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Nuclear Medicine and Hematology

BQ 91 Is FDG-PET recommended to stage malignant lymphoma and diagnose its recurrence?

Statement

PET is recommended for staging highly FDG-avid malignant lymphoma tissue types. Screening for recurrence with FDG-PET is recommended when recurrence is suspected based on evidence such as clinical symptoms and laboratory test findings.

Background

A characteristic of malignant lymphoma is that it occurs throughout the body. Determining the extent of malignant lymphoma lesions and staging them is necessary to determine a treatment strategy and prognosis. Previously, ^{68}-Ga scintigraphy was used for detailed examinations of the whole body. In recent years, however, it has been replaced by ^{18}F-FDG-PET, which is superior both in sensitivity and specificity. Moreover, with the development of and advances in CT and fusion PET/CT systems, diagnostic accuracy has improved dramatically, and ^{18}F-FDG-PET/CT examinations ("FDG-PET" below) have come into mainstream use. FDG-PET is used to evaluate treatment efficacy in many histologic subtypes of malignant lymphoma, and staging by PET also plays a role as a pretreatment evaluation.

Explanations

Malignant lymphoma is classified as Hodgkin lymphoma and non-Hodgkin lymphoma, and non-Hodgkin lymphoma is further classified as low-, intermediate-, and high-grade lymphoma. To stage malignant lymphoma, the Ann Arbor classification system is used. The system emphasizes involvement of both the upper and lower sides of the diaphragm and extranodal involvement.

Malignant lymphoma shows a wide range of FDG uptake depending on the tissue type. Hodgkin lymphoma and intermediate- and high-grade lymphomas show high FDG uptake. Consequently, the detection performance of PET for nodal and extranodal lesions is high in these types of lymphomas.[1)] In malignant lymphomas with high FDG uptake, PET sensitivity was found to be ≥ 90%, and the stage was changed as a result of PET in 10% to 30% of patients.[2, 3)] In a study that compared PET/CT and contrast-enhanced CT, sensitivity for nodal lesions was 94% and 88%, respectively, and specificity was 100% and 86%, respectively. Sensitivity for extranodal lesions was 88% and 50%, respectively, and specificity was 100% and 90%, respectively.[4)]

The Lugano classification (2014), a revised version of the Ann Arbor classification, was created at the 2014 International Conference on Malignant Lymphoma.[5)] Under the Lugano classification system (2014), staging is performed by PET before treatment if PET is used to assess treatment efficacy in malignant lymphoma with high FDG uptake. It was found that, because PET provides high performance in detecting

bone marrow infiltration in Hodgkin lymphoma and diffuse large B-cell lymphoma, bone marrow biopsy can be omitted if FDG-PET is performed.[6)]

The usefulness of PET in staging tissue types with low FDG avidity (chronic lymphocytic leukemia/small lymphocytic lymphoma, lymphoplasmacytoid lymphoma, mycosis fungoides, nodal marginal zone B-cell) is not well defined. PET is therefore not recommended for these tissue types, and their staging is performed using contrast-enhanced CT.[6)] Evaluation by MRI is recommended in primary lymphoma of the central nervous system.[5)] In primary gastrointestinal malignant lymphoma, the main lesions are extranodal lesions. Consequently, they often diverge from the Ann Arbor classification, and a classification for primary gastrointestinal malignant lymphoma, established at the International Conference on Malignant Lymphoma, is used in addition to the Ann Arbor classification.

For the posttreatment follow-up and evaluation of malignant lymphoma, determinations are made clinically by appropriate history-taking, physical findings, blood counts, biochemical test results, and imaging examinations. In 50% to 80% of patients who show clinical signs during posttreatment follow-up, the signs are associated with recurrence.[7)] Approximately 80% of recurrence takes place at sites where the lesions were initially located.[6)] It is thought that many facilities perform CT as an imaging examination to screen for the recurrence of malignant lymphoma. However, there is no evidence that periodic imaging examinations, including FDG-PET, are useful for this purpose, and they are not recommended.[8-10)]

Periodic screening for recurrence with FDG-PET has a false-positive rate of > 20%, resulting in unnecessary tests and biopsies and patient anxiety. FDG-PET should be performed if recurrence is suspected based on factors such as clinical symptoms and test findings.

Search keywords and secondary sources used as references

In relation to malignant lymphoma staging, PubMed was searched using the following keywords: malignant lymphoma, FDG PET, and staging. In relation to diagnosing malignant lymphoma recurrence, PubMed was searched using the following keywords: malignant lymphoma, FDG PET, relapse, and surveillance.

In addition, the following were referenced as secondary sources.

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BQ 92 Is FDG-PET recommended to assess treatment efficacy for malignant lymphoma?

Statement

The use of FDG-PET to assess treatment efficacy when treatment is completed is recommended for malignant lymphomas of FDG-avid tissue types (e.g., diffuse large B-cell lymphoma, follicular lymphoma, Hodgkin lymphoma).

Background

Chemotherapy is the main treatment selected for malignant lymphoma, with surgery, radiation therapy, and radioimmunotherapy performed according to the circumstances. FDG-PET, which is considered excellent for evaluating lesion activity, is used to assess treatment efficacy, and a consensus on its usefulness has been published based on the accumulated data.[1, 2)]

Explanation

In assessing treatment efficacy for malignant lymphoma, ^{68}-Ga scintigraphy was previously used to evaluate lesion activity, in addition to the use of CT to observe the size of the lesion. FDG-PET (PET/CT) began to be used instead of ^{68}-Ga scintigraphy in the early 2000s, and numerous reports regarding its usefulness were published. The role of FDG-PET in treatment efficacy assessment was clarified by the International Harmonization Project Criteria, which were compiled by Cheson et al. in 2007. PET has since come to play a central role in assessing the efficacy of malignant lymphoma treatment. Various investigations were subsequently conducted,[1-7)] and the Lugano classification, a revised version of the 2007 criteria, was published in 2014.

The Lugano classification involves visual assessment on a 5-point scale. If FDG uptake in the area of the lesion is equal to or lower than that in the liver (score, ≤ 3), there is considered to be no active lesion (negative) in malignant lymphoma with standard therapy. This visual assessment is widely used at present. The 2007 criteria specified the mediastinal blood pool as background. However, due to the large number of posttreatment false positives, the criteria were modified after an international conference in 2009.[5, 6, 8-11)] In malignant lymphoma of FDG-avid tissue types (i.e., many lymphomas, such as diffuse large B-cell lymphoma, follicular lymphoma, Hodgkin lymphoma), this classification is used to assess treatment efficacy at treatment completion. However, if no FDG uptake is seen before treatment, CT is used to assess treatment efficacy.[2)] Efficacy assessment using a quantitative index such as the standardized uptake value (SUV) supplements visual assessment. However, it is not necessarily required because the accumulated data are still insufficient, and there is large variability between systems and facilities.

In view of factors such as inflammation associated with treatment, treatment efficacy should be assessed at least 3 weeks after treatment completion and, ideally, 6 to 8 weeks after completion and beyond. Immune

checkpoint inhibitors have also been used to treat malignant lymphoma in recent years. However, because of the pronounced inflammatory response associated with the treatment, caution is needed with respect to false positives. If the progressive metabolic disease assessment is indeterminate with the Lugano classification, retesting is performed after 12 weeks.[12)]

Particularly in Europe, several investigations have recently been conducted on interim PET, whereby the treatment response is assessed early after the start of treatment, often after 2 cycles of chemotherapy, using FDG-PET's sensitivity to lesion activity. Interim PET determines the subsequent treatment strategy. Although there have been reports regarding the usefulness of this approach, no consistent assessment has been established, and it should not be adopted for routine clinical practice. In diffuse large B-cell lymphoma, a negative interim PET finding may indicate a good prognosis, but a positive finding does not necessarily suggest a poor prognosis.[9)] In advanced-stage Hodgkin lymphoma, on the other hand, negative and positive interim PET findings have both been found to be useful for determining the prognosis.[13)] A clinical study of the advisability of using the results of interim PET for treatment intervention is currently underway.

Search keywords and secondary sources used as references

PubMed was searched using the following keywords: lymphoma, PET, and response.

In addition, the following were referenced as secondary sources.

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CQ 23 Is the addition of FDG-PET/CT or PET recommended to evaluate the activity of multiple myeloma (MM) after treatment?

Recommendation

The addition of FDG-PET/CT or PET is weakly recommended to evaluate the activity of MM after treatment.

Recommendation strength: 2, strength of evidence: weak (C), agreement rate: 100% (8/8)

Background

In MM, the presence or absence and number of lesions seen on MRI are prognostic factors. Consequently, whole-body or total spinal/pelvic MRI has become the gold standard for the imaging evaluation of MM. Several studies that compared performance in detecting bone lesions in newly diagnosed MM (NDMM) showed the detection performance of MRI to be superior to that of modalities such as whole-body CT, plain radiography, bone scintigraphy, and FDG-PET/CT.[1)] In previously treated MM (PTMM), FDG-PET/CT has been found to be useful for predicting prognosis,[2)] evaluating minimal residual disease (MRD), and evaluating extraosseous lesions.[3)] However, few controlled studies have examined whether the addition of FDG-PET/CT or PET to MRI, the usual test, is effective in PTMM. Consequently, although MRI is generally used for the follow-up of PTMM in Japan, there is insufficient evidence that it improves the patients' prognosis and quality of life (QOL).

Explanation

A literature search was conducted for this CQ and, after the primary and secondary screenings, a qualitative systematic review of 5 cohort study articles[3-8)] and 1 case series study article[9)] was performed. An active lesion detection index was calculated as the diagnostic odds ratio (DOR) when MRI alone was used to evaluate active lesions in PTMM and when FDG-PET/CT or PET was added. The pooled value was 5.98 (95% CI, 2.99 to 12.0; $p < 0.001$), indicating that the DOR was significantly higher with the addition of FDG-PET/CT or PET and that the addition is useful for evaluating active MM lesions after treatment.[10)]

Points common to each of the reports were that pretreatment abnormal signals were prolonged, and that there was an overwhelmingly high number of false positives in MRI. Evaluating metabolic changes with FDG-PET/CT or PET enabled treatment efficacy and recurrent lesions to be evaluated more accurately. However, because FDG-PET/CT and PET involve radiation exposure, although at low levels, they cannot be performed for every evaluation in all patients with PTMM. No reports examining the risks and benefits of such evaluations were found in the searched literature, and this remains a topic to be addressed in the future.

Although MRI is used to evaluate PTMM bone lesions in Japan, the background described above indicates that the addition of FDG-PET/CT or PET enables treatment efficacy and recurrence to be assessed more accurately. Consequently, their use can be considered.

Search keywords and secondary sources used as references

PubMed was searched using the following keywords: multiple myeloma, previously treated multiple myeloma, FDG PET, and MRI.

In addition, the following were referenced as secondary sources.

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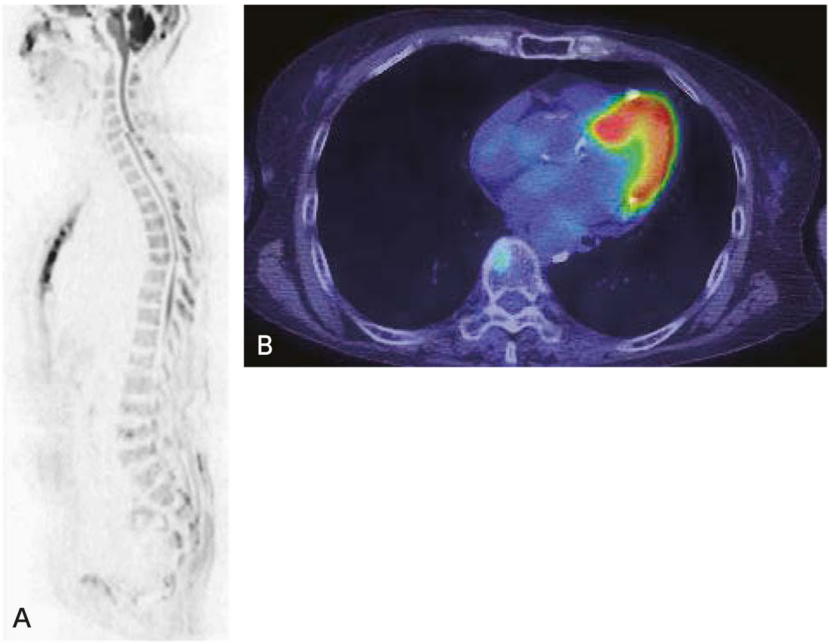

Figure. Evaluation of MM activity after treatment with FDG-PET/CT

The patient was a woman in her 60s. She had previously been treated for secretory multiple myeloma. A detailed examination was performed due to an elevated level of M protein in the blood.
A: FDG-PET/CT: There are no abnormal findings, and no abnormal signal is seen in the bone marrow of the vertebral bodies.
B: FDG-PET/CT fusion image: Abnormal uptake is seen in the 9th thoracic vertebra, indicating a recurrent lesion.

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