Open access • Journal Article • DOI:10.1007/S00259-019-04553-8

Good clinical practice recommendations for the use of PET/CT in oncology.

Pierre-Yves Salaun, Ronan Abgral, Olivier Malard, Solène Querellou-Lefranc ...+22 more authors

Institutions: Institut Gustave Roussy

Published on: 01 Jan 2020 - European Journal of Nuclear Medicine and Molecular Imaging (Eur J Nucl Med Mol Imaging)

Topics: Good clinical practice

Good clinical practice recommendations for the use of PET/CT in oncology

Pierre-Yves Salaun, Ronan Abgral, Olivier Malard, Solène Querellou-Lefranc, Gilles Quere, Myriam Wartski, Romain Coriat, Elif Hindie, David Taieb, Antoine Tabarin, et al.

Good clinical practice recommendations for the use of PET/CT in oncology

*,**,***

Pierre-Yves SALAÜN[1], Ronan ABGRAL[1], Olivier MALARD[2], Solène QUERELLOU-LEFRANC[1], Gilles QUERE[3], Myriam WARTSKI[4], Romain CORIAT[5], Elif HINDIE[6], David TAIEB[7], Antoine TABARIN[8], Antoine GIRARD[9], Jean-François GRELLIER[10], Isabelle BRENOT-ROSSI[11], David GROHEUX[12], Caroline ROUSSEAU[13], Désirée DEANDREIS[14], Jean-Louis ALBERINI[15], Caroline BODET-MILIN[16], Emmanuel ITTI[17], Olivier CASASNOVAS[18], Françoise KRAEBER-BODERE[13,16], Philippe MOREAU[19], Arnaud PHILIP[20], Corinne BALLEYGUIER[21], Alain LUCIANI[22], Florent CACHIN[23]

1 nuclear medicine, University hospital of Brest, Brest, France
2 head and neck, University hospital of Nantes, Nantes, France
3 thoracic oncology, University hospital of Brest, Brest, France
4 nuclear medicine, Cochin hospital AP-HP, Paris, France
5 gastroenterology, Cochin hospital AP-HP, Paris, France
6 nuclear medicine, University hospital of Bordeaux, Bordeaux, France
7 nuclear medicine, AP-HM, Marseille, France
8 endocrinology, University hospital of Bordeaux, Bordeaux, France
9 nuclear medicine, Eugène Marquis center, Rennes, France
10 nuclear medicine, Foch hospital, Paris, France
11 nuclear medicine, Paoli-Calmettes institute, Marseille, France
12 nuclear medicine, Hopital Saint Louis AP-HP, Paris, France
13 nuclear medicine, Ouest cancer institute, Nantes, France
14 nuclear medicine, Department of Medical Sciences, Citta della Salute e della Scienza, Turin, Italy
15 nuclear medicine, Georges-François Leclerc center - François Mitterrand University hospital, Dijon, France
16 nuclear medicine, University hospital of Nantes, Nantes, France
17 nuclear medicine, Henri Mondor hospital AP-HP, Paris, France
18 hematology, University hospital Le Bocage, Dijon, France
19 hematology, University hospital of Nantes, Nantes, France
20 centre du traitement de la douleur, CHRU de Brest, Brest
21 radiology, Gustave Roussy Institute, Villejuif, France
22 radiology, Henri Mondor Hospital AP-HP, Paris, France
23 nuclear medicine, Jean Perrin Cancer Institute, Clermont-Ferrand, France

Address correspondence to:
Pr P-Y SALAÜN
Nuclear Medicine Department
University hospital of Brest
5 avenue Foch
29609 Brest Cedex
France
pierre-yves.salaun@chu-brest.fr

* Publication realized at the initiative of the French Society for Nuclear Medicine (SFMN).

** The full-text and roll-up summary versions are both available on the SFMN website: https://www.sfmn.org/index.php/la-societe/guides-et-recommandations/94-societe/guides-et-recommandations/355-recommandations-de-bonne-pratique-clinique-pour-l-utilisation-de-la-tep-en-cancerologie.

*** These good clinical practice recommendations have been awarded joint French National Heath Authority (HAS) and French Cancer Institute (INCa) label status, in recognition that they were developed in line with HAS and INCa-recommended rules, methods and procedures.

ABSTRACT

Positron emission tomography/ Computed tomography (PET/CT) is a nuclear medicine functional imaging technique with proven clinical value in oncology. PET/CT indications are continually evolving with fresh advances made through research. French practice on the use of PET in oncology was framed in recommendations based on Standards–Options–Recommendations methodology and coordinated by the French federation of Comprehensive Cancer Centres (FNLCC). The recommendations were originally issued in 2002 followed by a update in 2003, but since then a huge number of scientific papers have been published and new tracers have been licensed for market release. The aim of this work is to bring the 2003-version recommendations up to date. For this purpose, a focus group was set up in collaboration with the French Society for Nuclear Medicine (SFMN) to work on developing good clinical practice recommendations. These good clinical practice recommendations have been awarded joint French National Heath Authority (HAS) and French Cancer Institute (INCa) label status—the stamp of methodological approval. The present document is the outcome of comprehensive literature review and rigorous appraisal by a panel of experts, organ specialists, clinical oncologists, surgeons and imaging specialists. These data were also used for the EANM Referral guidelines.

INTRODUCTION

Positron emission tomography/ Computed tomography (PET/CT) is a nuclear medicine functional imaging technique with proven clinical value, primarily in oncology. The fields of application for PET imaging are continually evolving with fresh advances made through research. The most commonly used tracer is 18F-fluorodeoxyglucose (FDG), which competes with glucose and accumulates in cancer cells. FDG gained European marketing authorization for use in oncology in 2002. France framed the use of FDG-PET in oncology under a set of recommendations issued in 2002 and updated in 2003 based on Standards–Options–Recommendations methodology coordinated by the French federation of Comprehensive Cancer Centres (FNLCC). Since then, a huge number of scientific papers have been published, and in practice PET/CT has become an essential tool in the care of patients with hypermetabolic cancers, whether for initial diagnosis, disease staging, therapeutic evaluation and recurrence assessment, while also providing independent prognostic information. Other tracers have

also obtained marketing authorization, and although less employed, they are gaining ground in cancer care. Given these contexts, it is high time the 2003-version recommendations were updated. The aim of this work is thus to bring the recommendations up to date.

METHODOLOGY

The project was initiated by the French Society of Nuclear Medicine (SFMN) and its oncology group, and the project procedure was awarded joint French National Heath Authority (HAS) and French Cancer Institute (INCa) label status. The methodology used to carry out this update is based on HAS procedure for "clinical practice recommendations".

Method for developing the recommendations

The full-text and roll-up summary versions are both available on the French Society for Nuclear Medicine website: https://www.sfmn.org/index.php/la-societe/guides-et-recommandations/94-societe/guides-et-recommandations/355-recommandations-de-bonne-pratique-clinique-pour-l-utilisation-de-la-tep-en-cancerologie.

The method was based:

- on critical analysis of the best available scientific data in order to attribute a level of evidence to conclusions drawn from the literature;
- and on the reasoned opinion of the working-group experts.

A systematic literature search was carried out on the period from 1st September 2003 or 1st January 2011 (depending on the items) May 1st May 2017. The literature research, methodological analysis and synthesis of the scientific data were carried out by the working group. The items were selected according to most common oncology clinical situations of FDG avid cancers except for prostate cancer for which labelled choline, fluciclovine (FACBC) and ligand of prostate-specific membrane antigen (PSMA) were also analysed in an ancillary analysis.

The recommendations were formulated by the multidisciplinary working group, and then reviewed by an independent panel of independent experts using quantitative (ratings) and qualitative (comments) evaluations. The working-group experts reviewed the comments collected in order to validate the final-version document at a project draft review meeting.

Graded strength of recommendations

Recommendations formulated are graded with two levels of strength:

- by default, the recommendation formulated is the clinical service unanimously recognized by the experts as the clinical reference standard; the text states that "PET/CT is recommended".
- if a clinical service was found to be acceptable on the basis of literature data or expert opinion but not unanimously recognized as the clinical reference standard, the text states that "PET/CT can be proposed".

Level of evidence

- The Level of Evidence is a rating of the literature data on which the recommendations formulated are based. Level depends on the type and quality of studies available and degree of consistency across their results. Details of the levels of evidence used are presented below.
- Level A: There is good-quality meta-analysis or good-quality randomized trials with cross-consistent results. New data will most likely not change confidence in the estimated effect.
- Level B: There is good-quality evidence (randomized trials [B1] or prospective or retrospective studies [B2] with overall cross-consistent results. New data may impact confidence in the estimate of effect or may change the estimate.
- Level C: The studies available carry methodological weaknesses and/or the results of the studies are not always cross-consistent. New data will most likely impact confidence in the estimate of effect and will likely change the estimate.
- Level D: There are no data or only case series. There is a great deal of uncertainty as to the estimated effect.

Working group—Formation and membership

These recommendations were produced by a multidisciplinary working group formed by the SFMN and its oncology group (project sponsor) with membership chosen to be representative of the medical specialties involved, their modes mode of practice and their geographical distribution.

The other scholarly societies that were sounded out to submit names of national experts for proofreading the recommendations are listed in the thesaurus.

The working-group experts were solicited *intuitu personae*, and not as representatives of any organization, scholarly society or professional body. INCa ensured that the experts put forward by the sponsor effectively enjoyed the independence needed to carry out the required expert appraisal work, based in particular on each expert's declarations of interests as published on the INCa website. As part of the HAS-INCa labelling procedure, the analysis of ties to potentially competing interest was submitted to the HAS Validation Committee on 9th June 2017 and to the INCa Expert Committee on 13th June 2017.

RECOMMENDATIONS

Head and neck – Aerodigestive tract squamous cell carcinoma – Carcinoma of unknown primary – Salivary gland tumours

Initial staging

- *Conclusion and Level of Evidence*

FDG-PET/CT is as sensitive as MRI in detecting mouth and oropharynx tumours and is more accurate than CT alone (Level of Evidence B2). However, MRI is still needed for local infiltration assessment.

Regarding larynx tumour assessment, only one paper suggests the value of FDG-PET/CT over conventional imaging (Level of Evidence C). CT is the recommended exam for assessing local infiltration and should respect the required recommendations with dynamic phonation and Valsalva manoeuvres.

A meta-analysis provide the evidence that PET/CT is superior to conventional imaging for staging node spread in head and neck squamous cell carcinoma, although sensitivity decreases if patients are cN0 status (Level of Evidence B1).

Some studies show that PET/MRI is at least equivalent to PET/CT in this indication, with the advantage of reduced radiation delivery while combining the functional information offered by PET and the anatomical precision offered by MRI (Level of Evidence C).

FDG-PET/CT gives highly accurate detection for distant metastasis, mainly in cases of high-risk tumours (stages III-IV, N2-N3), and also for synchronous cancer whatever the stage, with a real impact on treatment management (Level of Evidence A).

Quantification tools used for FDG-PET/CT during initial spread assessment (SUVmax, Metabolic tumor volume (MTV), Total Lesion Glycolysis (TLG)) can also have prognostic impact for patients (Level of Evidence C). Complementary studies are vital to define the measurement techniques and define consensual critical thresholds (Level of Evidence C).

- *Recommendations*

The following recommendations are mainly supported by literature data.

FDG-PET/CT is recommended for head and neck squamous cell carcinoma pre-treatment staging in advanced stages III and IV (T 3-4, N 1-3) to look for distant metastasis.

FDG-PET/CT can be proposed whatever the stage to look for synchronous carcinoma, and may modify the treatment plan.

Assessment of residual disease, diagnosis of recurrence, and follow-up

- *Conclusion and Level of Evidence*

To check for clinically suspected recurrence, some studies point to the very high diagnostic performance rate of FDG-PET/CT. FDG-PET/CT also provides an assessment of distant metastasis in

cases of proven recurrent disease, and valuable support for clinical treatment decisions. Many published reviews demonstrate its superiority to conventional imaging in this indication (Level of Evidence B1).

It has been established that FDG-PET/CT is very efficient modality for diagnosing residual disease after chemoradiotherapy. A meta-analysis highlights the diagnostic accuracy of the PET/CT exam in this indication, but recommends a 3-month delay after the end of the treatment to reduce the false-positive rate. It seems to have greater impact than conventional imaging, possibly being wrong due to post-treatment changes (Level of Evidence B1).

Several retrospective and prospective studies together with a recent meta-analysis demonstrate good performance during asymptomatic patient follow-up for occult recurrent disease diagnosis, with mean detection rates of 10–30% from 6 to 24 months post-treatment, mainly for poor-initial-prognosis (stages III-IV) patients (Level of Evidence B2). Further randomized prospective studies are needed before considering FDG-PET/CT exams in patient follow-up strategy. Moreover, post-treatment delay, cost–efficacy and overall survival data are expected (Level of Evidence D).

Whatever the indication in post-treatment follow-up, PET/CT has excellent negative predictive value (Level of Evidence A).

- *Recommendations*

The following recommendations are mainly supported by literature data.

FDG-PET/CT is recommended for resolving doubt if recurrence is clinically suspected and staging if recurrence is confirmed.

FDG-PET/CT can be proposed at the end of a treatment to check the possibility of residual disease.

FDG-PET/CT is not recommended for intermediate therapeutic assessment.

FDG-PET/CT can be proposed during systematic follow-up to confirm occult recurrence, particularly in cases of poor-initial-prognosis tumours.

Head and neck carcinoma of unknown primary

- *Conclusion and Level of Evidence*

Many literature reviews and a meta-analysis highlight the good diagnostic performance of FDG-PET/CT to look for primary in cases of metastatic-node carcinoma of unknown primary (CUP), offering a 30%–50% detection rate while also guiding the biopsies (Level of Evidence A). Both retrospective and prospective studies show its superiority to conventional imaging to find the primary, but also to detect asymptomatic distant metastasis, and helping treatment planning (Level of Evidence B1).

- *Recommendations*

The following recommendations are mainly supported by literature data.

FDG-PET/CT is recommended to look for primary in cases of head and neck metastatic-node carcinoma of unknown primary. The exam should be performed before pharynx biopsies, due to false-positive risks induced by inflammatory reactions.

Undifferentiated Carcinoma of Nasopharyngeal Type (UCNT)

- *Conclusion and Level of Evidence*

For staging and pre-treatment evaluation, FDG-PET/CT and MRI appear to offer complementary performances for node invasion status (MRI is more sensitive for retro-pharyngeal areas, and PET/CT for lateral neck nodes). For detecting distant metastasis, two meta-analyses find that FDG-PET/CT shows excellent diagnosis performance, surpassing results of conventional imaging, including hepatic sonography, chest X-ray, and bone scintigraphy, with a positive impact on treatment planning (Level of Evidence B1).

For assessing treatment response (residual disease enquiry) and diagnosing recurrence, two meta-analyses finnd that FDG-PET/CT was superior to CT-scan and MRI. Many studies consider that FDG-PET/CT should be performed at least 3 months after the end of chemoradiotherapy (Level of Evidence B1).

- *Recommendations*

The following recommendations are mainly supported by literature data.

FDG-PET/CT is recommended for pre-treatment assessment of nasopharynx tumours.

FDG-PET/CT is recommended if a recurrence is suspected.

FDG-PET/CT can be proposed to assess the possibility of residual disease.

Salivary gland tumours

- *Conclusion and Level of Evidence*

Although literature data remains limited, new PET parameters (MTV, TLG) may be useful to differentiate benign and malignant tumours and may even prove more relevant than SUVmax (Level of Evidence C).

FDG-PET/CT may be useful for node staging in cases of salivary gland malignancy (Level of Evidence C).

- *Recommendations*

The following recommendation is mainly supported by literature data.

FDG-PET/CT is not currently recommended for salivary gland tumour characterization.

The following recommendation is mainly supported by expert opinion.

FDG-PET/CT can be proposed for pre-treatment staging assessment.

Nasal and paranasal sinus tumours

- *Conclusion and Level of Evidence*

Data are limited but points to promising diagnostic performances of FDG-PET/CT for detection, pre-treatment planning and treatment response assessment in cases of nasal and paranasal sinus malignancies (Level of Evidence C).

Given the proven performances of FDG-PET/CT for metastatic spread extension in cases of oral cavity and pharyngo-laryngeal tumours, and the high risk of metastasis in cases of squamous cell carcinoma of the maxillary sinus (but not adenocarcinoma of the ethmoid sinus), FDG-PET/CT may be valuable before considering extended curative surgery (Level of Evidence D).

- *Recommendations*

The following recommendation is mainly supported by literature data.

FDG-PET/CT is not recommended for systematic characterization of nasal and paranasal sinus malignancy, nor for pre-treatment.

The following recommendation is mainly supported by expert opinion.

FDG-PET/CT can be proposed in cases of squamous cell carcinoma of the maxillary sinus before extended curative surgery in locally-advanced tumours associated with a high risk of distant metastatis.

Lung, medistinal and pleural cancer

Pulmonary nodule management

- *Conclusion and Level of Evidence*

FDG-PET/CT has high sensitivity (around 95%) for management of solid pulmonary nodules ≥ 8 mm (Level of Evidence A), although some inflammatory or infectious lesions (tuberculosis, sarcoidosis, and histoplasmosis) may give false-positive results. Moreover, some histological subtypes (adenocarcinoma with a predominant lepidic pattern and carcinoid tumours) may give false-negative results.

FDG-PET/CT performanes are lower in cases of ground glass components than in solid nodules (Level of Evidence C).

For nodules < 8 mm, FDG-PET/CT performances are less sensitive and depend on PET system resolution, with potentially lower uptake for neoplastic lesions (Level of Evidence C).

The use of PET parameters such as dual time acquisitions (semi-quantitative or visual methods) can be an aid in nodule management (Level of Evidence B2).

There is little data describing specific criteria for (quantitative or visual) interpretation and critical thresholds (Level of Evidence C). There are no data on other tracers to differentiate malignant and benign nodules (Level of Evidence D).

❖ *Recommendations*

The following recommendation is mainly supported by literature data.

FDG-PET/CT is recommended to manage a solid pulmonary nodule ≥ 8 mm.

Lung cancer staging

❖ *Conclusion and Level of Evidence*

FDG-PET/CT sensitivity is insufficient (75%–80%) to definitively rule out metastatic lymph node involvement. Given the specificity of FDG-PET/CT, a pathological assessment is necessary if lymph node involvement is suspected on FDG-PET/CT data (Level of Evidence A).

FDG-PET/CT performances for ≤ 3 cm and N0 tumours with mediastinal lymph nodes whose short axis diameter is shorter than 1 cm and with no FDG uptake allow abstaining from pathological assessment in the absence of FDG node uptake (Level of Evidence A).

FDG-PET/CT has excellent diagnostic performance (sensitivity 93% and specificity 96%) for metastasis staging in patients with non-small-cell lung cancer, especially adrenal and bone lesions, when baseline CT (chest, abdomen, brain) with contrast does not show metastasis (Level of Evidence A).

FDG-PET/CT is the most effective imaging modality for the detection of bone metastases (91% sensitivity and 98% specificity) in patients with non-small-cell lung carcinoma compared against conventional imaging (CT or MRI) and bone scans (Level of Evidence A). Nevertheless, if FDG-PET/CT highlights potential bone metastasis, we recommend pathological assessment or complementary imaging, as far as practicable, to confirm the lesion and to guide biopsy.

For oligometastatic patients potentially eligible for curative treatment, FDG-PET/CT can be used to complete the staging (Level of Evidence D)

Data are not sufficient to validate FDG-PET/CT in small-cell lung cancer staging (Level of Evidence C).

❖ *Recommendations*

The following recommendation is mainly supported by literature data.

FDG-PET/CT is recommended for staging in patients with non-small-cell lung cancer without metastasis.

The following recommendations are mainly supported by expert opinion.

FDG-PET/CT can be proposed in specifically oligometastatic patients potentially eligible for treatment. FDG-PET/CT can be proposed for small-cell lung cancer staging.

Prognostic value

- *Conclusion and Level of Evidence*

Staging according to PET/CT is an independent prognostic parameter. Indeed, improvement of baseline staging, especially for lymph node involvement, is an independent prognostic value (Level of Evidence A).

The new literature data are concordant and conclude that the prognostic value of PET quantification parameters (Level of Evidence B2) can be a help in therapeutic management (Level of Evidence B2).

However, quantification parameters and measurement techniques for FDG-PET imaging (SUVmax, MTV, and TLG) during staging and follow-up must be standardized with threshold and validated by well-conducted prospective studies (Level of Evidence B2).

- *Recommendations*

The following recommendation is mainly supported by literature data.

Using quantitative parameters for FDG-PET imaging is not currently recommended for prognostic evaluation in order to modify future treatments.

Optimization of radiation therapy (RT) target volumes

- *Conclusion and Level of Evidence*

Literature data is too short to recommend FDG-PET/CT for planning target volumes (Level of Evidence D). However, FDG-PET/CT may help oncologists plan RT (especially for patients with atelectasis) but there is no formal evidence or efficacy data on survival or toxicity (Level of Evidence B2).

Further data are needed before we can firmly conclude that FDG-PET/CT is useful for recurrence-free survival and overall survival as well as for potentially reducing RT toxicity (Level of Evidence C).

- *Recommendations*

The following recommendation is mainly supported by literature data.

FDG-PET/CT may help oncologists plan radiation therapy (especially for patients with atelectasis).

Assessment of therapeutic response

- *Conclusion and Level of Evidence*

There is insufficient data to systematically recommend FDG-PET/CT in therapeutic assessment, where the criteria remain morphological (Level of Evidence C). In addition to morphological imaging, FDG-PET/CT can also serve to evaluate tumour response to antineoplastic treatments (Level of Evidence B2).

There is no single homogeneous PET/CT parameter that can be endorsed for assessing response and PET/CT delay, as the data is too poor-quality (Level of Evidence D).

In order to avoid interference with the effects of treatments, the response assessment of response must be spaced away from the treatments. Consensus is settling around a 3-week delay after chemotherapy and a 3-month delay after radiation therapy. Time-delay to evaluate therapeutic response by FDG-PET/CT for new treatments (immunotherapy or antiangiogenic drugs) is not yet defined (Level of Evidence D).

Further studies are required to document the predictive value of FDG-PET/CT in terms of survival in this indication (Level of Evidence D).

- *Recommendations*

The following recommendation is mainly supported by literature data.

FDG-PET/CT can be proposed to assess tumour response to systemic therapy.

Residual disease and recurrence assessment

- *Conclusion and Level of Evidence*

FDG-PET/CT outperforms conventional imaging in cases of suspected recurrence (Level of Evidence B2). PET/CT thus holds promise in the follow-up of patients with lung cancer, but this promise needs to be confirmed with well-conducted prospective randomized studies. Lesions highlighted with PET/CT should be confirmed by pathological assessment or other imaging studies to confirm recurrence. Further studies are needed to define specific criteria for recurrence due to post-treatment anatomical modifications (Level of Evidence D).

FDG-PET/CT can be useful for differential diagnosis between recurrence or residual disease and post-radiation fibrosis. A 3-month delay is necessary after conventional radiation therapy (Level of Evidence B2). The time-delay required between FDG-PET/CT and stereotactic radiotherapy has yet to be defined (Level of Evidence D).

The usefulness and frequency of PET/CT for monitoring progression-free survival and overall survival have not yet been adequately assessed (Level of Evidence D).

- *Recommendations*

The following recommendations are mainly supported by literature data.

FDG-PET/CT is recommended in cases of suspected recurrence in lung cancers.
FDG-PET/CT can be proposed for the differential diagnosis between recurrence or residual disease and post-radiation fibrosis.

Pleural diseases

- *Conclusion and Level of Evidence*

Due to too little evidence, heterogeneity in PET/CT interpretation (qualitative or semi-quantitative analysis) and the delay in performing PET/CT acquisitions (early and late), there is insufficient data to validate systematic use of FDG-PET/CT in the evaluation of pleural lesions (Level of Evidence C).

FDG-PET/CT can nevertheless help characterize pleural lesions in neoplastic or non-neoplastic settings, notably to define the biopsy site, bearing in mind the risks of false-positives (inflammatory lesions, granulomas, poudrage) and false-negatives (small lesions or low FDG uptake) (Level of Evidence B2).

- *Recommendations*

The following recommendation is mainly supported by literature data.

FDG-PET/CT can be proposed to manage pleural lesions.

Mediastinal tumours

- *Conclusion and Level of Evidence*

FDG uptake is higher in thymic carcinomas or high-grade thymic tumours than in low-grade tumours (Level of Evidence B2).

However, further studies are needed to better define critical thresholds for differentiating thymic tumours and better define the calculation methods (Level of Evidence D).

- *Recommendations*

The following recommendation is mainly supported by literature data.

FDG-PET/CT can be proposed as an additional parameter to manage thymic tumours.

Colorectal Cancer

Initial staging

- *Conclusion and Level of Evidence*

FDG-PET/CT has high sensitivity and specificity for detecting liver metastases in colorectal cancer (Level of Evidence A).

FDG-PET/CT has high sensitivity and specificity for detecting extra liver metastases in colorectal cancer (Level of Evidence A).

In case of known and resectable metastasis of colorectal cancer, FDG-PET/CT has high sensitivity and specificity for detecting other metastatic sites (Level of Evidence A).

- *Recommendations*

The following recommendations are mainly supported by literature data.

FDG-PET/CT is recommended in pre-therapeutic staging of colorectal cancer in cases of suspected metastases.

FDG-PET/CT is recommended in cases of known and resectable metastasis of colorectal cancer, to detect other occult metastatic sites.

Recurrence assessment

- *Conclusion and Level of Evidence*

To identify a recurrence site, FDG-PET/CT performs well, and better than morphological imaging, especially in cases when carcinoembryonic antigen (CEA) levels are increased (Level of Evidence A) or when morphological imaging is inconclusive (Level of Evidence B2).

FDG-PET/CT induces therapeutic change in a substantial proportion of patients with known and operable recurrence of colorectal cancer (Level of Evidence B2).

- *Recommendations*

The following recommendations are mainly supported by literature data.

FDG-PET/CT is recommended in suspected recurrence of colorectal cancer, especially in cases involving increased CEA levels.

FDG-PET/CT is recommended before surgery of local or distant recurrence of colorectal cancer.

Assessment of therapeutic response

- *Conclusion and Level of Evidence*

FDG-PET/CT shows good performances in the detection of recurrence after local treatment of liver metastases, with an excellent negative predictive value (Level of Evidence B2).

In rectal cancer, FDG-PET/CT has high sensitivity and specificity for assessing response to chemoradiotherapy to identify patients with a complete metabolic response (Level of Evidence B2).

- *Recommendations*

The following recommendations are mainly supported by literature data.

FDG-PET/CT can be proposed to detect recurrence after local treatment of liver metastases.

In rectal cancer, FDG-PET/CT can be proposed to assess end of chemoradiotherapy response.

Radiotherapy planning

- *Conclusion and Level of Evidence*

In rectal cancer, FDG-PET/CT shows good performances in volume delineation before radiotherapy (Level of Evidence B2).

- *Recommendations*

The following recommendation is mainly supported by literature data.

FDG-PET/CT can be proposed to improve volume delineation before radiotherapy of rectal cancer.

Anal cancer

Initial staging

- *Conclusion and Level of Evidence*

FDG-PET/CT has excellent performances in initial staging of anal cancer, for inguinal and pelvic lymph node involvement, and for detecting distant metastases (Level of Evidence B2).

- *Recommendations*

The following recommendation is mainly supported by literature data.

FDG-PET/CT is recommended at initial staging for T2-T4N0 and N+ anal cancer.

Recurrence assessment and assessment of therapeutic response

- *Conclusion and Level of Evidence*

FDG-PET/CT has high sensitivity, specificity, positive predictive value and especially negative predictive value for detecting residual disease or recurrence of anal cancer. A negative FDG-PET/CT at 12 weeks after the end of treatment is associated with better outcomes in anal cancer (Level of Evidence B2).

- *Recommendations*

The following recommendation is mainly supported by literature data.

FDG-PET/CT can be proposed for end-of-chemoradiotherapy therapeutic assessment in anal cancer.

Radiotherapy planning

- *Conclusion and Level of Evidence*

FDG-PET/CT brings additional information to radiotherapy planning in anal cancer (Level of Evidence B2).

- *Recommendations*

The following recommendation is mainly supported by literature data.

FDG-PET/CT can be proposed for volume delineation before radiotherapy of anal cancer.

Oesophageal cancer

Initial staging

- *Conclusion and Level of Evidence*

FDG-PET/CT outperforms morphological imaging for the detection of distant metastases in oesophageal cancer (Level of Evidence A).

FDG-PET/CT performs well, and better than morphological imaging, in detecting regional or distant lymph node involvement (Level of Evidence B2).

- *Recommendations*

The following recommendation is mainly supported by literature data.

FDG-PET/CT is recommended at initial staging of oesophageal cancer, before chemoradiotherapy or surgery.

Assessment of therapeutic response

- *Conclusion and Level of Evidence*

FDG-PET/CT offers high performances for assessing early and end-of-treatment response in oesophageal cancer (Level of Evidence B2).

FDG-PET/CT can identify patients with good prognosis in cases of compete metabolic response after chemoradiotherapy for oesophageal cancer (Level of Evidence B2).

- *Recommendations*

The following recommendation is mainly supported by literature data.

FDG-PET/CT can be proposed to assess chemoradiotherapy or neoadjuvant chemotherapy response in oesophageal cancer.

Radiotherapy planning

- *Conclusion and Level of Evidence*

FDG-PET/CT can help delineate radiotherapy volume in oesophageal cancer but without significant improvement of local control or outcome (Level of Evidence C).

- *Recommendations*

The following recommendation is mainly supported by expert opinion.

FDG-PET/CT can be proposed for volume delineation before radiotherapy of oesophageal cancer.

Recurrence assessment

- *Conclusion and Level of Evidence*

In oesophageal cancer, FDG-PET/CT shows good sensitivity for the diagnosis of recurrence, but lacks specificity, meaning histological proof of a local FDG focus appears necessary (Level of Evidence B2).

- *Recommendations*

The following recommendation is mainly supported by literature data.

FDG-PET/CT can be proposed in cases of suspected recurrence of oesophageal cancer.

Pancreatic cancer

Pancreatic mass characterization

- *Conclusion and Level of Evidence*

FDG-PET/CT shows varying performances in characterizing a pseudo-tumoural pancreatic mass, differentiating chronic autoimmune pancreatitis from pancreatic adenocarcinoma, and identifying a neoplastic component of an intraductal papillary mucinous neoplasm (Level of Evidence B2).

- *Recommendations*

The following recommendations are mainly supported by literature data.

Due to insufficient data, FDG-PET/CT is not recommended to differentiate between chronic autoimmune pancreatitis and pancreatic adenocarcinoma. Due to insufficient data, FDG-PET/CT is not recommended to identify a neoplastic component of an intraductal papillary mucinous neoplasm.

Initial staging

- *Conclusion and Level of Evidence*

FDG-PET/CT offers accurate analysis for initial staging of pancreatic adenocarcinoma, especially for detecting distant metastases (Level of Evidence B2).

- *Recommendations*

The following recommendation is mainly supported by literature data.

FDG-PET/CT can be proposed at initial staging for a potentially resectable pancreatic adenocarcinoma.

Recurrence assessment

- *Conclusion and Level of Evidence*

There is insufficient data available on FDG-PET/CT in suspected recurrence of pancreatic adenocarcinoma (Level of Evidence C).

- *Recommendations*

The following recommendation is mainly supported by literature data.

FDG-PET/CT can be proposed in suspected recurrence of pancreatic adenocarcinoma.

Adrenal incidentaloma

- *Conclusion and Level of Evidence*

Published data does not allow to draw firm conclusions on the most reliable second-line imaging method for characterization of indeterminate adrenal masses > 2 cm (Level of Evidence C).

- *Recommendations*

The following recommendation is mainly supported by literature data.

FDG-PET/CT can be proposed for characterization of indeterminate adrenal incidentaloma.

Bladder cancer

Bladder tumour characterization

- *Conclusion and Level of Evidence*

There is no suitable literature data to establish the role of FDG-PET/CT in the management of patients with suspected bladder tumour (Level of Evidence D).

- *Recommendations*

The following recommendation is mainly supported by literature data.

FDG-PET/CT is not presently recommended in cases of suspected bladder tumour.

Initial staging

- *Conclusion and Level of Evidence*

Some tailored FDG-PET/CT procedures should be carried out to provide a better visualization of primitive bladder tumour in comparison to standard PET/CT images performed 60 minutes after FDG injection. These imaging protocols may include early or delayed PET/CT images, oral hydration and/or voiding-refilling procedures (Level of Evidence C).

To date, no significant difference has been found between FDG-PET/CT and CT alone or MRI for detection of pelvic lymph node involvement in the management of muscle-invasive bladder cancer (MIBC) or non-muscle-invasive bladder cancer (NMIBC) patients before cystectomy (Level of Evidence C).

FDG-PET/CT may detect neoplastic involvement of subcentimeter pelvic lymph nodes in the management of MIBC patients before cystectomy (Level of Evidence C).

FDG-PET/CT reveals more metastases or second primary cancers than morphologic imaging alone in the management of MIBC patients before cystectomy (Level of Evidence B2).

FDG-PET/CT changes the management strategy in 13.5%–67% of patients (Level of Evidence B2).

The presence of extravesical FDG-avid lesions is a factor of poor prognosis on overall survival (Level of Evidence C).

There is no suitable literature data to establish the role of FDG-PET/CT in the initial staging of NMIBC (Level of Evidence D).

- *Recommendations*

The following recommendations are mainly supported by literature data.

FDG-PET/CT can be proposed for initial extravesical staging of MIBC before cystectomy.
FDG-PET/CT is not recommended for initial staging of NMIBC.

Assessment of treatment response

- *Conclusion and Level of Evidence*

FDG-PET/CT performed after two cycles of palliative chemotherapy can differentiate responders from non-responders (Level of Evidence C).

FDG-PET/CT performed after four cycles of induction chemotherapy can differentiate responders from non-responders (Level of Evidence C).

- *Recommendations*

The following recommendation is mainly supported by expert opinion.

FDG-PET/CT can be proposed for assessment of response to treatment after induction or palliative chemotherapy for bladder cancer.

Recurrence assessment

- *Conclusion and Level of Evidence*

FDG-PET/CT offers good diagnostic performances for identifying pelvic or distant relapse of bladder cancer (Level of Evidence C).

- *Recommendations*

The following recommendation is mainly supported by expert opinion.

FDG-PET/CT can be proposed if there is suspected extravesical recurrence of bladder cancer

Prostate cancer

Background and pointers on prostate cancer-specific tracers

PSMA is a trans membrane glycoprotein, highly expressed in prostate malignant epithelial cells. This glycoprotein acts as a glutamate carboxy-peptidase enzyme. Many PSMA inhibitory molecules have been developed, labeled with different positron-emitting isotopes. In clinical diagnosis, isotope-

labeled PSMA Gallium 68 has been the most widely studied, while recent works on Fluor 18-labeled PSMA show excellent diagnostic performance. This complex has physicochemical qualities with a strong affinity for the PSMA membrane antigen, which gives it a good image quality and good contrast with healthy tissue. PSMA is particularly overexpressed in prostate cancer cells and its overexpression increases with tumor grade, while the choline hyper metabolism is increased more irregularly in prostatic cancer cells, hence the growing interest of PSMA; only about 8% of prostate cancers do not have overexpression of PSMA [1].

Choline is a precursor substrate for membrane phospholipid labeled either by 18-Flour or 11-Carbon (F-choline or C-choline). Only F-choline is available in France, while C-choline is available in various other European countries, the United States, Australia, and Japan. The two choline tracers have equivalent diagnostic accuracy.

FACBC is an amino acid synthesis analogue (isoleucine) incorporated into cells by active amino acid transporters. One of its advantages is that it undergoes only weak clearance in the urinary tract. In 2016, the F-FACBC received its FDA authorization in the United States in the search for recurrence sites in cases of biochemical relapse. FACBC also has a European marketing authorization in cases of suspected recurrence, after first-line curative treatment.

Initial staging

- *Detection of intraprostatic lesions*

Conclusion and Level of Evidence

PSMA-PET/CT correctly detects intra-prostatic lesions, compared to histology, with an overall sensitivity of 70% (95% CI: 53-83%) and an overall specificity of 84% (95% CI: 24 -99%) at initial extension assessment [2].

the combination of PSMA PET and MRI allows better visualization of high-grade foci [3,4]. PSMA-PET is an interesting tool to guide biopsies, or to guide a focal treatment [2,5].

The combination of PSMA-PET and MRI could be proposed to identify the topography and characterize the grade of cancerous foci in the prostate gland. In the future, these imaging may allow better targeting of treatment to the portion of the prostate containing the most aggressive cancer (Level of Evidence B2).

Performance of choline PET/CT seems insufficient to topographically diagnose cancerous lesions into the prostate, largely because choline cannot differentiate malignant lesions from benign lesions such as inflammation and benign prostatic hyperplasia (Level of Evidence A).

There is currently not enough data in the literature to confirm the performance of FACBC-PET/CT or FACBC-PET/MRI for detecting prostatic tumour at initial assessment. Furthermore, the studies on FACBC have focused on very small patient sample (Level of Evidence C).

Recommendations

The following recommendation is mainly supported by literature data.

PET/CT is not recommended for the initial diagnosis of intraprostatic cancer.

The following recommendation is mainly supported by expert opinion.

PSAM PET/CT can be proposed to guide biopsies in suspected prostate cancer patients with negative biopsies.

- *Detection of pelvic lymphadenopathy and bone metastases*

Conclusion and Level of Evidence

Radiolabeled PSMA PET/CT shows moderate sensitivity but high specificity for the detection of metastatic lymph nodes in intermediate or high risk prostate cancer (ISUP 3, ISUP4, ISUP5); the benefit of PSMA PET/CT appears to be identifying metastatic nodes earlier and in uncommon locations [2,5,6,7,8]

There was no statistically significant difference in the abilities of detecting or excluding lymph nodes cancer between 68Ga-PSMA PET/CT and 18F-Choline PET/CT,

even if PSMA PET/CT shows a slightly higher sensitivity and specificity, probably related to better image quality; thus both should be considered for staging [9]

PET/CT is insufficient for accurate lymph node staging as it may miss nodes < 5 mm: lymphadenectomy remains the gold standard. However, PET/CT is the most effective non-invasive screening tool for node metastasis, especially in intermediate or high risk patients (ISUP 3, ISUP 4, ISUP5) (Level of Evidence A).

PSMA PET/CT demonstrated the highest detection rate of bone metastases compared to bone scintigraphy, choline PET/CT, FNa PET/CT and whole body MRI [10]

PET/CT is more sensitive and more specific than bone scintigraphy, especially for low PSA values for the detection of bone metastases. (Level of Evidence A).

PET/CT with PSMA or choline also provides further value by concurrently detecting lymph node metastases and low-volume bone metastasis in one-time examination, in D'Amico high-risk patients (ISUP 4, ISUP 5) that have high-metastatic-prevalence nodes. Indeed, PET appears better to perform re-staging than combined pelvic CT and bone scintigraphy, and thus offers a more suitable treatment to D'Amico high-risk patients (ISUP4, ISUP 5) (Level of Evidence A).

PET/CT can thus be proposed in patients with curative intent (Level of Evidence B1).

Bone scintigraphy mains the gold standard for bone metastases diagnosis when PSA level is very high (>> 20 ng/mL), but Bone scintigraphy is insufficient when PSA level < 20 ng / ml.

Recommendations

The following recommendation is mainly supported by literature data.

PSMA PET/CT (if not available, Choline-PET/CT) can be proposed in the initial assessment of high-risk patients (ISUP 3, ISUP 4 and ISUP 5) before curative treatment.

Optimization of initial curative radiotherapy or adjuvant radiotherapy

- *Conclusion and Level of Evidence*

Evidence from the literature converges to say that irradiation of prostatic tumour, lymph node lesions or bone oligo metastases, is better defined by choline PET/CT, and more recently by PSMA TEP/CT, with modification of radiotherapy schedule, (boost, dose escalation, PET-guided radiation therapy), without increase radiation toxicity, and with better local control of the disease [11-16]. It results in considerably prolonged biochemical progression free survival (PFS). Repeated PET/CT guided radiotherapy represent a treatment option in well selected patients with relapse after Radiotherapy for oligo metastatic disease. PET/CT performs better than bone scintigraphy, CT and MRI.

According to the meta analysis from Han et al, [16], the pooled proportion of management changes is 54% (95% confidence interval 47-60%).

PSMA PET/CT imaging (if not available, Choline PET/CT) is widely proposed before radiotherapy, during initial diagnosis and relapse (Level of Evidence B1).

There is currently insufficient literature data to confirm the performance of FACBC-PET/CT for tailoring pelvic radiotherapy schedules in patients with biological relapse (Level of Evidence C).

- *Recommendations*

The following recommendation is mainly supported by literature data.

PSMA-PET/CT (if not available, Choline-PET/CT) can be proposed to improve radiotherapy planning.

Recurrence assessment

- *Conclusion and Level of Evidence*

Data from the literature demonstrates that choline PET/CT detect the site of recurrence in patients with biological relapse, particularly if PSA level ≥ 1 ng/ml. However, at low PSA levels (<2 ng/ml), PSA kinetics should be known for selecting patients with a high probability of benefitting from PET (Level of Evidence A).

PET with PSMA ligands appears better than choline PET/CT for PSA levels ≤ 2 ng/ml in patients with biological relapse.

For PSA levels <0.5 ng / ml, between 0.5 and 0.9 ng / ml, between 1 and 1.99 ng / ml, or greater than 2 ng / ml, the PSMA PET/CT appears positive respectively in about 45%; 60%; 75% and 95% [2,17]. These results are higher than those obtained with choline PET/CT and concern both node relapses, bone or visceral relapses.

PSMA PET/CT may be positive whereas choline PET/CT is negative: This contributive PSMA TEP/CT gain is mainly observed for low PSA levels < 2 ng / ml. The detection rate of relapse with the ligands of PSMA is about 85% versus 70% for choline [18-21]; all the metastases detected in choline are also identified with the PSMA ligands, and the number of patients with positive PET is greater in PSMA versus choline imaging. As a result, the performance of PET-68Ga-PSMA appears to be much higher than that of PET-choline for low PSA levels.

PSMA PET/CT appears today as the best examination of early detection of relapse site allowing a more effective focused treatment, while the disease is not disseminated, especially for PSA levels ≤ 2 ng/ml. (Level of Evidence A).

It seems that there is also an influence of the kinetics of the PSA on the detectability of the site of relapse: shorter PSA doubling time (PSAdt), may be predictor of PSMA PET/CT positivity in patients with biochemical recurrent prostate cancer [22,23] (level of Evidence B1)

Although PET-choline has made it possible to provide remedial treatments, it remains insufficient and is not recommended for PSA values <2 ng / ml. PET-68Ga-PSMA appears much more sensitive and specific (Level of Evidence A).

Hormone therapy does not contraindicate choline PET/CT, but the PET examination must be performed before starting hormone therapy or adjusting an existing hormone therapy course (Level of Evidence B1).

The performance of choline PET/CT is insufficiently documented in the evaluation of systemic therapies in castration-resistant patients but it seems to be interesting (level of Evidence B2).

The performance of fluciclovine PET/CT is poorly documented but suggests that PET with FACBC may show equivalent performances to choline PET/CT (Level of Evidence C).

- *Recommendations*

The following recommendations are mainly supported by literature data.

PSMA-PET/CT is recommended for the diagnosis of biological recurrence, even in case of very low PSA levels ≤ 1 ng/mL.

If PSMA PET/CT is not available, Choline PET/CT is an alternative, especially if PSA level is ≥ 1 ng/ml; In case of PSA < 1ng/ml, the rapid PSA kinetics with a doubling time of ≤ 6 months can be used to select patients with high probability of benefitting from choline PET/CT.

FACBC-PET/CT can be offered as an alternative of choline PET/CT.

Breast Cancer

Background data on FDG uptake in breast tumours

Appropriate interpretation of FDG-PET/CT exams requires sharp knowledge of potential false-negatives, which might result from small tumour size (partial volume effect) or low FDG uptake. The main factors influencing tumoural uptake are:

- Except for the brain, FDG-PET/CT allows analysis of all organs in a single-run examination with performances that are superior to those of conventional imaging techniques (contrast-enhanced CT of thorax-abdomen-pelvis, liver ultrasound, bone scan).
- Tumour SBR (Scarff–Bloom–Richardson) grade: grade 1 or 2 tumours show lower FDG uptake than grade 3 tumours [24];

- Histological subtype: lower FDG-avidity of invasive lobular carcinomas than invasive ductal carcinomas [24]. Intraductal carcinomas (*in-situ* tumours) are thought to usually show low uptake compared to invasive carcinomas;
- Proliferation index: lower uptake in low-proliferative tumours as assessed on the Ki67 index [25,26];
- p53 status: FDG uptake is lower in tumours with functional p53 than mutated p53 [24] ;
- Hormone receptor status: FDG uptake is lower in well-differentiated oestrogen receptor (ER)-positive tumours than ER-negative tumours. This is also the case for progesterone receptor (PR)-positive tumours compared to PR-negative tumours [24];
- Tumour phenotype: triple-negative tumours (ER-negative, PR-negative and having no overexpression of c-erbB2) show substantially higher SUVs than other tumours. Among luminal tumours, FDG uptake is lower in luminal-A tumours than luminal-B tumours [27].

Breast lesion/tumour characterization

❖ *Conclusions and Level of Evidence*

FDG-PET/CT has low sensitivity and specificity for informing on the malignancy of a breast lesion (Level of Evidence C).

FDG-PET/CT cannot substitute for biopsy in determining the malignancy of a breast lesion (Level of Evidence C).

When an FDG-avid focus is seen in the breast during an FDG-PET/CT exam performed for other reasons, the possibility of a malignant breast lesion cannot be neglected and should be considered (Level of Evidence B2).

❖ *Recommendations*

The following recommendations are mainly supported by literature data.

FDG-PET/CT is not recommended for characterizing a breast lesion as 'diagnosing malignancy'.

When FDG exams performed for other reasons come up with incidental finding of an FDG-avid intra-mammary focus, it is recommended to pursue investigations, even though some benign lesions such as fibroadenomas may give false-positive uptake.

Assessment of breast cancer multifocality and T status (TNM staging)

❖ *Conclusions and Level of Evidence*

FDG-PET/CT performs suboptimally on delimitating primary tumour volume and assessing for multifocality (Level of Evidence B1), where MRI offers greater sensitivity (Level of Evidence B1).

There is still not enough good data on breast-dedicated PET systems (PEM) or PET-MR to conclude on their performances for assessing multifocality or determining the T status of a breast cancer in the TNM staging system (Level of Evidence D).

- *Recommendations*

The following recommendation is mainly supported by literature data.

FDG-PET/CT is currently not recommended for assessing multifocality or determining the precise T status of a breast cancer in the TNM staging system.

FDG-PET/CT compared to sentinel node biopsy for determining axillary status

- *Conclusions and Level of Evidence*

The spatial resolution of PET imaging is insufficient for depicting small axillary node metastases (Level of Evidence A).

- *Recommendations*

The following recommendation is mainly supported by literature data.

FDG-PET/CT is not recommended to replace sentinel node biopsy.

Initial staging

- *Conclusions and Level of Evidence*

FDG-PET/CT is useful for initial staging of breast cancer, independently of tumour phenotype (triple-negative, luminal or HER2+) and regardless of tumour grade (Level of Evidence B2). Considering histological subtype, FDG-PET/CT performs better for staging invasive ductal carcinoma (invasive carcinoma of no specific subtype) than for staging invasive lobular carcinomas (Level of Evidence B2).

Based on the available data, FDG-PET/CT becomes useful for staging starting from clinical stage IIB (Level of Evidence B1). FDG-PET/CT is possibly useful in patients with clinical stage IIA (T1N1 or T2N0), but there is not enough strong data to recommend routine use in this subgroup (Level of Evidence C). For clinical stage-I (T1N0) patients, staging with FDG-PET/CT offers no added value (Level of Evidence A).

- *Recommendations*

The following recommendations are mainly supported by literature data.

FDG-PET/CT is recommended for initial staging in patients with clinical stage ≥ IIB breast cancer, and is better when performed before surgery. FDG-PET/CT can be proposed for staging patients with clinical stage IIA (T1N1 or T2N0) breast cancer, and is better when performed before surgery. FDG-PET/CT is not recommended for staging patients with clinical stage I (T1N0) breast cancer.

Prognostic value

- *Conclusions and Level of Evidence*

Occult distant metastases uncovered by FDG-PET/CT are associated with decreased overall survival (Level of Evidence B1).

High-intensity FDG uptake in primary tumour (high SUV value) is associated with worse prognosis (Level of Evidence B2). However, the data is currently insufficient to validate using FDG uptake intensity to modify treatment (such as deciding whether or not to use chemotherapy) (Level of Evidence C).

- *Recommendations*

The following recommendation is mainly supported by literature data.

It is currently not recommended to use quantitative FDG uptake values for selecting treatment strategy.

Recurrence assessment

- *Conclusions and Level of Evidence*

FDG-PET/CT performs better than conventional imaging techniques for identifying sites of loco-regional or distant recurrence of breast cancer, whatever the setting prompting suspected recurrence, clinical or radiological signs, or elevated tumour markers (Level of Evidence A).

FDG-PET/CT offers good performance in identifying a suspected recurrence even with non-elevated tumour marker levels (Level of Evidence B2).

FDG-PET/CT offers good performance in delivering whole body restaging of disease when breast cancer recurrence is known (Level of Evidence B2).

- *Recommendations*

The following recommendation is mainly supported by literature data.

FDG-PET/CT is recommended in cases of suspected recurrence of breast cancer as well as for global restaging of a documented recurrence.

Follow-up

- *Conclusions and Level of Evidence*

FDG-PET/CT does not perform well enough for routine follow-up of breast cancer (Level of Evidence B2).

- *Recommendation*

The following recommendation is mainly supported by literature data.

FDG-PET/CT is currently not recommended for post-treatment follow-up of breast cancer patients.

Assessment of therapeutic response

Neoadjuvant chemotherapy

- *Conclusions and Level of Evidence*

FDG-PET/CT enables early assessment of response to neoadjuvant chemotherapy in breast cancer, but the proposed assessment methods vary broadly between studies (Level of Evidence A). Taking into account the specific tumour phenotype may serve to better homogenize the response criteria (Level of Evidence B1).

FDG-PET/CT is unable to identify residual disease at the end of neoadjuvant therapy for breast cancer (Level of Evidence B2).

- *Recommendations*

The following recommendations are mainly supported by literature data.

FDG-PET/CT can be proposed for early evaluation of response to neoadjuvant therapy, particularly in triple-negative or HER2+ disease, but it is currently not recommended to modify treatment on the basis of FDG-PET/CT results.

FDG-PET/CT is not recommended as an intervention to search for residual breast tumour at the end of neoadjuvant treatment.

Chemotherapy and hormonal therapy for metastatic disease

- *Conclusions and Level of Evidence*

FDG-PET/CT offers good performance in evaluating response to systemic treatments of metastatic breast cancer (Level of Evidence B2). Because PET/CT offers functional as well as morphological information, it is better than CT alone or bone scan for assessing response to treatment of bone metastases (Level of Evidence A).

As regards assessment of response to hormonal treatments, a paradoxical increase in FDG uptake in the days that follow the start of treatment called 'metabolic flare' would seem to predict good response (Level of Evidence B2).

- *Recommendations*

The following recommendation is mainly supported by literature data.

FDG-PET/CT can be proposed for assessing response to systemic treatments of metastatic breast cancer (especially for bone metastases).

Ovarian, cervical and endometrial carcinomas

Ovarian carcinomas

- *Conclusions and Level of Evidence*

Data from the many retrospective studies and a few prospective studies dealing with the value of FDG-PET/CT during assessment of extension at the initial diagnosis and at recurrence give results that

are consistent overall but not enough to determine recommendations. The data is nevertheless encouraging (Level of Evidence B2).

The new data on diagnosis of recurrence (although exclusively from retrospective studies) added to the pre-existing data show that FDG-PET/CT is more effective than conventional imaging for detecting recurrences with isolated elevated CA125 or doubt after morphological imaging (Level of Evidence B1).

- *Recommendations*

The following recommendations are mainly supported by literature data.

FDG-PET/CT is recommended in cases of suspected recurrence of ovarian carcinoma, particularly with elevated serum CA 125.

FDG-PET/CT can be proposed for the local-regional or whole body extension assessment of advanced ovarian carcinoma (≥ FIGO stage III).

FDG-PET/CT can be proposed for recurrence/extension assessment in ovarian carcinoma.

Endometrial carcinoma

- *Conclusion and Levels of Evidence*

Data from the many retrospective studies, a few prospective studies and two meta-analyses dealing with the value of FDG-PET/CT, during assessment of endometrial carcinoma extension at the initial diagnosis, excluding stage I, generally give results that are consistent but not enough to determine recommendations. Nevertheless, some studies show that FDG-PET/CT improves extrapelvic lymph node extension in endometrial carcinomas (Level of Evidence B2).

The new data are insufficient to define a new recommendation in cases of suspected endometrial carcinoma recurrence, but data from the meta-analysis on 11 studies show encouraging results with a real impact of FDG-PET/CT in patient therapy management (Level of Evidence B2).

- *Recommendations*

The following recommendations are mainly supported by literature data.

FDG-PET/CT can be proposed in the endometrial carcinoma extension assessment for high risk of metastatic carcinoma ≥ FIGO II stage.

FDG-PET/CT can be proposed if there is a suspected recurrence of endometrial carcinoma.

Cervical carcinoma

- *Conclusion and Level of Evidence*

Data from the many retrospective studies, a few prospective studies and two meta-analyses dealing with extrapelvic lymph node extension assessment in advanced cervical carcinoma (≥ stage IB2)

converge to show that FDG-PET/CT is more effective than conventional imaging (Level of Evidence B1).

The meta-analysis dealing with the value of FDG-PET/CT in proven recurrence of cervical carcinoma finds results that are consistent overall but not enough to determine recommendations. The data is nevertheless encouraging (Level of Evidence B2).

The data found on FDG-PET/CT for assessment of residual cervical carcinoma disease is insufficient to establish any recommendations or options in this indication (Level of Evidence C).

- *Recommendations*

The following recommendations are mainly supported by literature data.

FDG-PET/CT is recommended for initial extension assessment in cervical cancers ≥ FIGO IB2 stage.

FDG-PET/CT can be proposed in proven recurrence of cervical carcinoma, particularly to help decide therapeutic strategy.

FDG-PET/CT is not currently recommended for residual disease assessment at the end of treatment.

Cutaneous, ocular and mucosal melanoma

Cutaneous melanoma stage I - II

- *Initial staging*

Conclusion and Level of Evidence

In early-stage melanoma (stage I-II), the literature confirms that FDG-PET/CT examination has no added value compared to the sentinel lymph node technique due to its limited sensitivity for detecting lymph node micro-metastases and the risk of false-positive findings.

In addition, the risk of distant metastases in these patients is low, and even in patients at higher localized risk (Breslow > 4 mm or ulcerated melanoma), FDG-PET/CT has not shown any significant impact on patient treatment management in this setting (Level of Evidence B2).

All studies found have reported on the possibility of detecting secondary cancer, demonstrating the need to investigate the origin/aetiology of isolated lesions on FDG-PET/CT scans before linking them to the diagnosis of melanoma. However, this situation remains occasional (Level of Evidence B2).

Recommendations

The following recommendations are mainly supported by literature data.

FDG-PET/CT is not routinely recommended in initial local and distant staging of patients with stage I-II melanoma.

FDG-PET/CT is not recommended in place of the sentinel lymph node technique.

Cutaneous melanoma stage III - IV

- *Initial staging of melanoma with positive sentinel lymph nodes (stage IIIA)*

Conclusion and Level of Evidence

In this setting, the literature data is limited but highlights that the risk of distant metastases in patients with stage IIIA melanoma, and particularly asymptomatic patients, remains moderate, thus limiting the interest of using FDG-PET/CT in this setting (Level of Evidence C).

Recommendations

The following recommendation is mainly supported by literature data.

FDG-PET/CT is not currently recommended in the initial staging of patients with subclinical micro-metastatic stage IIIA melanoma (without ulceration melanoma with positive sentinel lymph nodes).

- *Initial staging in cases of high-risk melanoma with distant metastases, macroscopic lymph node involvement and /or known distant metastases (stage IIIB-C and IV) and assessment of recurrence*

Conclusion and Level of Evidence

In this setting, the literature data shows that FDG-PET/CT has as central role in staging melanoma patients with lymph node localization and high risk of distant metastases (AJCC stage III BC) or in staging known AJCC stage IV patients (Level of Evidence B2). In terms of direct comparison between FDG-PET/CT and conventional imaging (particularly with diagnostic CT), data from the literature demonstrates that FDG-PET/CT is more accurate for detecting distant metastases in patients with suspected or proven recurrence, particularly for abdominal sites, lymph node sites, subcutaneous nodules and soft tissue localizations; on the other hand, diagnostic CT appears more accurate in assessing lung metastases (Level of Evidence B2). Data on direct comparison with MRI is limited, but MRI appears to be the gold standard for brain metastases and it can be a helpful technique to characterize bone lesion. (Level of Evidence B2).

Recommendations

The following recommendations are mainly supported by literature data.

FDG-PET/CT is recommended in staging of cutaneous melanoma with known macroscopic lymph nodal location or at high risk of distant metastases (stage IIIB-C).
FDG-PET/CT is recommended in pre-therapeutic staging for patients with known stage IV disease.
FDG-PET/CT is recommended in the restaging of cutaneous melanoma recurrence in either lymph node or distant metastases sites.

- *Pre-surgical staging of resectable lymph node disease or isolated distant metastasis*

Conclusion and Level of Evidence

Data from the literature shows that FDG-PET/CT can identify occult metastases in the pre-surgical staging of resectable lymph node disease or in cases of a single presumed metastatic localization (Level of Evidence B2).

Recommendations

The following recommendations are mainly supported by literature data.

FDG-PET/CT is recommended for pre-surgical staging of cutaneous melanoma with resectable macroscopic lymph node disease (stage IIIB-C).
FDG-PET/CT is recommended in the pre-surgical staging of stage-IV cutaneous melanoma in cases of a single presumed metastatic localization.

- *Follow-up*

Conclusion and Level of Evidence

In the follow-up of patients with melanoma, there is no standardized role for FDG-PET/CT in routine surveillance. The impact of FDG-PET/CT surveillance on patient management is moderate when patients are in remission with low risk of recurrence or low risk of distant metastases.

New studies need to be conducted to clarify the role of FDG-PET/CT in monitoring asymptomatic patients (Level of Evidence C).

However, FDG-PET/CT could be used to detect the onset of distant metastases in patients who are symptomatic and/or with high risk of metastatic disease and/or with high levels of tumour markers (Level of Evidence C), although there is still no certainty that FDG-PET/CT can play a complementary role in when PS100B is elevated or at-threshold (Level of Evidence D).

Recommendations

The following recommendation is mainly supported by literature data.

FDG-PET/CT is currently not recommended in the routine follow-up of asymptomatic stage I to IIIA patients.

The following recommendation is mainly supported by expert opinion.

FDG-PET/CT can be proposed for follow-up in cases of suspicious clinical symptoms or in cases of high-risk melanoma for distant metastases and stages IIIB-C.

Assessment of treatment response

- *Conclusion and Level of Evidence*

FDG-PET/CT has been proven useful for assessing early metabolic response to targeted therapy or immunotherapy, but the timing, predictive value and best semi-quantitative parameter to predict or define the response have not yet been explored (Level of Evidence D). Further research is needed to validate and standardize the use of FDG-PET/CT in this indication.

The use of FDG-PET/CT in the differential diagnosis between pseudo-progression and true progression has not yet been explored in patients on immunotherapy, and so in this case, a close re-assessment still has to be performed (Level of Evidence C).

- *Recommendations*

The following recommendation is mainly supported by expert opinion.

FDG-PET/CT can be proposed for assessing response to systemic treatments.

Prognostic value

- *Conclusion and Level of Evidence*

The presence and intensity of metastatic uptake at FDG-PET/CT appears to be an important prognostic factor, particularly in terms of progression-free survival, but the choice of the best semi-quantitative parameter remains to be explored (Level of Evidence D). The role of FDG-PET/CT in this indication needs to be further explored and verified in additional and prospective studies to confirm the data (Level of Evidence C).

- *Recommendations*

The following recommendation is mainly supported by literature data.

FDG-PET/CT is currently not recommended for the prognostic assessment of melanoma.

Ocular or mucous melanomas

- *Conclusion and Level of Evidence*

The literature data on the role of FDG-PET/CT in the assessment of ocular and/or mucosal melanoma is limited. FDG-PET/CT appears to have limited value for assessing primary tumour and in patients with low risk of recurrence (Level of Evidence D). On the other hand, it appears to offer good performance for detecting distant metastases in advanced disease, but its superiority over conventional imaging has not yet been proven (Level of Evidence D).

- *Recommendations*

The following recommendation is mainly supported by expert opinion.

FDG-PET/CT can be proposed for staging high-metastatic-risk ocular or mucosal melanoma.

Bone sarcoma

Initial staging

- *Conclusion and Level of Evidence*

In initial staging, FDG-PET/CT is more accurate than bone scintigraphy or conventional imaging for detecting bone, lymph node and soft tissue metastases, particularly in Ewing sarcoma. However, CT scan has better sensitivity for lung metastasis in osteosarcoma and Ewing sarcoma (Level of Evidence B2).

- *Recommendations*

The following recommendation is mainly supported by literature data.

FDG-PET/CT is recommended in initial staging for bone sarcomas.

Recurrence assessment

- *Conclusion and Level of Evidence*

Very few studies aim to assess the performance of FDG-PET/CT in case of suspected relapse. However, FDG-PET/CT appears to outperform morphological imaging which lead to a higher rate of false-positives results (Level of Evidence C).

- *Recommendations*

The following recommendation is mainly supported by literature data.

FDG-PET/CT can be proposed in suspected recurrence of bone sarcoma.

Pre-therapeutic prognostic value

- *Conclusion and Level of Evidence*

The literature shows contradictory results: some studies did not differentiate the results obtained in bone and soft tissue sarcomas and no obvious quantitative parameter was identified (SUVmax seems to have higher prognostic value than tumour-to-background ratio and TLG seems to have higher prognostic value than MTV (Level of Evidence C).

Nevertheless, the existence of a link tying metabolic tumour activity and volume to presence of metastases would be an argument for worse prognosis (Level of Evidence C).

- *Recommendations*

The following recommendation is mainly supported by literature data.

FDG-PET/CT is not currently recommended for pre-therapeutic prognostic evaluation of bone sarcomas.

Assessment of therapeutic response

- *Conclusion and Level of Evidence*

SUVmax before neoadjuvant chemotherapy, which reflects metabolic tumour activity, appears to be higher in osteosarcoma than in Ewing sarcoma. SUVmax variation of the lesion from pretherapeutic to post therapeutic PET seems weaker in osteosarcoma. Quantification parameters for predicting histological response should be different in osteosarcoma and Ewing sarcoma. FDG-PET/CT seems to be more efficient in predicting histological response in osteosarcoma. It has been shown that the threshold that should be used to differentiate good and bad histological response should be 2.5 for

SUVmax after neoadjuvant chemotherapy and 50%–55% for the SUVmax variation of the lesion from pre therapeutic to post therapeutic PET. These criteria alone do not perform well enough to predict histological response in osteosarcoma, but they do appear to perform better than MRI-measured tumour volume (Level of Evidence B2).

For this reason, other quantification parameters have been studied (MTV, TLG, retention index) that take into account tumour volume and metabolic activity as well as time-course variation after FDG injection. It would appear that the combination of several parameters (relative variations in SUVmax and apparent diffusion coefficients, relative variation in MTV or TLG) would improve performances (Level of Evidence C).

- *Recommendations*

The following recommendation is mainly supported by literature data.

FDG-PET/CT is not currently recommended for predicting histological response to neoadjuvant chemotherapy for bone sarcoma.

Lymphomas

Hodgkin lymphoma, Diffuse large B cel lymphoma and Follicular lymphoma

- *Staging/re-staging*

Conclusion and Level of Evidence

Pre-therapy FDG-PET/CT is useful for evaluating disease extent in FDG-avid lymphomas at diagnosis and as a baseline reference for further assessment of therapeutic response.

Compared with CT alone, the sensitivity and specificity of FDG-PET/CT for lesion detection exceeds 95 % in Hodgkin Lymphoma (HL), Diffuse Large B Cell Lymphoma (DLBCL) and Follicular Lymphoma (FL), responsible for stage modifications in 20% to 30 % of cases (mainly upstaging), with a major therapeutic impact in stage I/II patients, leading to changes of therapeutic management in about 15% of cases (Level of Evidence A).

Focal and intense skeletal uptakes are strong indicators of suspected bone marrow involvement and eliminate the need for Bone marrow biopsy (BMB) in HL and DLBCL. Diffuse skeletal uptake without focal lesion may indicate bone marrow hyperplasia in HL or DLBCL patients with severe inflammatory syndrome. In DLBCL, however, BMB may be indicated when FDG-PET/CT is normal on the skeleton (particularly when a low-grade lymphoma is suspected and when BMB results may prompt changes to therapeutic management). In FL, BMB remains indicated whenever its positivity may prompt changes to therapeutic management (Level of Evidence A). MRI is the first-line reference exam for staging primary central nervous system lymphomas (Level of Evidence A). Intensity of FDG uptake is higher in aggressive than indolent lymphomas, and FDG-PET/CT can guide biopsy site in patients with an indolent lymphoma when an aggressive transformation is suspected (Level of Evidence B1). Among different prognostic biomarkers, assessment of tumour burden by calculating the total metabolic tumour volume (TMTV) seems to add additional and independent prognostic value, but

variability of segmentation methods, threshold levels and patient populations prevent its definitive validation for routine clinical use (Level of Evidence C).

Recommendations

The following recommendations are mainly supported by literature data.

FDG-PET/CT is recommended at initial staging of HL, DLBCL and FL, as well as other FDG-avid lymphomas.
FDG-PET/CT is recommended for the assessment of bone marrow involvement in HL and DLBCL, and in most case eliminates the need for a systematic bone marrow biopsy.
FDG-PET/CT is recommended to guide biopsy site in patients with an indolent lymphoma when an aggressive transformation is suspected based on clinical, biological or radiological signs.

- Assessment of therapeutic response and interim assessment

Conclusion and Level of Evidence

The prognostic value of interim PET (iPET) (after two or four cycles of chemotherapy) has been widely demonstrated in HL and DLBCL for early identification of responding and non-responding patients (Level of Evidence A).

Tailoring of therapeutic strategies according to individual iPET response has been demonstrated in HL patients treated by ABVD or BEACOPP (Level of Evidence A). Tailoring of therapeutic strategies according to individual iPET response, although often performed in routine practice, is not yet demonstrated in other lymphoma types, and current ongoing trials are set to answer this question in the near future (Level of Evidence C).

Interpretation of iPET must be reported using the Deauville scale and Lugano classification in medical records.

Recommendations

The following recommendations are mainly supported by literature data.

FDG-PET/CT is recommended for interim assessment of therapeutic response to identify early responders from non-responders in HL and DLBCL.
FDG-PET/CT is currently not recommended for adapting therapeutic strategies (escalation, de-escalation) in DLBCL.
FDG-PET/CT is recommended for adapting therapeutic strategies in selected HL populations.

- *Assessment of end-of-treatment response*

Conclusion and Level of Evidence

FDG-PET/CT is considered the reference exam for routine evaluation of end-of-treatment response in FDG-avid lymphomas (HL, DLBCL, FL) (Level of Evidence A). There is an extensive body of literature to support this fact, even though most studies date back to before the 2007 and 2014 interpretation criteria reports.

Recommendations

The following recommendation is mainly supported by literature data.

FDG-PET/CT is recommended for the evaluation of end-of-treatment response in HL, DLBCL, FL, and other FDG-avid lymphomas, in order to ensure complete metabolic response.

- *Follow-up*

Conclusion and Level of Evidence

FDG-PET/CT has a low positive predictive value in the systematic follow-up of patients treated for lymphoma (Level of Evidence B1).

In contrast, when a relapse is suspected at clinical examination, FDG-PET/CT has an excellent negative predictive value to rule out a relapse (Level of Evidence B2); alternatively, it may help to guide the biopsy site and re-stage the disease (Level of Evidence A).

Recommendations

The following recommendation is mainly supported by literature data.

FDG-PET/CT is currently not recommended for systematic follow-up of patients treated for lymphoma, regardless of lymphoma type. FDG-PET/CT can be proposed to rule out a relapse or restage the disease and guide the biopsy when a relapse is suspected at clinical examination

Mantle cell lymphoma and T-cell lymphoma

- *Conclusion and Level of Evidence*

Mantle cell lymphomas

All the data underline the value of FDG-PET/CT for initial staging of patients with Mantle cell lymphoma (MCL), with excellent sensitivity for identifying all localizations except bone marrow and digestive tract for which BMB and endoscopy remain recommended (Level of Evidence A).

Some data suggest the potential value of semi-quantitative analysis in this indication: the determination of SUV at diagnosis would indeed bring important prognostic information (Level of Evidence C).

For interim assessment, while various results seem to show a prognostic impact of FDG-PET/CT, the published data are currently too sparse and too heterogeneous to draw definitive conclusions. New standardized prospective studies are needed to define the role of this imaging modality in adapting therapeutic strategies (Level of Evidence C).

For end-of-treatment assessment, FDG-PET/CT is used in order to confirm complete metabolic response (Level of Evidence B2). Nevertheless, while various results seem to show the prognostic impact of a complete metabolic remission, the published data are too sparse and too heterogeneous in terms of interpretation criteria, populations, and therapeutic protocols (Level of Evidence C).

T-cell lymphoma

For initial staging, FDG-PET/CT allows a better assessment of disease extent than conventional approaches (Level of Evidence A).

FDG avidity varies with histological subtypes of T-cell lymphoma, with higher avidity in T/NK lymphomas, peripheral T-cell lymphomas, adult T-cell leukaemia-lymphomas, and anaplastic lymphomas, and much more moderate avidity for cutaneous T-cell lymphoma (Level of Evidence A). FDG-PET/CT does not have good enough sensitivity to assess bone marrow involvement, and therefore BMB remains recommended (Level of Evidence B1).

For cutaneous lymphomas, FDG-PET/CT can be used to detect extra-nodal involvement whose presence modifies therapeutic management. FDG-PET/CT can be used to guide biopsy when aggressive transformation is suspected (Level of Evidence B2).

For histological subtypes of the most FDG-avid T-cell lymphomas (T/NK and peripheral T-cell lymphoma), SUVmax and TMTV seem to add additional and independent prognostic value, but variability of segmentation methods, threshold levels and patient populations prevent its definitive validation for routine clinical use (Level of Evidence C).

While some studies suggest the potential value of intermediate metabolic evaluation, particularly for histological subtypes of the most FDG-avid T-cell lymphomas, the published data are currently too sparse and too heterogeneous in terms of populations and interpretation criteria to draw definitive conclusions. Standardized prospective studies are needed to clarify the role of this imaging modality to adapt therapeutic management (Level of Evidence C).

For end-of-treatment assessment, FDG-PET/CT is used in order to confirm complete metabolic response. Nevertheless, while various results seem to show the prognostic impact of a complete metabolic remission, the published data are too sparse and too heterogeneous in terms of interpretation criteria, populations and therapeutic protocols (Level of Evidence B2).

- *Recommendations*

The following recommendations are mainly supported by literature data.

FDG-PET/CT is recommended for initial staging of mantle cell lymphoma.

FDG-PET/CT is recommended for end-of-treatment assessment in mantle cell lymphomas to confirm complete metabolic response.

FDG-PET/CT is currently not recommended for systematic interim assessment of therapeutic response in mantle cell lymphomas.

FDG-PET/CT can be proposed for initial staging of T-cell lymphoma (except cutaneous forms).

FDG-PET/CT is currently not recommended for systematic interim assessment of therapeutic response in T-cell lymphoma.

FDG-PET/CT can be proposed for end-of-treatment assessment in T-cell lymphomas (non-cutaneous forms) to confirm complete metabolic response.

FDG-PET/CT can be proposed to diagnose extranodal involvement or aggressive transformation of cutaneous T-cell lymphoma.

FDG-PET/CT is currently not recommended for systematic end-of-treatment assessment in cutaneous T-cell lymphoma.

Multiple Myeloma

Initial staging

- *Conclusion and Level of Evidence*

FDG-PET/CT has very good sensitivity and specificity for the detection of bone lesions in the initial diagnosis of symptomatic multiple myeloma. Sensitivity is comparable to that of MRI (Level of Evidence A). However, if a medullary compression is suspected, an MRI or CT scan of the spine should also be performed (Level of Evidence A).

FDG-PET/CT is able to detect extramedullary lesions associated with a negative prognostic value at the initial diagnosis of symptomatic multiple myeloma (Level of Evidence A).

FDG-PET/CT has good performances for the initial staging of solitary plasmacytoma (Level of Evidence B2).

FDG-PET/CT can detect bone lesions in patients with smouldering multiple myeloma (SMM) (Level of Evidence B2).

- *Recommendations*

The following recommendations are mainly supported by literature data.

FDG-PET/CT is recommended for the initial assessment of symptomatic multiple myeloma.

FDG-PET/CT is recommended for the initial assessment of plasmacytoma.

FDG-PET/CT can be proposed in cases of suspected progression of smouldering multiple myeloma.

- *Assessment of therapeutic response*

- *Conclusion and Level of Evidence*

FDG-PET/CT is more efficient than MRI for the therapeutic assessment in MM, as it can assess the response earlier than MRI, and with prognostic value, especially in patients eligible for stem cell transplantation (Level of Evidence A).

However, the FDG-PET/CT interpretation criteria and quantification tools (SUVmax, MTV, TLG) for therapeutic assessment need to be standardized and validated by prospective studies (Level of Evidence B1).

FDG-PET/CT can be coupled with a biological technique for detecting minimal residual disease (MRD) to define the complete response (Level of Evidence B2).

❖ *Recommendations*

The following recommendation is mainly supported by literature data.

FDG-PET/CT is recommended for assessment of therapeutic response in multiple myeloma, particularly in patients eligible for transplantation.

Prognostic value at baseline

❖ *Conclusion and Level of Evidence*

At baseline, FDG-PET/CT is an independent prognostic tool for symptomatic multiple myeloma patients. Indeed, most studies find that SUVmax value at initial staging, the existence of extramedullary lesions and the number of focal bone lesions are independent prognostic factors (Level of Evidence B1).

However, the PET/CT quantification tools (SUVmax, number of focal lesions, MTV, TLG) at initial staging need to be standardized by determining critical thresholds and then validated by prospective studies (Level of Evidence B1).

In patients followed for a solitary plasmacytoma, the positivity of FDG-PET/CT increases the risk of progression to a multiple myeloma (Level of Evidence B2).

In patients followed for SMM, the positivity of FDG-PET/CT increases the risk of progression to a multiple myeloma (Level of Evidence B2).

❖ *Recommendations*

The following recommendation is mainly supported by literature data.

FDG-PET/CT can be proposed for prognostic assessment of multiple myeloma.

Diagnosis of recurrence

❖ *Conclusion and Level of Evidence*

FDG-PET/CT is a sensitive and specific imaging method for the detection of bone lesions in relapsing multiple myeloma patients (Level of Evidence A).

At relapse, the number of focal lesions and the presence of extramedullary lesions are negative prognostic factors for survival (Level of Evidence C).

❖ *Recommendations*

The following recommendation is mainly supported by expert opinion.

FDG-PET/CT can be proposed for exploring a suspected recurrence of multiple myeloma.

Reference:

[1] Maurer T, Gschwend JE, Rauscher I, Souvatzoglou M, Haller B, Weirich G, et al. Diagnostic Efficacy of (68)Gallium-PSMA Positron Emission Tomography Compared to Conventional Imaging for Lymph Node Staging of 130 Consecutive Patients with Intermediate to High Risk Prostate Cancer. The Journal of urology. 2016;195(5):1436-43.

[2] von Eyben FE, Picchio M, von Eyben R, Rhee H, Bauman G. (68)Ga-Labeled Prostate-specific Membrane Antigen Ligand Positron Emission Tomography/Computed Tomography for Prostate Cancer: A Systematic Review and Meta-analysis. Eur Urol Focus. 2018;4(5):686-93.

[3] Bauman G, Martin P, Thiessen JD, Taylor R, Moussa M, Gaed M, et al. [(18)F]-DCFPyL Positron Emission Tomography/Magnetic Resonance Imaging for Localization of Dominant Intraprostatic Foci: First Experience. Eur Urol Focus. 2018;4(5):702-6.

[4] Giesel FL, Hadaschik B, Cardinale J, Radtke J, Vinsensia M, Lehnert W, et al. F-18 labelled PSMA-1007: biodistribution, radiation dosimetry and histopathological validation of tumor lesions in prostate cancer patients. European journal of nuclear medicine and molecular imaging. 2017;44(4):678-88.

[5] Udovicich C, Perera M, Hofman MS, Siva S, Del Rio A, Murphy DG, et al. (68)Ga-prostate-specific membrane antigen-positron emission tomography/computed tomography in advanced prostate cancer: Current state and future trends. Prostate Int. 2017;5(4):125-9.

[6] Yaxley JW, Raveenthiran S, Nouhaud FX, Samartunga H, Yaxley AJ, Coughlin G, et al. Outcomes of Primary Lymph Node Staging of Intermediate and High Risk Prostate Cancer with (68)Ga-PSMA Positron Emission Tomography/Computerized Tomography Compared to Histological Correlation of Pelvic Lymph Node Pathology. The Journal of urology. 2019;201(4):815-20.

[7] Kim SJ, Lee SW, Ha HK. Diagnostic Performance of Radiolabeled Prostate-Specific Membrane Antigen Positron Emission Tomography/Computed Tomography for Primary Lymph Node Staging in Newly Diagnosed Intermediate to High-Risk Prostate Cancer Patients: A Systematic Review and Meta-Analysis. Urologia internationalis. 2019;102(1):27-36.

[8] Gupta M, Choudhury PS, Rawal S, Goel HC, Singh A, Talwar V, et al. Risk stratification and staging in prostate cancer with prostatic specific membrane antigen PET/CTObjective: A one-stop-shop. Hell J Nucl Med. 2017;20 Suppl:156.

[9] Lin CY, Lee MT, Lin CL, Kao CH. Comparing the Staging/Restaging Performance of 68Ga-Labeled Prostate-Specific Membrane Antigen and 18F-Choline PET/CT in Prostate Cancer: A Systematic Review and Meta-analysis. Clinical nuclear medicine. 2019;44(5):365-76.

[10] Dyrberg E, Hendel HW, Huynh THV, Klausen TW, Logager VB, Madsen C, et al. (68)Ga-PSMA-PET/CT in comparison with (18)F-fluoride-PET/CT and whole-body MRI for the detection of bone metastases in patients with prostate cancer: a prospective diagnostic accuracy study. European radiology. 2019;29(3):1221-30.

[11] Hegemann NS, Wenter V, Spath S, Kusumo N, Li M, Bartenstein P, et al. Distribution of prostate nodes: a PET/CT-derived anatomic atlas of prostate cancer patients before and after surgical treatment. Radiation oncology. 2016;11:37.

[12] Wu SY, Boreta L, Shinohara K, Nguyen H, Gottschalk AR, Hsu IC, et al. Impact of Staging (68)Ga-PSMA-11 PET Scans on Radiation Treatment Plansin Patients With Prostate Cancer. Urology. 2019;125:154-62.

[13] Roach PJ, Francis R, Emmett L, Hsiao E, Kneebone A, Hruby G, et al. The Impact of (68)Ga-PSMA PET/CT on Management Intent in Prostate Cancer: Results of an Australian Prospective Multicenter Study. Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 2018;59(1):82-8.

[14] Soldatov A, von Klot CAJ, Walacides D, Derlin T, Bengel FM, Ross TL, et al. Patterns of Progression After (68)Ga-PSMA-Ligand PET/CT-Guided Radiation Therapy for Recurrent Prostate Cancer. International journal of radiation oncology, biology, physics. 2019;103(1):95-104.

[15] De Bari B, Mazzola R, Aiello D, Aloi D, Gatta R, Corradini S, et al. ((68)Ga)-PSMA-PET/CT for the detection of postoperative prostate cancer recurrence: Possible implications on treatment volumes for radiation therapy. Cancer radiotherapie : journal de la Societe francaise de radiotherapie oncologique. 2019;23(3):194-200.

[16] Han S, Woo S, Kim YJ, Suh CH. Impact of (68)Ga-PSMA PET on the Management of Patients with Prostate Cancer: A Systematic Review and Meta-analysis. European urology. 2018;74(2):179-90.

[17] Perera M, Papa N, Roberts M, Williams M, Udovicich C, Vela I, et al. Gallium-68 Prostate-specific Membrane Antigen Positron Emission Tomography in Advanced Prostate Cancer-Updated Diagnostic Utility, Sensitivity, Specificity, and Distribution of Prostate-specific Membrane Antigen-avid Lesions: A Systematic Review and Meta-analysis. European urology. 2019.

[18] Afshar-Oromieh A, Zechmann CM, Malcher A, Eder M, Eisenhut M, Linhart HG, et al. Comparison of PET imaging with a (68)Ga-labelled PSMA ligand and (18)F-choline-based PET/CT for the diagnosis of recurrent prostate cancer. European journal of nuclear medicine and molecular imaging. 2014;41(1):11-20.

[19] Bluemel C, Krebs M, Polat B, Linke F, Eiber M, Samnick S, et al. 68Ga-PSMA-PET/CT in Patients With Biochemical Prostate Cancer Recurrence and Negative 18F-Choline-PET/CT. Clinical nuclear medicine. 2016;41(7):515-21.

[20] Pfister D, Porres D, Heidenreich A, Heidegger I, Knuechel R, Steib F, et al. Detection of recurrent prostate cancer lesions before salvage lymphadenectomy is more accurate with (68)Ga-PSMA-HBED-CC than with (18)F-Fluoroethylcholine PET/CT. European journal of nuclear medicine and molecular imaging. 2016;43(8):1410-7.

[21] Rauscher I, Maurer T, Beer AJ, Graner FP, Haller B, Weirich G, et al. Value of 68Ga-PSMA HBED-CC PET for the Assessment of Lymph Node Metastases in Prostate Cancer Patients with Biochemical Recurrence: Comparison with Histopathology After Salvage Lymphadenectomy. Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 2016;57(11):1713-9.

[22] Perera M, Papa N, Christidis D, Wetherell D, Hofman MS, Murphy DG, et al. Sensitivity, Specificity, and Predictors of Positive 68Ga-Prostate-specific Membrane Antigen Positron Emission Tomography in Advanced Prostate Cancer: A Systematic Review and Meta-analysis. European urology. 2016;70(6):926-37.

[23] Pereira Mestre R, Treglia G, Ferrari M, Pascale M, Mazzara C, Azinwi NC, et al. Correlation between PSA kinetics and PSMA-PET in prostate cancer restaging: A meta-analysis. Eur J Clin Invest. 2019;49(3):e13063.

[24] Groheux D, Giacchetti S, Moretti J-L, Porcher R, Espié M, Lehmann-Che J, *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;38:426–35.

[25] Buck A, Schirrmeister H, Kühn T, Shen C, Kalker T, Kotzerke J, *et al.* FDG uptake in breast cancer: correlation with biological and clinical prognostic parameters. Eur. J. Nucl. Med. Mol. Imaging. 2002;29:1317–23.

[26] Bos R, van Der Hoeven JJM, van Der Wall E, van Der Groep P, van Diest PJ, Comans EFI, *et al.* Biologic correlates of (18)fluorodeoxyglucose uptake in human breast cancer measured by positron emission tomography. J. Clin. Oncol. 2002;20:379–87.

[27] Humbert O, Berriolo-Riedinger A, Cochet A, Gauthier M, Charon-Barra C, Guiu S, *et al.* Prognostic relevance at 5 years of the early monitoring of neoadjuvant chemotherapy using (18)F-FDG PET in luminal HER2-negative breast cancer. Eur. J. Nucl. Med. Mol. Imaging. 2014;41:416–27.

Compliance with Ethical Standards:

Funding: No funding has to be declare

Conflict of Interest: All authors's conflict of interest were checked independently by the French National Heath Authority (HAS) ad hoc commission and no conflict of interest of any authors has to be declare

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and

with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Acknowledgements

Reviewers

The list of reviewers is available in the thesaurus.

INCa and HAS project managers

MOROIS Sophie, Project manager in the Good Practices Department, INCa
DUPERRAY Marianne, Head of the Good Practices Department, INCa
DAHAN Muriel, Director of the Recommendations and Drugs Department, INCa
VERMEL Christine, Responsible for the quality mission and conformity of the expertise, INCa
LAURENCE Michel, Head of the Good Professional Practice Department, HAS