Cancer/Radiothérapie xxx (2018) xxx–xxx

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Review article

Role of FDG PET-CT in the treatment management of Hodgkin lymphoma

Place de la TEP-tomodensitométrie au fluorodésoxyglucose dans la prise en charge thérapeutique du lymphome de Hodgkin

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ARTICLE INFO

Article history:
Received 29 March 2018
Accepted 21 June 2018

Keywords:
PET-CT
Hodgkin lymphoma
Interim PET

ABSTRACT

Fluorodeoxyglucose (FDG) positons emission tomography (PET)-computed tomography (CT) is used in many ways at baseline and during the treatment of patients with Hodgkin lymphoma. Many properties of the technique are used in the different steps of patient's management. Initial staging with PET-CT is more accurate than conventional imaging and PET-CT also became the gold standard imaging at the end of treatment with a negative PET-CT mandatory for reaching a complete remission. Early assessment of response by PET-CT is one of the most powerful prognostic factors for progression-free survival of patients with localized and advanced stages and allows guiding treatment. Conversely, previous studies showed that there is no role of FDG PET-CT for the patient's follow-up.

Mots clés :
TEP-scanographie
Lymphome de Hogkin
Imagerie

RÉSUMÉ

La tomographie par émission de positrons (TEP)-tomodensitométrie au fluorodésoxyglucose est utilisée de différentes manières au moment du diagnostic et pendant le traitement des lymphomes de Hodgkin. Plusieurs particularités de la TEP sont utilisées à différentes étapes de la prise en charge des patients. Lors du bilan initial, la TEP-tomodensitométrie est plus performante que les techniques d'imageries conventionnelles, mais l'est aussi en fin de traitement, un examen normal étant indispensable pour affirmer l'obtention d'une rémission complète. L'évaluation précoce en cours de traitement est un des facteurs pronostiques les plus puissants pour la survie sans progression et pour guider le traitement dans les maladies localisées et disséminées. À l'inverse, la TEP-tomodensitométrie n'a pas de rôle dans le suivi des patients.

1. Introduction

Hodgkin lymphoma is certainly one of the best models of malignant tumour where tumour staging has played and still plays a key role for treatment decision in daily practice. At diagnosis, accurate disease extension is indispensable for choosing therapy and

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https://doi.org/10.1016/j.canrad.2018.06.001
1278-3218/

assess patients' prognosis. Staging requires describing the disease location, and gives at diagnosis a "baseline" picture, indispensable for therapy efficacy assessment. In clinical trials, staging procedures have to be standardized for direct comparison between trials particularly when new strategies or therapies are investigated. Hodgkin lymphoma staging has improved during the last decades since the Ann Arbor classification set up, with the Costwolds classification, which implemented computed tomography (CT) scan to the recent International Working Group (IWG), which introduced fluorodeoxyglucose (FDG)-positrons emission tomography (PET). The international recommendations for staging and response assessment of malignant lymphoma – the Lugano classification – were recently published along with revised recommendations for the use of imaging lymphoma [1,2]. These consensus papers recommend the routine use of FDG PET-CT for staging of Hodgkin lymphoma, which is FDG-avid in almost all cases [3].

At the end of treatment, PET-CT became the backbone of imaging tumour assessment and is mandatory for the classification of response. The uncertain complete response category no longer exists; if the residual lesion has no FDG uptake, the patient has to be considered in complete remission regardless of the residual mass size.

2. Role of PET-CT for the staging at diagnosis

PET scans are usually reported using visual assessment [4], noting the location of increased focal uptake in nodal and extra nodal sites which is distinguished from physiologic uptake and other patterns of disease with increased FDG uptake including infection and inflammation, according to the distribution and/or CT characteristics.

Recommendations

"Staging of FDG-avid lymphoma is recommended using visual assessment, with PET-CT images scaled to fixed SUV display and colour scale; focal uptake is sensitive for bone marrow involvement and may obviate need for biopsy" [1].

It appeared rapidly that FDG-PET has a high sensitivity for nodal staging and is clearly more sensitive than CT in detecting extra nodal including bone marrow, further improved by the introduction of integrated FDG PET-CT [5–11] (Table 1). However, the better sensitivity of PET-CT was not based on histological verification of the new lesions detected by PET-CT not recognized by conventional radiological modalities. In most of the studies, the diagnosis of Hodgkin lymphoma lesions was relied to the FDG uptake disappearance at the end of therapy and ultimately persistent disease control. Focal FDG uptake of nodal and extra nodal sites including spleen, liver, bone, thyroid, that is considered related to lymphoma, according to the distribution and/or CT characteristics.

Overall PET-CT assessment has an impact on initial staging leading to therapy modification in approximately 15% of the patients [9,12]. This modification of staging is usually associated with a more advanced disease for 10% to 30% of patients [8,10,11]. Disease is downstaged by PET-CT for 3% to 6% of the patients [8,11]. Improving staging ensures that fewer patients will be under-treated or over-treated.

Splenic involvement is best determined by PET-CT and may be characterized by homogenous splenomegaly, diffuse infiltration with military lesions, focal nodular lesions or a large solitary mass [13]. There is no agreement on whether single, multiple, or volumetric measurements should be used to measure spleen size or what cutoff to use for splenomegaly. The recommendation is to use a cutoff for splenomegaly of more than 13 cm [2]. Liver size by physical examination or CT scan is not a reliable measure of hepatic involvement by lymphoma. Similar to splenic involvement diffusely increased or focal uptake with or without focal or disseminated nodules supports liver involvement.

Recently published data have suggested that focal uptake in Hodgkin lymphoma using PET-CT accurately demonstrate bone marrow involvement [14–17]. Patients with early stage disease have rarely a bone marrow involvement in the absence of a suggestive PET finding. PET-CT has much higher sensitivity for bone marrow involvement than conventional bone marrow biopsy. Bone marrow biopsy is no longer indicated for Hodgkin lymphoma [2]. Diffuse increased uptake without abnormal focal uptake often represents reactive hyperplasia and should not be confused with lymphoma involvement [14].

The CT part of a PET-CT scan may be performed without contrast using a lower radiation dose. Lower dose CT is used to correct for the attenuation of radioactivity within the patient and to localize abnormalities seen on PET, with less radiation than a full diagnosis examination. CT must be acquired during shallow breathing or end of expiration to avoid misregistration and artifacts [1].

The international guidelines concluded that contrast-enhanced CT had limited application, as it rarely altered staging (although it may identify additional findings) [2]. Contrast-enhanced CT may be required if accurate nodal measurement is needed like in clinical trials, but performed after the PET-CT acquisition, and if necessary, to more accurately distinguished bowel from lymphadenopathy; but also in the setting of compression/thrombosis of central/mediastinal vessels. Low-dose unenhanced CT might suffice afterward, depending on the results of the baseline examination.

The use of contrast when performing PET-CT may result in small errors in the measurement of FDG uptake due to an effect on attenuation correction, this may cause errors in comparison of uptake between tumour and reference sites by causing FDG uptake to be overestimate in the mediastinum and liver by 10 to 15%. Although these errors are unlikely to be clinically important for staging purposes, they may be important for response assessment during and after treatment [18,19].

Assessing tumour bulk remains an important objective in Hodgkin lymphoma [20,21]. Bulk disease at baseline assessed by CT scan was shown to have a prognosis impact in HL [22–24] but remained difficult to implement in clinical practice. Quantifying the volume rather than the single largest diameter of the mass probably gives a more relevant estimation of tumour burden for prognostic purposes, particularly in advanced Hodgkin lymphoma. Total metabolic tumour volume assessed on the baseline FDG-PET is a novel approach of tumour burden measurement. The better sensitivity of PET compared with CT in staging highly FDG-avid tumours may improve tumour burden assessment. Baseline metabolic tumour volume was shown to influence the outcome of patients with diffuse large B cell lymphoma [25,26].

Kanoun et al. showed in a retrospective series that bulky tumours (larger than 10 cm) were associated with lower survival rate in progression-free survival analysis ($P < 0.04$) but not in freedom from treatment failure analysis ($P = 0.09$) while that metabolic tumour volume was more predictive of patient outcomes in progression-free survival analysis ($P = 0.001$) and also associated in freedom from treatment failure analysis ($P = 0.0015$) [27]. In addition, the combination of metabolic tumour volume with the early chemosensitivity assessed using interim PET2 response identifies three subsets of patients with different prognosis. Patients with low baseline metabolic tumour volume and complete response at interim PET2 had shown a very good prognosis that could be compared to early stage (4-year progression-free survival: 92%) whereas a high metabolic tumour volume and incomplete response at interim PET2 allows an early identification of patients with a very

Please cite this article in press as: Berriolo-Riedinger A, et al. Role of FDG PET-CT in the treatment management of Hodgkin lymphoma. Cancer Radiother (2018), https://doi.org/10.1016/j.canrad.2018.06.001