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REVIEW

Lymphoma: imaging in the evaluation of residual masses

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Abstract

In the management of patients with lymphoma, imaging is essential not only for diagnosis but also to define prognosis and treatment by staging. Imaging is also used to assess the response to treatment that may affect the treatment strategy: new chemotherapeutic drug combinations and autologous stem cell transplantation. These different therapies have increased the need for higher accuracy to assess the response to treatment. Standardised imaging response criteria must be well known by radiologists involved in the management of patients with lymphoma. Criteria are mainly volumetric, and are obtained from CT scans. Functional imaging techniques have been shown to provide better information on the viability of residual masses than does CT assessment of size changes.

CT remains the main imaging technique to assess response to treatment based on volumetric international criteria. New functional imaging tools evaluating perfusion (CT and MRI), and particularly glucose uptake (PET), will probably play an important role in bringing additional information on the metabolism of lymphomatous masses.

Keywords: *lymphoma; MR; CT; tissue characterisation; residual mass.*

Introduction

Lymphomas encompass a spectrum of diseases among which Hodgkin's disease (HD) is distinct from non-Hodgkin lymphomas (NHL). The pathological classification of HD is well known. The nodular sclerosis subtype is the most common, occurring in up to three-quarters of all cases. The pathological classification of NHL is more complex. The revised European and American lymphoma (REAL) and World Health Organisation (WHO) classifications are widely accepted[1,2]. The histological subtypes include low, intermediate, and high-grade NHL. Low-grade or so-called indolent NHL have a prolonged clinical course but cure is usually not achieved unless the disease is strictly localised. By contrast, aggressive lymphoma, i.e. high and intermediate grade NHL, is often a rapidly progressive disease characterised by high proliferation rates. Treatment of aggressive NHL with combination chemotherapy results in long-term cure in a proportion of patients.

Prognostic indices have been devised with the aim of identifying patients at risk of disease progression. At diagnosis, three main factors have been shown to adversely affect prognosis including the performance status, the serum lactate deshydrogenase level, and particularly the Ann Arbor stage reflecting the anatomic extent of the disease[3]. A bulky mass, larger than 10 cm in diameter, may also confer an increased risk of disease progression. These prognostic factors are useful to ensure comparable patient groups among clinical trials and acquisition of similar data. Using these factors, the most appropriate therapeutic strategies can be applied for each patient.

Imaging is, then, essential not only for diagnosis but also to define prognosis and treatment by staging. Imaging is also used to assess the response to treatment that may affect the treatment strategy: new chemotherapeutic drug combinations and autologous stem cell transplantation. These different therapies have increased the need for higher accuracy to assess the response to

treatment[4]. Standardised imaging response criteria are, then, essential when serial CT assessments are performed during and after treatment[4]. These criteria must be well known by radiologists involved in the management of patients with lymphoma.

Radiological response to treatment

CT scans (thorax, abdomen, pelvis) remain the standard for the volumetric evaluation of nodal disease even if those areas were not initially involved because of the unpredictable pattern of recurrence in NHL[4].

(i) Complete Response (CR) requires that (a) all lymph nodes must have regressed to normal size (<1.5 cm in their greatest diameter); (b) the spleen must have regressed to normal size and (c) any nodules in the spleen, liver or kidneys should no longer be present.

(ii) CR/unconfirmed (CRu) requires a residual lymph node mass greater than 1.5 cm in greatest transverse diameter that has regressed by more than 75% in the products of the greatest diameters (perpendicular).

(iii) In partial response (PR) there must be (a) at least a 50% decrease in the sum of the products of the greatest diameters of the six largest nodal masses; (b) a regression of at least 50% in the sum of the products of the greatest diameters of splenic and hepatic nodules; (c) no increase in the size of the other nodes, liver or spleen and (d) no new sites of disease.

(iv) Stable disease is defined as less than PR but is not progressive disease

(v) Progressive disease (PR, non-responders) requires (a) at least a 50% increase in the sum of the products of the greatest diameters and (b) the appearance of any new lesion.

(vi) Relapsed disease occurring after a CR or CRu requires (a) at least a 50% increase in the sum of the products of the greatest diameters (compared to CR or CRu) and (b) the appearance of any new lesion.

Radiological follow-up

The manner in which patients are observed after treatment may differ between different centres and clinical trials. A number of imaging studies are often performed on a routine basis after every few courses of treatment and every few months thereafter. After induction treatment, CR and CRu must be differentiated from other situations in order to adapt the therapeutic strategy. Therefore, CT must always be performed during treatment, after the induction phase and after the completion of treatment[4]. The timing of further follow-up imaging studies was a topic of controversy when patients achieved CR or CRu. Some studies assessed the role of imaging screening for relapse. Only two of 36 relapses in aggressive NHL were detected before symptoms were reported[5]. In our institution, after complete remission is achieved, we perform CT every six months during the first two years and then every year for three years. Using this protocol, CT diagnosed pre-clinical relapse in seven of 18 relapsing patients with HD[6]. It is recommended that screening studies should not be site-specific and that the frequency of CT should be determined by the patient's risk of relapse and whether there is a potentially curative salvage therapy. However, whether or not these conclusions are relevant to patients with follicular lymphoma remains to be studied.

Additional Studies for Evaluation

A number of additional imaging techniques have been proposed to evaluate response to treatment. 'Functional' imaging techniques include CT measurement of perfusion, MR imaging, Gallium and more recently 18 fluorodeoxyglycose (18F-FDG) PET scan. All these techniques have been shown to provide better information on the viability of residual masses than does CT assessment of size changes.

Lymph nodes

It is well known that tumours require a capillary network to grow and survive. Ribatti *et al.* have shown that the micro-vessel number was low in benign lymphadenopathies, and increased in NHL[7]. Aggressive NHL showed the highest count. With treatment of lymphoma and cell death in the mass, there is induction of inflammation, with subsequent fibrous tissue and destruction of the existing capillary network. This should be visible by a reduction in the perfusion and permeability of the mass over time. Dugdale *et al.* recently showed that perfusion measurements from dynamic contrast-enhanced CT were higher in patients with active residual masses and aggressive NHL[8]. Low perfusion measurements implied inactive disease. CT perfusion measurements of nodes have potential for assessing lymphoma grade, activity, and treatment response.

The signal intensity of lymphoma in MR imaging changes during the course of the disease. The theoretical basis of signal changes is that (a) active, untreated tumour tissue contains an excess of free water, increasing the T2 signal intensity and (b) with successful treatment, cellular elements and the water-content of the tumour are reduced, while the collagen and fibrotic stroma of

the original tumour become the main component of the signal. These factors reduce the T2 signal intensity of the residual mass. Active versus inactive residual masses can be identified on the basis of signal intensity patterns, as determined by optical reference to muscle and fat on T1 and T2-weighted images. The sensitivity of MR imaging for predicting relapse in a residual mass ranges from 45% to 90% with a specificity of 80% to 90% in the different studies. Active tumour foci may be found within a residual mass with a low T2 signal intensity. Necrosis, immature fibrotic tissue, edema and inflammation associated with responding disease can simulate the high signal intensity of a viable tumour, particularly within the first six months after therapy. At diagnosis, gadolinium enhancement of lymphomatous masses of the mediastinum is very different among patients; it falls after treatment in patients in continuous complete remission, but not in patients who relapse. MR evaluation of residual lymphomatous masses requires a pre-treatment baseline MR study for comparison, and can be done not only with T2-weighted images but also with gadolinium-enhanced sequences[9].

The mechanism of localisation of Gallium-67 citrate in tumours is complex. Larson *et al*. propose a mechanism in which the gallium ion after injection binds to plasma transferrin and is then transported across the cell membrane to the lysosomes[10]. Therefore several local factors, such as vascularity and ion exchange through membrane pores, can contribute to the uptake of the gallium ion by the malignant cell. Gallium-67 scintigraphy has played an important role in monitoring follow-up of patients; however the sensitivity of 67Ga scintigraphy depends on the subtype of lymphoma and the size and location of the disease. 67Ga scintigraphy is valid for thoracic examination. No gallium uptake can be seen in about 20% of lymphomatous masses at diagnosis depending on tumour avidity and technique of scanning[11,12]. The best results have been reported from groups that used single-photon emission tomography (SPECT). Studies comparing MR and gallium imaging showed no superiority of the latter in predicting relapses.

Increased glycolysis, a biochemical feature of malignant cells, explains ^{18}F-fluorodeoxyglucose (^{18}F-FDG) uptake by lymphomatous masses in positron emission tomography (PET). This complex technique offers at least equivalent results to CT for detecting lymphoma during initial staging[13,14]. It may also identify patients requiring intensification after completion of chemotherapy[15]. Promising results have also recently been obtained in the detection of residual disease. False-positive and rare false-negative cases have been reported. The main advantage of PET is the imaging of almost the entire body.

Bone marrow

Both MR imaging and 18F-FDG PET improve the detection of bone marrow involvement. They can also be used to assess the response to treatment, particularly using dynamic gadolinium-enhanced MR imaging.

Conclusion

In conclusion, CT remains the main imaging technique for assessing response to treatment based on volumetric international criteria. New functional imaging tools evaluating perfusion (CT and MRI) and particularly glucose uptake (PET) will probably play an important role in bringing additional information on the metabolism of lymphomatous masses.

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