Eur Radiol (2018) 28:1187–1193
DOI 10.1007/s00330-017-5071-x

ONCOLOGY

Whole body magnetic resonance in indolent lymphomas under watchful waiting: The time is now

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Received: 29 April 2017 / Revised: 26 July 2017 / Accepted: 11 September 2017 / Published online: 10 October 2017

Abstract

The indolent non-Hodgkin lymphomas (i-NHLs) are characterised by 'indolent' clinical behaviour with slow growth and prolonged natural history. The watchful waiting (WW) strategy is a frequently employed treatment option in these patients. This implies a strict monitoring by imaging examinations, including 18F-fluorodeoxyglucose-positron emission tomography/computed tomography (18F-FDG-PET/CT) and CT. A major concern is radiation exposure due to regularly monitoring by conventional imaging procedures. Several studies have demonstrated the reliability of whole-body magnetic resonance imaging (WB-MRI) for lymphoma staging. WB-MRI could be useful for active surveillance in i-NHLs providing the suspect of disease progression that can be then confirmed by additional diagnostic procedures, including 18F-FDG-PET/CT. The directive 2013/59 by the European Union claims that if a radiation-free imaging technique allows obtaining the same diagnostic results, it should be invariably used. In this setting, WB-MRI may be considered a reasonable option in i-NHLs under WW, replacing imaging modalities that cause exposure to ionising radiations. This will help to reduce the cancer risk in i-NHL patients for whom chemo-/radiotherapy remain the usual treatment options following the usually long WW phase. The scientific community should raise the awareness of the risk of ionising radiations in i-NHLs and the emphasise the need for establishing the proper place of WB-MRI in lymphoma imaging.

Key Points

- *Watchful waiting is a reasonable option in patients with indolent non-Hodgkin lymphomas.*
- *Imaging is crucial to monitor patients with indolent non-Hodgkin lymphomas.*
- *CT and ^{18}F-FDG-PET/CT are commonly used, implying a substantial radiation exposure.*
- *WB-MRI is highly reliable in lymphoma staging.*
- *WB-MRI may be considered to monitor indolent non-Hodgkin lymphomas under watchful waiting.*

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Keywords Magnetic resonance imaging · Whole body imaging · Ionising radiation · Lymphoma · Watchful waiting

Abbreviations

^{18}F-FDG-PET/CT	^{18}F-fluorodeoxyglucose-positron emission tomography/computed tomography
FL	Follicular lymphoma
i-NHL	Indolent non-Hodgkin's lymphoma
LL	Lymphoplasmacytic lymphoma
MCL	Mantle cell lymphomas
MZL	Marginal zone lymphoma
SLL	Small lymphocytic lymphoma
WB-MRI	Whole body magnetic resonance imaging
WW	Watchful waiting

Introduction

Indolent non-Hodgkin's lymphomas (i-NHLs) are mainly characterised by 'indolent' clinical behaviour with slow growth, prolonged natural history, and lack of clinical symptoms [1]. Patients with i-NHLs are often actively monitored using blood tests, clinical examination, and imaging follow-up, rather than immediately treated. This watchful waiting (WW) strategy enables therapies to be delayed until they are really needed. Armitage and Longo suggested that asymptomatic clinical picture, no lymphomatous involvement in dangerous sites, and patient's desire to delay the treatment are the key factors that should encourage the clinician to consider WW as a treatment option [2].

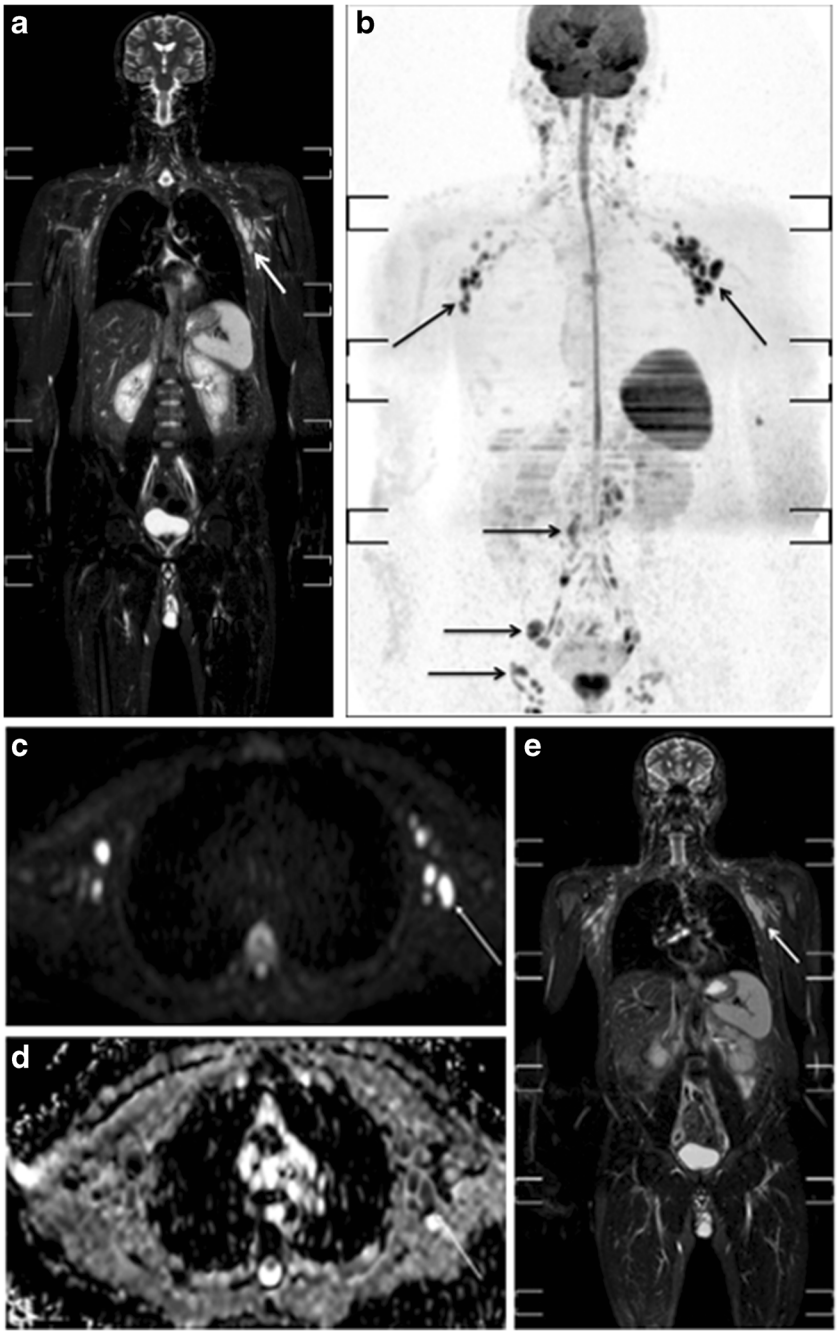

Fig. 1 A 50-year-old man with non-Hodgkin's follicular lymphoma. At the time of diagnosis, coronal T2w-STIR (**a**), MIP grey-scale inverted diffusion-weighted imaging (DWI) (**b**), axial high b-value DWI (**c**) and ADC map (**d**) showed multiple pathological lymph nodes (arrows) in supradiaphragmatic and subdiaphragmatic regions. After 6 months under watchful waiting, coronal T2w-STIR (**e**), MIP grey-scale inverted DWI (**f**), axial high b-value DWI (**g**) and ADC map (**h**) showed a slight increase of lymph nodes (arrows), especially in the left axillary region. The patient was asymptomatic with a low tumour burden and is still under watchful waiting

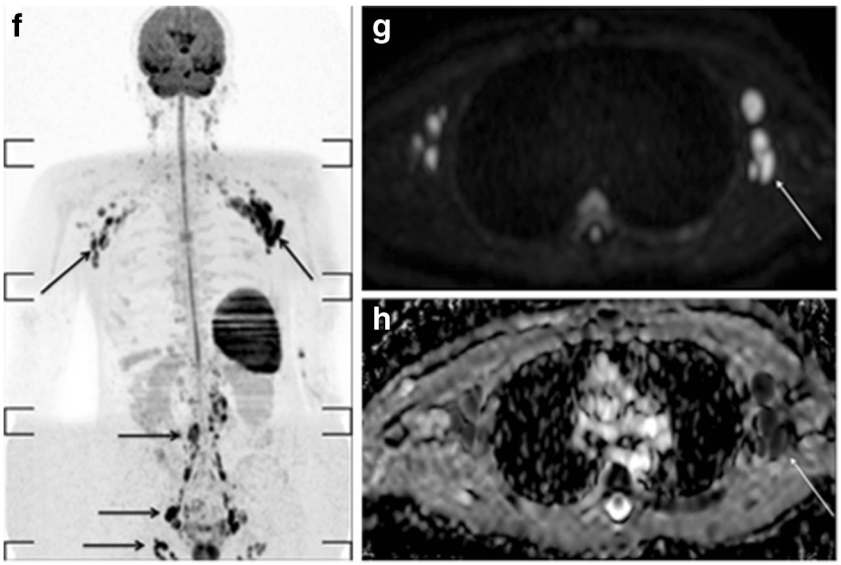

Fig. 1 continued.

The most common i-NHL subtypes include follicular lymphoma (FL), marginal zone lymphoma (MZL), lymphoplasmacytic lymphoma (LL), small lymphocytic lymphoma (SLL), and a small subset of mantle cell lymphoma (MCL). FL is the second most common NHL following diffuse large-B-cell lymphoma, representing more than 20 % of NHLs. Taken together, all i-NHLs have a high incidence, close to that of the most frequent diffuse large-B-cell lymphoma subtype [2].

The watchful waiting (WW) strategy in indolent non-Hodgkin's lymphoma (i-NHL)

Previous studies have not demonstrated an increased overall survival rate with active treatment over WW in asymptomatic patients with low-grade FL, making WW a reasonable treatment approach in the immunochemotherapy era [3]. The Italian Society of Haematology, the Italian Society of Experimental Haematology, and the Italian Bone Marrow Transplantation Group have published guidelines for the management of both follicular and non-follicular i-NHL patients [4, 5], suggesting WW as a valuable initial option especially in asymptomatic patients with FL stage II–IV and low tumour burden [4]. Similar to FL, asymptomatic patients with splenic MZL are commonly monitored without any treatment since WW does not compromise survival [6]; nevertheless, patients should be treated if they are symptomatic or have bulky disease or cytopenia [7]. Some MALT lymphoma patients can be monitored with WW as well, without significantly modifying survival rates [8]. The WW strategy can also be pursued with good results in some ocular, adnexal, and pulmonary MALT lymphomas [9, 10]. The LL patients may be treated with several approaches, including WW in those who are asymptomatic with low tumour burden [11]. In patients with SLL, a WW strategy is indicated as an initial approach, with treatment considered only for patients with disease-related symptoms or progressive or advanced stage disease [12]. A small subset of MCL, identified by lack of SOX11 expression, is associated with indolent behaviour and favorable prognosis with no need for immediate treatment, compared to the common SOX11+MCL [13]. These patients are generally asymptomatic, with a normal serum lactate dehydrogenase level and no lymphadenopathies. Again, these patients may be monitored through periodical clinical and radiological examinations, even delaying treatment for several years [14].

Imaging monitoring and WW

Imaging evaluation is crucial for monitoring patients with i-NHL under WW, for surveillance purposes of their variable risk of disease progression. ^{18}F-fluorodeoxyglucose-positron emission tomography/computed tomography (^{18}F-FDG-PET/CT) is the standard imaging modality for FDG-avid lymphoma staging, whereas CT is recommended for non-FDG-avid histotypes and is commonly used for monitoring and imaging follow-up [15]. Thus, ^{18}F-FDG-PET/CT is widely applied in FL for staging and end-of-treatment assessment, while it is not recommended in other i-NHL subtypes. Ultrasound is also used to follow i-NHLs as a cheap, safe, and effective diagnostic tool that does not involve ionising radiations. However, ultrasound may be less reproducible compared to other imaging modalities, it has reduced accuracy on retroperitoneum evaluation due to possible overlaying fat or bowel gas, and it is unable to investigate either the mediastinum or the bones. In addition, it is noteworthy that novel and effective, though very expensive, drugs such as immunomodulatory agents and

checkpoint inhibitors, are under development for patients with lymphoma. Despite the documented clinical efficacy, conventional imaging evaluation procedures are often inadequate for clearly detecting disease during treatment with these novel targeted drugs [16]. Indeed, continued revision of response criteria, along with a definition of precise imaging timepoints, is urged [16]. Thus, guidelines on imaging examinations should be updated for the monitoring of i-NHL patients undergoing both WW and treatment with novel targeted drugs.

A major concern regarding the follow-up of lymphoma patients through CT is the possible association of several scans with increased cancer risk. Brenner and Hall argued that up to 2 % of cancers can be related to radiation exposure associated with CT examinations [17]. Previous studies reported an increased secondary cancer risk due to surveillance CT scans in patients with NHL [18, 19]. As regards to the use of ^{18}F-FDG-PET/CT, it is well known that involves exposure to a substantial dose of ionising radiations, again with increasing cancer risk [20]. However, ^{18}F-FDG-PET/CT has a crucial role in FL management. ^{18}F-FDG-PET/CT is highly sensitive for disease staging in FL, allowing better identification of nodal and extra-nodal disease locations in comparison with CT [21].

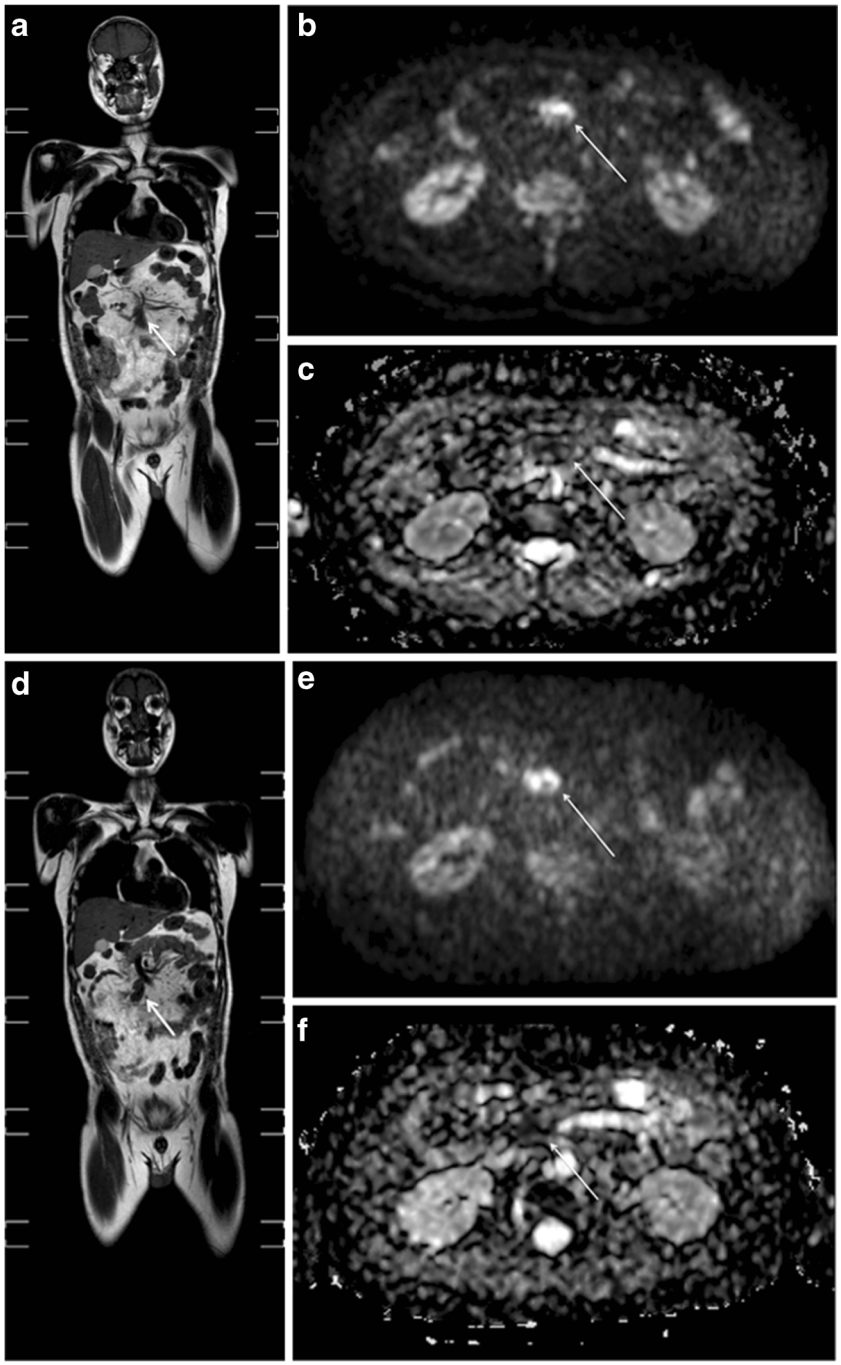

Fig. 2 A 37-year-old man with non-Hodgkin's follicular lymphoma. At the time of diagnosis, coronal T1w (**a**), axial high b-value diffusion-weighted imaging (DWI) (**b**) and ADC map (**c**) showed a pathological mesenteric lymph node (arrow). After 6 months under watchful waiting, the lymph node did not show any change in size as demonstrated by coronal T1w (**d**), axial high b-value DWI (**e**) and ADC map (**f**)

Moreover, it enables accurate detection of lymphoma transformation due to the significantly increased FDG uptake in histologically transformed areas [22]. Furthermore, it has to be stressed that, among all the i-NHL subtypes, FL has a higher risk of secondary tumours or transformation in a more aggressive lymphoma, most commonly diffuse large B-cell lymphoma [23].

The emerging role of whole-body magnetic resonance imaging for disease monitoring in NHL

Over the last years, several studies have demonstrated the good reliability of whole-body magnetic resonance imaging (WB-MRI) for lymphoma staging, mainly using ^{18}F-FDG-PET/CT as the reference standard [24–27]. WB-MRI enables avoiding radiation exposure and intravenous contrast agent administration, allowing the evaluation of all potential lymphomatous sites through morphological and functional sequences (Figs. 1 and 2) [28]. Indeed, while CT provides only morphological information regarding nodal and extra-nodal locations of disease, diffusion-weighted imaging allows the random motion of water molecules in biological structures to be investigated and allows easy identification of hypercellular tissues like lymphoma [29]. In addition, several studies have shown that WB-MRI equals or betters CT in lymphoma staging [30, 31], suggesting it be used in place of CT. Both WB-MRI and ^{18}F-FDG-PET/CT have been shown to be reliable tools for the detection of bone marrow involvement in patients with lymphoma [32, 33]. In this setting, both techniques seem to have distinct diagnostic accuracy in aggressive lymphomas, showing reduced sensitivity for the detection of low-volume bone marrow involvement in i-NHLs, where imaging modalities are complementary to bone marrow biopsy [32, 33]. In fact, bone marrow biopsy is still recommended in NHL [15], being essential for both diagnosis and evaluation of marrow cellularity and hematopoietic reserve [34–36], while it is no longer required for Hodgkin's lymphoma [15]. Finally, previous studies have shown the potential role of WB-MRI in the early detection of osteonecrotic lesions in lymphoma patients treated with high doses of corticosteroids, allowing prompt referral of these patients to orthopaedists and providing the opportunity for early intervention [37–39].

Of note, the directive 2013/59 by the European Union claims that if a radiation-free imaging technique enables the same diagnostic results to be obtained, it should always be used [40]. Based on this recommendation, WB-MRI should be considered as a reasonable option in i-NHLs under WW. When possible, WB-MRI may replace those imaging modalities that involve exposure to ionising radiations, allowing the cancer risk in patients who will ultimately receive chemo- and radiotherapy following the usually long WW phase to be reduced. Although WB-MRI has demonstrated similar diagnostic accuracy to ^{18}F-FDG-PET/CT in aggressive lymphomas, the latter imaging modality is well and widely standardized, and WB-MRI will probably have a complementary role in these patients.

However, WB-MRI could be an ideal diagnostic tool in i-NHLs, allowing regular disease monitoring and providing early detection of signs of disease progression or transformation. These warning signs may be the occurrence of new nodal or extra-nodal lesions, progressive and rapid enlargement of pathological lymph nodes with short doubling time of the maximum diameter, bulky disease (greater diameter ≥ 7 cm) and serosal effusions [5]. These findings identified by WB-MRI may then be validated by additional ^{18}F-FDG-PET/CT, the capability of which in identifying the histological transformation of FL is well established [22]. Moreover, Wu et al. have recently found that FL and diffuse large B-cell lymphoma could be differentiated by means of texture analysis on post-contrast T1-weighted images [41]. It might potentially help in early identification of a transformed lymphoma during imaging follow-up of FL patients, but this needs to be confirmed by larger studies.

Perspectives

In conclusion, i-NHLs are lymphomas characterised by 'indolent' behaviour, with slow growth, and a prolonged natural history. WW is a valuable and widely employed option to manage i-NHL patients with a low tumour burden. In this setting, patients need to be regularly monitored through imaging examinations, including CT and ^{18}F-FDG-PET/CT, with exposure to substantial ionising radiations. Since WB-MRI has a well-demonstrated reliability in lymphoma patients, future studies should focus on the application of this imaging modality in the follow-up of patients with i-NHL under WW in order to reduce radiation exposure and, as consequence, secondary cancer risk. The scientific community should raise the awareness of the risk of ionising radiation, defining the proper place of WB-MRI in lymphoma imaging and establishing precise imaging timepoints for the optimal management of patients with i-NHL, with particular attention to those under a WW strategy.

Funding The authors state that this work has not received any funding.

Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Massimo Galia.

Conflict of interest The authors of this manuscript declare no relationships with any companies whose products or services may be related to the subject matter of the article.

Statistics and biometry No complex statistical methods were necessary for this article.

Ethical approval Institutional review board approval was not required because this article does not involve patient data.

Methodology Editorial

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