CT imaging. The list of indications that should be reimbursed from public payment sources has also been proposed. The recommendations have been worked out based on evidence-based medicine principles (EBM). Three sets of indications are specified, namely those clinically unequivocally confirmed and absolutely useful in clinical practice (category A), probable and potentially useful (category B) and individually accessed indications (category C).

In the majority of cases, the recommendations are based on the use of fusion PET-CT with ^{18}F-FDG while some — marked separately — refer to the use of other radiotracers.

The authors of this paper are specialists in different fields of medicine (included: clinical oncologists, radiotherapists, surgeons and nuclear medicine specialists).

Lung cancer

Lung cancer is one of the main indications for the use of PET-CT imaging in oncology. PET-CT imaging is applied to diagnose and to access the stage of the disease prior and post anticancer treatment. The majority of clinical trials testing PET-CT applicability refer to the non-small cell lung cancer (NSCLC). There is an increasing clinical evidence for the utility of PET-CT also in the diagnostic process of small cell lung cancer (SCLC). Present data prove the cost effectiveness of PET-CT imaging in lung cancer.

However, PET-CT imaging is not recommended as a screening tool for the early detection of lung cancer.

PET-CT imaging with ^{18}F-FDG is not recommended in NSCLC patients with previously detected metastasis. In the neuroendocrine neoplasms the aim of PET-CT imaging is to assess the biological malignancy of the tumour/tumours (the increased uptake ^{18}F-FDG within the tumour indicates more aggressive disease and helps to choose the appropriate treatment method).

A negative result of the PET-CT of the mediastinal lymph nodes imaging proves limited disease. A positive result of PET-CT in mediastinal lymph nodes may be related to an inflammatory process and demands a further invasive diagnostics (ultrasound controlled trans-bronchial or trans-oesophageal biopsy, mediastinoscopy or thoracoscopy).

Initial diagnostics and pre-treatment staging

The pre-treatment indications for PET-CT diagnostic include:

— staging in patients with the diagnosis of NSCLC who are candidates for radical surgery or radiotherapy;
— characterization of an suspected pulmonary nodules of diameter exceeding 5 mm (nodules of diameter below 5 mm may be an indication for PET-CT imaging only when recommended by a multidisciplinary team with the participation of a nuclear medicine specialist);
— radiotherapy planning in selected NSCLC patients (e.g. extensive atelectasis of the lung) who are candidates for radical radio-chemotherapy or radiotherapy;

Table 1. Summary of the recommendations for PET-CT imaging in oncology

Recommendation	Initial PET-CT in order to define treatment strategy (making diagnosis and/or staging of disease)	Monitoring and treatment results evaluation, re-staging after the anticancer treatment, relapse of disease detection, further PET-CT imaging in disease follow-up
Non-small cell lung cancer	**Yes** Staging before planned radical treatment — **A** (except from patients with neuroendocrine cancer and patients with distant metastases)	**Yes** Staging of residual disease after anticancer therapy — **A** Differentiation of the changes in case of the suspicion of disease relapse — **A**
Small-cell lung cancer	**Yes** Staging before radical treatment of limited disease — **A**	**No**
Malignant pleural mesothelioma	**Yes** Staging before radical combined treatment — **A**	**No**
Single lung tumour of unknown character	**Yes** Differentiation of benign and malignant tumours smaller than 5 mm if histopathological testing cannot be performed — **A**	**No**
Neoplasms in the mediastinum (thymus, heart, mediastinum)	**Yes** Staging before radical surgical or combined treatment — **B**	**No**
Lymphomas	**Yes** Staging before treatment — **A**	**Yes** Final evaluation of treatment efficacy, re-staging of disease during post-treatment follow-up, staging of relapse — **A** Evaluation of early response to treatment — **B** Radiotherapy field planning — **C**
Multiple myeloma	**Yes** Initial disease staging — **B** Detection of extra-skeletal changes — **C**	**Yes** Detection of disease relapse — **B**
Colorectal cancer	**Yes** To define possibility of surgical treatment in patients with potentially resectable metastases — **A** Staging in pre-operative evaluation in patients with rectal carcinoma and suspicion on distant metastases — **B**	**Yes** Confirmation or exclusion of disease relapse in cases of rising CEA levels or of unequivocal results of imaging test — **A**
Oesophageal cancer	**Yes** Staging at qualification for primary radical treatment — **B**	**Yes** Detection of distant metastases in cases of local relapse post radical treatment — **C**

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Table 1. Summary of the recommendations for PET-CT imaging in oncology

Pancreatic neoplasms	**Yes** Differentiation of changes in pancreas in initial diagnostics — **B** Staging of pancreatic cancer — **C**	**No**
Liver and intrahepatic biliary ducts neoplasms	**Yes** Defining character of focal change in liver (only with use of acetate tracer) — **C*** Staging of hepatocellular cancer (only with use of carbon isotope-labelled acetate) — **B***	**Yes** Defining staging after treatment and at relapse (with use of fluorine-labelled choline analogues, carbon-labelled acetates) — **B***
Gastric cancer	**Yes** Pre-operative staging in patients with ambiguous results of radiological exams (only with use of ^{18}FLT) — **B***	**No**
Gall bladder and extrahepatic biliary ducts neoplasms	**Yes** Staging prior to making therapeutic decisions in cases when all other imaging exams do not supply exact diagnosis — **B**	**No**
Breast cancer	**Yes** Exclusion of distant metastases in locally-advanced disease if results of standard imaging tests are unequivocal — **B**	**Yes** Confirmation or exclusion of relapse of disease after radical treatment if results of other imaging exams are ambiguous and PET-CT may change treatment method — **B** Evaluation of response to induction chemotherapy — **C** Evaluation of results of chemotherapy applied due to disease dissemination — **C**
Neoplasms of the uterus	**Yes** To define possibility of radical treatment in locally advanced cervical cancer and endometrial cancer if results of other imaging exams suggest metastatic changes (especially in lymph nodes) — **B**	**Yes** Confirmation or exclusion of disease relapse in patients treated radically — **A**
Ovarian and ovary duct neoplasms	**Yes** To define disease extension in patients with potentially resectable metastases — **A**	**Yes** Confirmation or exclusion of disease relapse in patients with elevated Ca125 levels and unequivocal results of imaging exams — **A**
Prostate cancer (PET-CT performed with labelled choline, acetate, carbon and PSMA)	**Yes** Diagnosing of changes in cases of high PSA levels indicating presence of malignant neoplasm and negative results of repeated biopsies — **B** Disease staging before radical treatment when there is a suspicion of metastases to lymph nodes and to bones and when results of other imaging exams are ambiguous — **A**	**Yes** Confirmation or exclusion of relapse in the cases of rising PSA levels and negative results of all other imaging exams — **A**

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Table 1. Summary of the recommendations for PET-CT imaging in oncology

Testicular cancer	**Yes** Neoplasm staging (with exception of mature teratomas) — **A**	**Yes** Detection and evaluation of residual changes extension, detection of relapse — **B** Evaluation of response to treatment — **B**
Urinary bladder cancer	**Yes** Staging of disease in patients with potentially resectable metastases — **B**	**Yes** Detection of relapse of disease after radical treatment if results of other imaging exams are unequivocal and PET-CT result may change treatment strategy — **B**
Melanomas	**Yes** Evaluation of disease extension in patients with clinical metastases to regional lymph nodes (stage IIIBC) — **A** Evaluation of neoplasm extension in patients with potentially resectable metastases to distant organs (stage IV) — **A** Neoplasms diagnosis in patients with metastasis with unknown primary site — **A**	**No**
Merkel cell cancer	**Yes** Staging before treatment — **A**	**Yes** Confirmation or exclusion of neoplasm relapse — **A**
Connective tissue/other soft tissues neoplasms (including gastrointestinal stromal tumour)	**Yes** Differentiation of benign and malignant changes — **B** Planning of tumour biopsy — **C** Initial staging — **C**	**Yes** Evaluation of disease response to treatment and detection of relapse on treatment in patients with gastrointestinal stromal tumours — **A** Evaluation of response to treatment in other sarcomas (especially in small cell sarcomas) — **B**
Neoplasm of bone/cartilage	**Yes** Differentiating of benign and malignant changes — **B**	**Yes** Detection of relapse and distant metastases — **A**
Head and neck neoplasms	**Yes** Detection of primary site of the neoplasm in patients with metastases in cervical lymph nodes from unknown primary site — **A** Evaluation of primary site condition and of changes in the lymph nodes in loco-regionally advanced neoplasms — **B** Radiotherapy planning in case of loco-regionally advance disease — **B**	**Yes** Detection of local or regional relapse when results of other imaging exams are ambiguous — **A**
Neoplasms of central nervous system (imaging examination indicated with the use of fluorine labelled tyrosine, carbon-labelled methionine or of fluorine-labelled DOPA)	**Yes** Planning of stereotactic biopsy in the case of suspicion of central nervous system neoplasm — **B*** Detection of regions of higher histological grade within central nervous system neoplasms — **B***	**Yes** Detection of neoplasm relapse — **C***

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Table 1. Summary of the recommendations for PET-CT imaging in oncology

Thyroid cancer	**No**	**Yes** Differentiation of changes in course of mature thyroid cancer after total thyroidectomy in cases of elevated thyroglobulin levels (≥ 10 ng/ml) and negative result of the ^{131}I scintigraphy — **A**
Other neuroendocrine neoplasms	**Yes** Evaluation of somatostatin receptors expression — **B*** Evaluation of biologic malignancy of primary and metastatic sites — **B***	**No**
Neoplasms of unknown primary site	**Yes** Evaluation of primary site if results of other imaging exams are negative or unequivocal (value of exam depends on metastases localization) — **A**	**No**
Radical radiotherapy	**Yes** If results of another exams cannot be used in radiotherapy planning — **A**	**No**

*Radiotracer other than FDG; CEA — carcinoembryonic antigen; PSA — prostate specific antigen; FDG — fluorodeoxyglucose; PSMA — prostate-specific membrane antigen
Recommendations for performing PET-CT imaging have been divided based on the EBM rules with the specification of the categories listed below regarding utility in clinical practice:
A — utility equivocally confirmed; B — potential utility; C — utility in individual indications.
The proposed categories presents the recommendation to perform the PET-CT imaging. In all other clinical situations the value of the PET-CT imaging was not proven or there are no EBM based data evaluating it utility.

— initial staging in a selected group of patients with limited SCLC being candidates for radio-chemotherapy.

Post-treatment follow-up

Post-treatment PET-CT imaging is indicated in patients only if CT indicates the possibility of relapse (to differentiate between treatment side-effects and neoplasm relapse).

Mesothelioma

PET-CT imaging is a clinically useful method in the initial diagnosis of patients with suspicion of mesothelioma.

The indications include:

— selection of the most suitable site for a the effective biopsy in patients with suspicion of mesothelioma (this concerns patients with pleural thickening; PET-CT imaging is not useful in those patients who present only pleural effusion or who underwent pleurodesis);
— exclusion of neoplastic sites beyond the thorax in patients being candidates for combined treatment including surgery (pleurectomy/decortication/pleuro-pneumonectomy).

PET-CT imaging is not indicated during monitoring after the anticancer treatment in patients with mesothelioma.

Thymus neoplasms

PET-CT imaging with the use of ^{18}F-FDG is a valuable method in the diagnostics of thymus cancer. The value of PET-CT in remaining thymus neoplasms has not been proven. Due to the persistent risk of thymus cancer, the PET-CT imaging is recommended before the surgical treatment of the thymus tumour.

PET-CT imaging has no value in monitoring patients post-thymus neoplasm treatment.

Lymphoma

Precise initial disease staging is crucial for selecting an optimal treatment strategy in lymphoma patients. PET-CT imaging is currently recommended for patients with diagnosed lymphoma that is potentially curable and ^{18}F-FDG avid, which applies mostly to Hodgkin lymphoma (HL), diffused large B cell lymphoma (DLBCL) and follicular lymphoma (FL). The utility of PET-CT imaging depends on histological type,

location and size of pathological changes (the sensitivity and specificity of the test decreases with a pathological site diameter below 10 mm) and in evaluation of the extra-nodal changes (e.g. eye socket, skin, spleen, stomach or intestines).

Initial diagnostics and pre-treatment staging

PET-CT imaging with the use of ^{18}F-FDG, compared to another imaging methods, is characterized by the highest sensitivity and specificity in diagnosing pathological changes, except for changes in the CNS (MRI imaging as the highest value in the diagnostics of focal changes in the CNS). Therefore CT imaging should not be performed before PET-CT.

PET-CT imaging is recommended in the initial staging of early and advanced stages of HL and DLBCL. PET-CT imaging is also useful in cases of diagnosis of the FL or mantle cell lymphoma (MCL). The result of PET-CT imaging with the use of ^{18}F-FDG modifies the primary staging in about 25–30% of patients with HL and/or DLBCL and in about 60% of patients with the early stages of FL, which in consequence leads to a treatment plan modification in almost 30% of patients. PET-CT imaging allows for the more accurate measurement of the neoplastic lymph nodes, differentiation of the lymph nodes from intestinal loops or to detect the compression or thrombosis of the large mediastinal vessels. PET-CT is also a method used to detect bone marrow involvement. In patients with HL performing PET-CT imaging, regardless of its result, permits one to avoid bone marrow trepanobiopsy. In patients with DLBCL positive bone marrow involvement PET-CT imaging result permits to avoid trepanobiopsy, but in case of negative PET-CT result performing trepanobiopsy is obligatory (especially when the bone marrow infiltration may influence the treatment schedule). The interpretation of the images should be performed visually and with the use of a five degree rating scale (the Deauville system).

The initial staging of the lymphomas with differentiated accumulation of the radiotracer should be based on the CT scans with the use of an intravenous contrast. In cases of negative ^{18}F-FDG PET-CT images of the lymphoma sites, the initial staging should be evaluated based on the CT scans obtained by PET-CT testing and the efficacy of the treatment based on the CT scans. PET-CT imaging has a limited use in cutaneous lymphomas, extra nodular marginal zone lymphomas (MZL) and small B cell lymphomas (SLL).

Treatment response evaluation

If the initial staging has been assessed by a PET-CT imaging result it is recommended to perform an early PET-CT in order to evaluate the response to treatment (so-called interim PET-CT) and another one at the end of treatment. An early PET-CT should be performed after the second chemotherapy cycle (directly before the next cycle, so that the time between the former chemotherapy administration and the PET-CT imaging was the longest possible). The aim of the interim PET-CT imaging is an early evaluation of the treatment efficacy. According to the current evidence, modification of the treatment method based on the interim PET-CT imaging result is acceptable only when the result unequivocally indicates the disease progression. In other cases, modification of the primary treatment plan is acceptable only as part of the controlled clinical trials. The interim PET-CT imaging must be evaluated both qualitatively and quantitatively.

PET-CT imaging at the treatment completion should be performed after 6–8 weeks after the last chemotherapy administration and 12 weeks post radiotherapy. Complete metabolic remission is equivalent with a complete response to treatment even if CT scans reveal residual masses. If PET-CT imaging detects metabolically active disease — and any second line treatment can be considered — it is recommended to perform a residual mass biopsy in order to obtain pathologic confirmation of the neoplasm before treatment administration. In patients receiving combined treatment, the PET-CT imaging should be performed 2–3 weeks after the last chemotherapy cycle in order to avoid any delay in radiotherapy onset.

The results of currently published studies show that as a negative result of the early PET-CT imaging does not guarantee the achievement of the complete remission, one cannot terminate or limit the treatment without risking treatment failure. Likewise, a positive result does not currently ensure primary resistance of the disease demanding treatment intensification.

It is particularly difficult to interpret the post-treatment PET-CT images of foci/sites of a moderately increased radiotracer ^{18}F-FDG uptake (minimal residual uptake — MRU) which some authors would consider a risk factor for disease relapse.

Post-treatment follow-up

It is not recommended to perform PET-CT imaging in patients without any clinical symptoms and who have achieved complete remission after treatment. In cases of an ambiguous result, it is recommended to repeat the PET-CT not earlier than after four weeks. If the result is still uncertain one should consider performing a biopsy or, in cases of further morphologic regression, to continue observation.

PET-CT imaging is indicated to assess an extent of relapse.

Colorectal cancer

Although PET-CT imaging has no use in the initial diagnostics of colorectal cancer, it is a valuable method to evaluate the metastases to the other organs (especially to the liver) and in the diagnostics of the disease's relapse.

Initial diagnostics and pre-treatment staging

It is not recommended to use PET-CT imaging for the early detection and early diagnosis of colorectal cancer. The only exception is for patients with a high risk of disseminated disease (especially rectal cancer) being a contraindication for surgical treatment.

The detailed indications for the use of PET-CT imaging in the initial diagnostics of colorectal cancer are:
— liver metastases detection in patients being candidates for surgery;
— the detection of the dissemination beyond the liver as a part of the pre-operative diagnostics in the patients being potential candidates for recession of the liver metastases.

Post-treatment staging

PET-CT imaging is useful in the patients being candidates for local treatment of residual changes (resection, thermo-ablation, chemo-embolization).

The indications for PET-CT imaging in a post-treatment follow-up are:
— relapse detection (especially in cases of the elevated CEA level);
— differentiation between relapse and treatment induced changes (e.g. post radiation changes);
— differentiation between malignant and benign changes (e.g. in the lymph nodes).

Oesophageal cancer

PET-CT imaging constitutes a supplementary method of staging oesophageal cancer and detecting distant metastases (evaluation prior to the treatment and in cases of local reoccurrence).

The PET-CT imaging is less precise than endoscopic ultrasonography in evaluating the loco-regional disease.

The value of PET-CT imaging in the treatment efficacy evaluation has not been proven.

Gastric cancer

In advanced gastric cancer, PET-CT imaging with the use of ^{18}F-fluorothymidine (FLT) is useful in the pre-operative staging.

Hepatocellular cancer

In a case of suspected or diagnosed hepatocellular cancer, PET-CT imaging should be performed with the use of a carbon ^{11}C isotope-labelled acetate. The method is useful in the initial staging prior to the making of therapeutic decisions. PET-CT imaging with the use of ^{11}C traced acetate is also recommended to exclude potential distant metastases.

Pancreatic cancer

PET-CT imaging is useful in the initial differential diagnostics of suspicious changes in the pancreas and in the staging of pancreatic cancer at the different treatment stages.

There is no clinical evidence for the usefulness of PET-CT imaging in the evaluating of the treatment efficacy of pancreatic neoplasms or during post-therapy follow-up.

Liver metastases

PET-CT imaging is used in the differential diagnostics of the focal liver lesions when the neoplasm cannot be excluded by any other imaging method.

Breast cancer

PET-CT imaging in breast cancer is indicated in disease staging and in relapse detection.

Initial diagnostics and pre-treatment staging

Limited sensitivity in detecting primary neoplastic lesions of diameter less than 10 mm and lymph node axillary metastases, as well as relatively high risk of false positive results, does not allow to recommend PET-CT imaging in the initial diagnostics of breast cancer. In contrast, PET-CT imaging should be considered in patients with locally advanced disease and unequivocal results of the standard imaging methods.

Post-treatment staging

Although PET-CT imaging may be helpful for the evaluation of response to initial chemotherapy (especially in cases when clinical and mammographic evaluation is difficult), performing the initial PET-CT imaging prior to the onset of treatment is mandatory. The clinical value of the above-mentioned indication has not yet been confirmed in the prospective trials.

Post-treatment follow-up

The PET-CT imaging is useful in detecting cancer relapse in patients receiving radical treatment when the results of other tests are unequivocal and the PET-CT imaging result may contribute to changing the treatment method.

Uro-genital tract cancer

Initial diagnostics and pre-treatment staging

PET-CT imaging is useful in patients diagnosed with locally advanced cervical cancer before planning radical combined treatment (radio-chemotherapy, radiotherapy).

Although PET-CT imaging has no proved clinical value in the initial diagnostics of endometrial cancer and ovarian neoplasms, it is highly useful in disease staging.

The PET-CT imaging has no use in the primary diagnostics of testicular neoplasms. In contrast it is highly useful in disease staging (with exception of mature teratomas).

PET-CT imaging with the use of choline, fluorine (^{18}F), carbon (^{11}C) and prostate specific membrane antigen (PSMA)-labelled acetate is a useful test in prostate cancer staging. One should also consider performing a PET-CT test in the initial diagnostics of prostate cancer when the results of the repeated prostate biopsies are negative and, simultaneously, the prostate specific antigen level (PSA) is rising, or when one suspects the presence of metastases in the lymph nodes or bones in patients who are candidates for radical treatment.

PET-CT has no use in the initial diagnostics of the urinary bladder. The value of PET-CT in the initial diagnostics of renal cancer is limited.

Post-treatment staging

Although PET-CT imaging is useful to evaluate the efficacy of chemotherapy in patients with seminoma (also in the detection of the residual changes), it is mandatory to perform an initial PET-CT prior to the onset of treatment. PET-CT imaging cannot differentiate the character of the residual changes in a non-seminoma.

Post-treatment follow-up

PET-CT imaging is useful in detecting a relapse of the ovarian carcinoma (especially in cases of the elevated CA-125 levels) and in patients with potentially resectable metastases. There are no indications to perform a PET-CT imaging in the patients with ovarian cancer without any suspicion of a relapse.

PET-CT imaging is useful for detecting the reccurrence of cervical cancer and of endometrial cancer (especially in patients with potentially metastatic disease). PET-CT imaging is not recommended in the patients with cervical and endometrial neoplasms when there is no suspicion of a relapse.

PET-CT imaging can be used in cases of the suspicion of the local spread or distant metastases of the urinal bladder cancer in patients treated radically and when other imaging techniques have failed to distinguish the character of the changes.

PET-CT imaging with the use of choline and fluorine (^{18}F), carbon (^{11}C)-labelled acetate and gallium (^{68}Ga)-labelled PSMA is useful in patients with a suspicion of prostate cancer relapse.

PET-CT imaging has no use in post-treatment monitoring of patients with uro-genital neoplasms.

Melanoma and skin neoplasms

The recommendations for use of the PET-CT imaging in patients with skin melanoma without clinical signs of regional lymph node involvement (stage: I, II and IIIa/N1a and N2a) are limited.

The PET-CT imaging cannot substitute a sentinel lymph node biopsy and is not useful in staging the disease in patients with unresectable metastases or in evaluating the response to systemic treatment. PET-CT imaging is not recommended for post-treatment observation.

PET-CT imaging with the use of ^{18}F-FDG is characterized by a high accuracy in diagnosing Merkle cell carcinoma. In contrast, there are no recommendations for PET-CT in patients with basocellular cancer at any stage of the disease.

Initial diagnostics and pre-treatment staging

PET-CT imaging is useful in qualifying for surgery patients with melanoma in the II clinical stage (IIb/IIIc) with clinical symptoms of the metastases to the lymph modes — in 30% of patients, PET-CT imaging detects distant extra-nodal metastases which results in changing the treatment method. The early detection of distant metastases is actually important due to lack of any effective systemic treatment in the IV stage of the disease.

A second — but rarely used — indication for performing PET-CT imaging is the initial staging in patients with potentially resectable distant organ metastases (stage IV). In the former group of patients, the result of the PET-CT imaging may lead to the substitution of surgery with systemic treatment or to a more extensive resection.

A third indication is to evaluate disease stage in patients with melanoma with diagnosed potentially

resectable metastases (e.g. the lymph nodes) without a defined primary disease site.

Sarcomas

PET-CT imaging is especially useful in gastrointestinal stromal tumours (GIST) and in small-cell sarcomas (mainly Ewing sarcoma). In patients with GIST, PET-CT is the most sensitive method of monitoring the response to tyrosine kinase inhibitor treatment and of detecting the progression of the disease. PET-CT imaging differentiates, earlier than CT, the cases of disease sensitive to treatment from those which are resistant (the response can be evaluated after 1–2 weeks and after 2–6 months, respectively). In the majority of cases, an adequate evaluation of response and progression of the disease can be made by a careful interpretation of CT scans with the use of the Choi criteria to evaluate changes in size and density of the neoplastic sites.

In some individual cases, the PET-CT can be used to differentiate the primary sarcomas from benign changes in the bones and soft tissues (e.g. in von Recklinghausen's disease).

PET-CT imaging is also used to evaluate the response to systemic treatment in some types of sarcomas (an efficacy evaluation after 1–3 chemotherapy cycles compared to the initial PET-CT imaging result).

Head and neck cancer

The value of the PET-CT imaging in the initial diagnostics and in the evaluation of the response to the treatment in the patients with the epithelial head and neck neoplasms is becoming systematically greater.

Initial diagnostics and pre-treatment staging

PET-CT imaging is a diagnostic method of choice for the diagnosis of lymph node metastases from an unknown primary site and enables in many cases the localization of the primary site of neoplasm in the head and neck region. However, PET-CT imaging cannot substitute a precise endoscopy of the upper respiratory tracts and of the laryngeal part of the throat with a biopsy of the clinically suspicious cites.

PET-CT should be also considered in selected patients with the diagnosis of locally advanced cancer in order to get a reliable evaluation of the lymph nodes metastases and to assess the extension of the infiltration in the primary site (this is especially important in poorly differentiated neoplasms with submucosal infiltrations). PET-CT imaging has an advantage over other imaging methods, especially in the evaluation of the regional advancement of the disease since it detects the metastases to the regular lymph nodes (the sensitivity and the specificity to detect the metastases — respectively — 82–87% and 94–100%).

PET-CT imaging is useful in radiotherapy planning (mostly in more locally or regionally advanced neoplasms) since it permits precise definition of target volume relative to the normal tissues.

Post-treatment staging

PET-CT imaging is useful in detecting residual changes after treatment and local and regional relapses. However, one must consider the possibility of false positive results (inflammatory changes — especially after radiotherapy) and false negative (especially residual changes in the lymph nodes). It is obligatory to confirm the neoplastic character of the residual changes or relapse, based on the histopathological evaluation of the excision biopsy prior to qualifying any patient for salvage surgery. PET-CT imaging should not be performed earlier than after three months post radiotherapy or chemo-radiotherapy, due to the above-mentioned risk of false positive results, which is especially high in the early period after treatment.

Recently presented results justify the use of PET-CT imaging in locally advanced head and neck neoplasms after completing radiotherapy or radio-chemotherapy, as it may allow one to avoid performing a lymphadenectomy in nearly 80% of patients.

Neoplasms of the central nervous system

The aminoacid radiotracers — ^{11}C labelled methionine, ^{18}F labelled tyrosine, ^{18}F labelled dihydroxyphenylalanine (DOPA) — play an important role in central nervous system imaging. These radiotracers show a low uptake in the normal brain tissues and in benign changes (fibrosis, necrosis, oedema). PET-CT imaging is recommended in the differential diagnostics of neoplastic and non-neoplastic changes. The sensitivity of this test in the diagnostics of primary brain tumours reaches 78–94% while its specificity reaches 93–100%. PET-CT imaging may be used in the intraoperative navigating technique. The results of surgery using this method suggest the possibility of radicalizing the operation and prolonging survival in this group of patients compared to those operated on based only an MRI image.

PET-CT imaging may be indicated to perform the non-invasive grading of primary CNS tumours, to define the site of a stereotactic biopsy and in cases of the suspicion of the neoplasm's relapse.

Defining the biopsy site and tumour grading is based on the localization of the change in the PET-CT imaging and on the kinetics of the ^{18}FET uptake in the neoplastic tumour. In high grade tumours, according to the World Health Organization (WHO) classification, positive kinetics of the radiotracer uptake is observed. This method is used to evaluate tumours placed in the eloquent regions.

The vast majority of primary CNS neoplasms are characterised by isolated local growth and the risk of dissemination into the lymphatic system or the distant metastases is extremely low. Performing a whole body PET-CT in disease staging is not applicable. The only exceptions are low-differentiated, small-cell and embryonic neoplasms, occurring mostly in children and youths (e.g. medulloblastoma, low-differentiated neuroectodermal neoplasms, germ cell tumours). In this group of patients, one should consider performing a PET-CT imaging with the use of fluorine labelled tyrosine (^{18}F — FET) or of carbon-labelled methionine (^{11}C — MET). There are no evidence-based data for the role of PET-CT imaging in the differential diagnostics of the histological types of brain tumours.

PET-CT imaging with the use of the ^{18}F-FDG should be performed in patients with suspicion of a metastatic site in the brain of an unknown primary site.

It is indicated to perform PET-CT imaging with the use of the following: the ^{18}F — FET, ^{18}F — DOPA or ^{11}C — MET in differentiating between a resistant or recurrent and active neoplasm and a post-radiotherapy necrosis or the so-called "pseudo-progression" of the tumour. PET-CT imaging combined with the MRI spectroscopy are the methods of choice in the localization of the sites of increased cellular proliferation and higher metabolic activity. For this reason, the test should be performed before a planned stereotactic biopsy of the tumour in patients with suspected CNS neoplasm or of disease relapse in order to exclude the presence of active sites or regions of higher histological grading.

Performing PET-CT imaging with the use of the methionine tyrosine or DOPA after the neurosurgical operation is helpful in the residual tumour mass evaluation and in radiotherapy planning. PET-CT imaging with the use of methionine or fluoride-tyrosine is valuable in radiotherapy planning in patients with paragangliomas or meningiomas.

Endocrine system neoplasms

Each type of the endocrine system neoplasm has its own characteristics which can be used in PET-CT imaging. Currently, there is an access in Poland — apart from ^{18}F-FDG — to gallium (^{68}Ga)-labelled peptide radiotracers. These are very useful in diagnostics and in the monitoring of the clinical course of highly differentiated neuroendocrine neoplasms. There is a similar role for PET-CT using ^{18}FDOPA applied in the monitoring of malignant pheochromocytoma tumours and of medullary thyroid cancer. One should expect the introduction of another radiotracers, which will enable the specific differential diagnostic of neuroendocrine system neoplasms: metomidate (in the diagnostics of the adrenal cancer), iodine (^{124}I) (useful in dosimetry — a crucial procedure prior to planned radioiodine administration to treat thyroid cancer).

PET-CT imaging with the use of ^{18}F-FDG is not recommended in diagnostics, staging, the treatment efficacy assessment or the post-treatment follow-up — in the most frequent — a highly-differentiated thyroid cancer which uptakes ^{131}I. However, this method plays a key role in the detection and localization of the metastases in patients with an increased serum level of thyreoglobulin and a negative scintigraphy result with the use of ^{131}I. In patients with dissemination of a thyroid neoplasm with a positive iodine uptake test, the result of the ^{18}F-FDG-PET has a prognostic value: the increased uptake of the radiotracer suggests a higher resistance to the ^{131}I treatment.

In medullar thyroid cancer, PET-CT imaging is a reasonable method in order to localize a relapse in a case when the calcitonin level exceeds 500 pg/ml, (one should consider performing also a DOPA-PET, which is not reimbursed in Poland despite an EBM-confirmed recommendation).

In adrenal cortex carcinoma, PET-CT imaging is a complementary test in disease staging.

In some neuroendocrine neoplasms it is necessary to perform PET imaging with the use of ^{68}Ga and ^{18}F-FDG-labelled somatostatin derivates. The first of these radiotracers enables the evaluation of the expression of the somatostatin receptor system while the second defines the biological malignancy of the primary site and of the metastases. The results of both tests are the basis for choosing the optimal treatment method and predicting the clinical course of the disease.

Neoplasms with an unknown primary site

PET-CT imaging is useful in the diagnostics of selected patients with metastases with an unknown primary site of a neoplasm. The value of the PET-CT depends on the location of lesion (high — e.g. metastases to the cervical lymph nodes, low e.g. — metastases to the subdiaphragmatic lymph nodes).

Bone metastases

PET-CT (especially with the use of the ^{18}F-NaF tracer) is characterised by a high sensitivity in the

evaluation of bone metastases. This test is recommended in patients with an ambiguous result of a bone scintigraphy with the use of 99Tc-MDP. PET-CT with ^{18}F-FDG has a slightly lower sensitivity but a higher specificity.

Proposed criteria for qualification to PET-CT imaging and list of oncological recommendations which should be reimbursed from public sources:

— a solitary lung tumour larger than 5 mm in diameter — in order to differentiate between its benign and the malignant character if the diagnosis cannot be made by any other accessible method;
— non-small cell lung cancer — in order to stage the disease prior to a planned resection or radical radiotherapy and in order to evaluate regional disease extension and to exclude distant metastases (apart from formerly detected distant metastases);
— small-cell lung cancer in the stage of limited disease — prior to radical combined treatment;
— mesothelioma — prior to radical combined treatment with the use of surgery;
— mediastinal tumour — prior to combined radical treatment with the use of surgery;
— Hodgkin lymphoma and non-Hodgkin lymphomas — in order to perform initial staging, evaluation of treatment efficacy or for early relapse detection;
— colon cancer — in order to perform pre-operative clinical staging or for early relapse detection after the radical treatment (when the results of other imaging exams are ambiguous);
— oesophageal cancer — in order to access to staging prior to radical treatment and in early relapse detection post radical treatment (when the results of other imaging exams are ambiguous);
— gastric cancer — in preoperative disease staging in cases of unequivocal results of other exams;
— pancreatic cancer — in initial disease staging prior to radical treatment (when the results of other imaging exams are ambiguous);
— pathological changes in the pancreas and in the liver — evaluation of changes suspected of a neoplastic character when a diagnosis cannot be made using other methods;
— breast cancer — in the initial diagnostics in order to exclude distant metastases (when the results of other exams are unequivocal);
— breast cancer — during the follow-up post radical treatment in cases where there is a suspicion of relapse when the results of other imaging exams are ambiguous and the PET-CT result may change the treatment method;
— ovarian cancer — in order to define the disease stage in the patients with potentially resectable metastases and for early detection of the relapse post radical treatment (in cases of increased Ca125 levels or unequivocal results of other exams);
— cervical and endometrial cancer — in order to access the disease stage prior to radical treatment and for early detection of a relapse post radical therapy (when the results of the imaging exams are unequivocal);
— testis neoplasms (except from mature teratomas) — in disease staging and in the evaluation of treatment efficacy (including residual tumour and relapse detection) if evaluation cannot be made by the other methods;
— urinary bladder cancer — in disease staging in the patient with potentially resectable metastases and in order to detect the relapse of the disease after radical treatment when the imaging exams results are unequivocal;
— suspicion of prostate cancer in cases of elevated PSA levels and a negative result of a repeated transrectal prostate biopsy — in order to localize the neoplasm the exam should be carried out with the use of acetate, choline or PSMA);
— prostate cancer — prior to radical treatment but only when the metastases and the results of other exams are unequivocal (PTE-CT imaging with the use of the acetate, choline or PSMA);
— prostate cancer — in relapse (metastases) detection post radical treatment (an exam with the use of PSMA, choline or acetate), when the diagnosis cannot be made by other exams);
— renal cancer — in relapse (metastases) detection post radical treatment (an exam with the use of acetate), when the diagnosis cannot be made by other exams);
— melanomas — in patients with clinically overt metastases to regional lymph nodes and potentially resectable metastases in the distant organs or with potentially resectable metastasis with an unknown primary site;
— Merkel cell cancer — in initial disease staging prior to the treatment and in relapse or dissemination diagnostics;
— sarcomas — in order to differentiate benign and malignant changes and in staging prior to treatment and as the reference exam in chemotherapy efficacy evaluation and during chemotherapy (after 1–3 chemotherapy cycles in order to compare with the initial PET-CT exam) and for the early detection of relapse;
— gastrointestinal stromal tumours (GIST) — in order to monitor the molecular response to the target treatment and to detect relapse of the disease;

— head and neck neoplasms — in order to detect the relapse of the disease early and to evaluate loco-regional staging when the results of other exams are ambiguous;
— central nervous system — in order to evaluate the areas of higher malignancy, to detect relapse early and to define the biopsy site (imaging examination indicated with the use of fluorine-labelled tyrosine, methionine or DOPA);
— mature thyroid cancer — in order to differentiate and evaluate the localization of a relapse in the cases of elevated thyroglobulin levels if this site cannot be diagnosed by other exams (it is obligatory to perform a ^{131}I scintigraphy earlier);
— neuroendocrine tumours — in the initial disease staging; PET-CT with the use of radiotracers evaluating the expression of the receptors and with ^{18}F-FDG in order to define the character of the metastatic changes and the grade of the malignancy prior to the planned treatment with radioisotope-labelled somatostatin analogues;
— metastases of an unknown primary site — in order to localize the primary site when it cannot be defined by other accessible exams;
— suspicion of metastases to the bones — when the result of a scintigraphy is unequivocal;
— planning of radical radiotherapy — in order to localize the foci of living neoplastic cells, of hypoxia or of the proliferation of a tumour when such an evaluation cannot be done by the other methods.

PET-MRI imaging is recommended in diagnostics of the liver, of the pelvic organs and of the brain only if the aforementioned criteria are met.

PET-MRI is recommended in children up to 18 years of age only if the aforementioned recommendations for PET-CT imaging are met.

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