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REVIEW

New developments in staging and follow-up of patients with Hodgkin's lymphoma

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ABSTRACT

Adequate staging of newly diagnosed patients with Hodgkin's lymphoma enables optimal treatment planning, which is of particular importance for finding a balance between treatment efficacy and toxicity. In this review an overview is given of the current knowledge on initial staging and the role of imaging modalities during and after treatment. A promising new tool is whole-body positron emission tomograpy (PET) scanning with fluorodeoxyglucose (FDG). This modality is particularly useful for the evaluation of a residual mass at the end of treatment and for the assessment of the prognostically relevant 'early response' to chemotherapy. Although high survival rates have been reported for patients treated within the context of clinical trials these rates are generally lower in population-based series. In the general population comorbidity is present in half of all elderly Hodgkin patients. Since comorbidity has great impact on treatment planning and survival, this prognostic factor should be taken into account in future trials.

DIAGNOSIS AND HISTOLOGY

In 80 to 90% of the patients the first manifestation of Hodgkin's lymphoma (HL) is lymphadenopathy, most frequently located in the neck. For diagnosis an excisional lymph node biopsy is required to fully appreciate the architecture of the lymph node, in which the relative proportion of reactive bystander cells and malignant Hodgkin/Reed Sternberg cells (H/RS cells) can vary widely. The former histological classification (the Rye classification) recognised four subtypes: lymphocyte predominant (LP), mixed cellularity (MC), nodular sclerosis (NS) and lymphocyte depletion (LD).[1] The Revised European-American classification of malignant lymphomas (REAL classification) included some modifications, which have been adopted by the recent World Health Organisation (WHO) classification.[2] The nodular lymphocyte predominance type of Hodgkin's lymphoma is now considered to be a separate entity because of its distinct histological and clinical features with a prolonged indolent clinical course (*table 1*).[3]

The cellular composition of the neoplastic nodules varies widely among patients with the nodular sclerosis subtype. This prompted the British National Lymphoma Investigation (BNLI) group to propose a histological grading based on the number of H/RS cells and amount of fibrosis, which appeared to be of prognostic value.[4] Several groups[5,6] confirmed this prognostic significance, although others reported no survival differences.[7] In a recent population-based study this grading lost its independent prognostic value with the more frequent use of chemotherapy eradicating occult abdominal disease, which is more prevalent in the group with the worst prognostic.[8]

Table 1
Histological classifications of Hodgkin's lymphoma

RYE CLASSIFICATION	REAL/WHO CLASSIFICATION
Lymphocyte predominance	Nodular lymphocyte predominance
	Classical Hodgkin's lymphoma
Nodular sclerosis	Nodular sclerosis (*grades 1 and 2*)
Mixed cellularity	Mixed cellularity
Lymphocyte depletion	Lymphocyte depletion
	Lymphocyte-rich

STAGING

Staging classifications

Staging is necessary to determine the location and extent of disease, to define evaluable manifestations and prognostic factors and is the hallmark for the choice of treatment. Furthermore, staging allows comparison of treatment results between different study groups.

The Ann Arbor classification was modified at the Cotswold meeting in 1988, driven by the greater appreciation of the prognostic significance of tumour burden and the increased use of CT scanning (*table 2*).[9,10] In essence the staging is based on the number of sites of lymph node involvement, whether lymph nodes are involved on both sides of the diaphragm, whether there is visceral involvement and whether B symptoms are present.[11]

Conventional work-up

The initial work-up includes a complete history, physical examination, laboratory investigations and radiological examination. Thoracic CT scanning is useful as it has a considerable potential to influence the initial treatment policy. Staging below the diaphragm is hampered by false-negative results of CT scanning due to inability to detect HL in normal sized nodes and the difficulties in detecting HL in the spleen by CT scanning or ultrasound.[12]

Although bone marrow involvement is relatively uncommon a bone marrow biopsy is recommended, because of the high impact of a positive bone marrow on treatment planning.

Lymphangiography has nearly vanished from the work-up, not because of its diagnostic value but mainly because it is invasive, it requires great skill on the part of the radiologist, it has a prolonged examination time and is poorly rewarding economically.

Nowadays, staging laparotomy is rarely performed because of the lack of survival benefit, since the use of certain clinical criteria have made it easier to define patients likely to have occult abdominal disease.[13]

Gallium-67 scintigraphy is not believed to be accurate for the initial staging of Hodgkin patients. However, a pretreatment gallium scan is useful in the assessment of residual radiographic abnormalities after treatment, as a negative mass after treatment is likely to represent fibrosis if it was positive before.[14]

At presentation, most patients (70 to 80%) have stage II or III, whereas 10 to 15% have either stage I or stage IV disease.

New imaging modalities for staging

Magnetic resonance imaging (MRI) appears to be sensitive for the evaluation of bone and/or bone marrow involvement. However, this modality has the disadvantage that only a limited area of the body can be investigated, and therefore is used for evaluation of clinically suspected areas.[15]

The diagnostic yield of somatostatin receptor scintigraphy has been reported to be inferior and this modality is not performed routinely.[16]

Table 2

Staging notation of Hodgkin's lymphoma according to the Cotswold-modified Ann Arbor classification

Stage I	Involvement of a single lymph node region or lymphoid structure (spleen, thymus, Waldeyer's ring)
Stage II	Involvement of two or more lymph node regions on the same side of the diaphragm (the mediastinum is a single site, whereas hilar lymph nodes are considered bilaterally). The number of anatomical sites is indicated by a subscript (e.g. II_3)
Stage III	Involvement of lymph node regions or structures on both sides of the diaphragm III_1 With splenic, hilar, celiac or portal nodes III_2 With para-aortic, iliac, mesenteric nodes
Stage IV	Diffuse or disseminated involvement of one or more extranodal organs or tissue, with or without associated lymph node involvement
DESIGNATIONS APPLICABLE TO ANY DISEASE STAGE	
A	*No systemic symptoms*
B	*B symptoms present, one or more:* *– Unexplained weight loss >10% during previous six months* *– Unexplained fever (>38°C) during the previous months* *– Recurrent drenching night sweats during the previous months* *B symptoms generally correlate with advanced stage and bulk disease. Fever and weight loss have more negative prognostic impact than drenching night sweats*
X	*Bulky disease is present when:* *– A palpable lymph node defined by the largest dimension is >10 cm* *– The maximum width of a mediastinal mass is > one-third of the internal transverse diameter of the thorax at the level of T5/6 interspace on a chest X-ray*
E	*The subscript 'E' is used for documented limited extranodal extension contiguous or proximal to the known nodal site. More extensive extranodal disease is designated stage IV*
CS	*Clinical stage*
PS	*Pathological stage (as determined by laparotomy)*

Positron emission tomography (PET) with fluorodeoxyglucose (FDG) is a very promising noninvasive modality for the staging of Hodgkin patients. With whole-body FDG-PET, tomograpic images can be generated of the entire patient, displaying increased cellular glucose uptake and metabolism enabling the detection of disease, also in nonenlarged nodes/organs. Whole-body PET has been reported to be at least as sensitive as conventional staging procedures for initial staging,[17,18] being particularly useful for detection of extra-nodal localisations.[19,20] However, additional PET scanning in a study of 33 consecutive Hodgkin patients[21] did not influence planned treatment strategies based on conventional staging.
Although FDG-PET is still relatively scarce in the Netherlands hampering its routine use in staging of Hodgkin patients, its availability is growing. The high absolute costs of FDG-PET have to be put in the perspective of the better diagnostic yield and, more important, on the impact on patient management (*table 3*).

Elderly patients and comorbidity
For patients with other cancers it has been demonstrated that the presence of comorbidity is associated with less aggressive treatment and impaired survival.[22]
Comorbidity can influence therapeutic decision-making, since it might be a contraindication for anticancer treatment or a reason for dose reduction. The reduced survival rates for patients with comorbidity might also be related to a higher rate of treatment-related complications or to the increased risk of death caused by the comorbid condition itself. Experimental studies may use comorbidity as one of their restrictive eligibility criteria, subsequently underestimating its prevalence and relevance.
The prevalence of comorbidity appeared to be more than 50% in Hodgkin patients >60 years in a population-based study in the southeast of the Netherlands. Comorbidity was associated with a 50% reduction in the application of chemotherapy and with impaired overall survival. Whether this policy is justified or not deserves further investigation, since with increasing life expectancy of the European population this issue will be of growing concern.[23] Comorbidity is probably one of the major reasons for the lower overall survival rates in the general healthcare environment compared with those reported by clinical trials or referral centres.[24] Since comorbidity has great impact on treatment planning and survival, this prognostic factor should be taken into account in future clinical trials.

TREATMENT SELECTION

Early stage
Selection of initial treatment for Hodgkin's disease is based on the stage at presentation and prognostic factors.[25] In the past, radiotherapy was only the treatment for early stage (CS I-II) disease. Nowadays there is a trend to minimise late treatment-related complications with the use of lower doses of radiotherapy with smaller fields and with more frequent application of chemotherapy to treat occult (abdominal) disease.[26] This philosophy is underscored by the result of a recent meta-analysis demonstrating that adjuvant chemotherapy in early stages halved the ten-year risk of treatment failure compared with adjuvant radiotherapy.[27] The European Organisation for Research and Treatment of Cancer (EORTC) subdivides patients with early stage Hodgkin's lymphoma in either '*favourable*' or '*unfavourable*' by using a set of clinical criteria, corresponding with the risk of undetected abdominal disease. Patients are considered 'unfavourable' if they had any of the following: an ESR >50 mm/h, an ESR >30 mm/h in the presence of B symptoms, a mediastinal mass with tumour/thorax ratio of >0.35 (see *table 2*), or four or more sites of disease. Phase III clinical trials are ongoing to prove that unfavourable patients will profit from more intensive treatment.[28]

Advanced stage
Patients with advanced stage (CS III-IV) should be treated with chemotherapy. The ABVD (adriamycin, bleomycin, vincristine, dacarbazine) regimen is at least as effective as MOPP (mechlorethamine, vincristine, procarbazine,

Table 3
Value of the use of several imaging modalities for initial staging, assessment of early response, restaging at end-of-treatment and for evaluation of a residual mass in patients with Hodgkin's lymphoma

SCAN	INITIAL STAGING	EARLY RESPONSE	END-OF-TREATMENT	RESIDUAL MASS
CT	Mandatory	Routine in trials (after 3-4 cycles)	Mandatory	CT scans with several months interval
PET	Sensitive for extranodal disease Probably not changing policy	Promising as prognosticator	Promising as prognosticator	Promising to rule out active disease
MRI	Useful for evaluation suspected bone-marrow involvement	–	–	–
Gallium	Useful for comparison in case of residual mass after treatment	–	–	Negative scan likely reflects fibrosis, if positive before

prednisone)/ABV and superior to MOPP alone.[25,29] In a recent update of a randomised trial comparing ABVD with the MOPP/ABV hybrid regimen the overall and disease-free survival were similar for both patient groups.[30] However, ABVD has less germ cell and haematopoietic stem-cell toxicity and for this reason ABVD is considered to be the treatment of choice for patients with advanced Hodgkin's lymphoma.[25,29,30] The German Hodgkin Study Group has introduced the BEACOPP (bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, prednisone) regimen. In this regimen the drug etoposide is introduced, the dose intensity is increased (especially in the escalated regimen) and the most cytotoxic drugs (doxorubicin, cyclophosphamide, and etoposide) are given early in each cycle. In the HD9 trial patients with advanced disease were treated with either COPP (cyclophosphamide, vincristine, procarbazine, prednisone)/ABVD (the former German standard regimen) or with baseline BEACOPP or with increased-dose BEACOPP. The COPP/ABVD arm was stopped prematurely because increased BEACOPP resulted in better tumour control and overall survival.[31] Whether BEACOPP leads to superior cure rates over ABVD without endangering the initial therapeutic win by a long-term loss caused by treatment-related sequelae remains a matter of debate and will be studied in a recently opened study for patients with advanced Hodgkin's lymphoma with the highest risk of treatment failure (International Prognostic Score of at least 3, see *table 4*).
The value of additional radiotherapy for patients with advanced disease who have achieved complete remission on treatment with chemotherapy is debatable. In a recent EORTC study no survival difference was reported for patients treated with or without involved field radiotherapy after achievement of complete remission on six to eight cycles of MOPP/ABV.[33] This is in line with a recent meta-analysis reporting better overall survival for patients who received additional cycles of chemotherapy as compared with patients who received additional radiotherapy following initial chemotherapy. This survival advantage was due to lower treatment-related late mortality for patients who only received chemotherapy.[34]
All newly diagnosed Hodgkin patients should, when possible, be treated in the context of a prospective clinical trial since this is the only way to improve survival for future patients.

MONITORING

Monitoring during treatment

History and physical examination during treatment should be directed towards B symptoms, toxicity and the reduction of involved sites, since chemotherapy should be changed in case of failure to respond. Laboratory testing is needed for follow-up of abnormal results and for dose scheduling. Chest radiographs are useful to monitor intrathoracic sites and to exclude infections or toxicity.
Patients with disease visible only on CT scan should be scanned halfway through chemotherapy. Such documentation is useful for evaluating the rate of response, since *early complete response* predicts superior overall and disease-free survival. Whether this should have impact on treatment planning (number of cycles, for example) is addressed in clinical trials.[35] PET scanning appears to be a promising tool for the assessment of this early complete response. A predictive value for lower risk for relapse has been reported when the PET scan is negative after three cycles[36] or even after one cycle of chemotherapy (*table 4*).[37]

Table 4
The International Prognostic Score (IPS) for patients with advanced Hodgkin's lymphoma includes seven unfavourable features at diagnosis[32]

FACTOR	UNFAVOURABLE
Serum albumin	<40 gram/l
Haemoglobin	<10.5 g/dl
Gender	Male
Age	>45 years
Stage	IV
Leucocyte count	$>15*10^9$/l
Lymphocyte count	$<0.6*10^9$/l and/or <8% of leucocyte count

This analysis showed a continuous decline in the five-year event-free survival with increasing number of clinical risk factors present.[32]

NUMBER OF UNFAVOURABLE FACTORS	FIVE-YEAR EVENT FREE SURVIVAL (%)
None	84
1	77
2	67
3	60
4	51
5 or more	42

Evaluation after completion of treatment (restaging)

About one to two months following the completion of therapy the response should be documented by history, clinical examination and imaging.
CT scanning is much more sensitive than the chest X-ray for assessment of complete remission in the chest.[38] Residual abnormality seen on CT must be evaluated to distinguish between residual fibrosis and active disease.[39] This distinction can be made by serial studies, since benign disease will remain stable or decrease, while persistent Hodgkin's disease will increase in size. Persistent and unexplained elevation of the ESR is an indication for close surveillance.[40]

The value of scintigraphy with 67-gallium lies primarily in assessing the results at the end of treatment and not at initial diagnosis. In the evaluation of residual disease is 67-gallium scanning particularly useful, because it helps to differentiate between active tumour tissue and fibrosis. A residual mass that is gallium negative usually represents fibrosis, and follow-up without therapy may be warranted.[41] For this purpose a pretreatment gallium scan is useful for comparison.

Of special interest is the promising role of PET scanning in restaging. In a study of residual post-treatment masses in 58 patients, the negative predictive value of PET scanning was 100%, whereas the significance of a positive scan was less certain.[42] In another study a negative PET scan did not exclude residual disease completely, although progressive disease was more consistently associated with a positive PET scan compared with residual masses found with CT scan.[43] In a study of 81 patients the accuracy of PET appeared to be superior (91% for PET *versus* 62% for conventional imaging) for restaging using biopsy and/or clinical follow-up as confirmation.[44] Since a PET scan can be false-positive at the end of treatment, for example due to residual inflammation, a pretherapy PET scan is advisable for comparison.

End-of-treatment PET scanning appears to have prognostic significance. In 60 patients who underwent end-of-treatment PET scanning the two-year progression-free survival was 91% for PET-negative *versus* 0% for PET-positive patients. Moreover, PET scanning was the first tool that became positive for relapse.[45] In another study, relapse was more frequent in patients with a PET-positive (6/10) *versus* a PET-negative residual mass (3/19).[46] Whether PET scanning will allow for intensified treatment and possible cure of more patients as well as the potential economic advantages has yet to be demonstrated.

Late complications after treatment

Awareness of treatment-related sequelae is important and deserves special attention during follow-up.[25] The most important sequelae are briefly mentioned here.

Hypothyroidism develops gradually after mantle field irradiation, with a 20-year cumulative incidence of up to 41%.[47]

The increased risk of coronary artery disease following irradiation to the mediastinum should be reduced by the use of modern radiation techniques.[48]

Pneumonitis and pulmonary fibrosis is a common complication following mantle field irradiation and can be potentiated by bleomycin.[49]

The chance of maintaining fertility is greater among females than males and cryopreservation of semen prior to treatment should be considered in each patient.[47]

Secondary acute myeloid leukaemia often presents initially as myelodysplastic syndrome and is frequently refractory to treatment. The cumulative risk tends to plateau after 10 to 15 years and is associated with drugs as mechlorethamine and procarbazine.[50]

Secondary non-Hodgkin's lymphoma develops 5 to 15 years post-treatment with a cumulative incidence of up to 4 to 5%.[50] The incidence of secondary solid tumours continues to increase with prolonged follow-up. The most common tumours are of the lung, female breast, stomach, thyroid and bone, frequently localising within the previous irradiated field.[50,51]

Long-term follow-up after treatment

Following restaging after the completion of therapy, patients should be seen at regular intervals. General history, physical examination, ESR, complete differential blood count (to screen for bone marrow dysfunction), alkaline phosphatase, gGT, LDH, serum albumin and a chest X-ray (particularly in smokers treated with radiation therapy) is recommended at each visit. Testing of thyroid function at least once a year is recommended after mantle irradiation. Annual mammography should be performed five to ten years after treatment in women treated with mantle irradiation, especially when treated at a young age.

The site of relapse is partially determined by the type of initial therapy given. The use of the proper radiation technique should achieve an in-field disease control rate of more than 96%. The appropriate use and frequency of imaging such as CT scanning in the routine follow-up is not clear, since retrospective studies have shown that the majority of relapses are detected from the evaluation of symptoms rather than routine examination or imaging studies.[52] Moreover, it is not clear whether earlier detection of relapse with routine imaging will have other implications on the outcome of retreatment other than providing lead-time.

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