Centralised multidisciplinary re-evaluation of diagnostic procedures in patients with newly diagnosed Hodgkin lymphoma


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Background: Hodgkin Lymphoma (HL) is highly curable when treated accurately. The challenge is to cure patients with the minimal risk of long-term complications. For that, optimal initial diagnostics are required to determine the optimal treatment plan. We offer non-academic hospitals in our Regional Comprehensive Cancer Centre network a centralised review of all diagnostic procedures from patients with newly diagnosed HL. We report our experience on concordances and discrepancies between local findings and central review results.

Patients and methods: A haematologist and radiation oncologist at the Hodgkin Radboud University Nijmegen Medical Centre outpatient clinic examined all patients with newly diagnosed HL between February 2006 and May 2010. In a multidisciplinary lymphoma conference, diagnostic information is reviewed and treatment advice formulated. Discordant findings in pathology, staging and therapy were recorded as ‘minor’, no therapeutic consequences or ‘major’, adapted therapy advice.

Results: Altogether, 125 patients were included. Pathology review showed 86% concordance, with 4% major discordance, mainly nodular lymphocyte predominant sub-type. Revision of initial staging was concordant in 77%; however 15% major discordance of which most were upstaged. This resulted in 19% treatment adaption.

Conclusion: Our findings highlight the discrepancies in interpretation of diagnostic tests. We advocate centralised review process for all newly diagnosed patients with HL.

Key words: centralized review, diagnostic procedures, Hodgkin lymphoma, multidisciplinary re-evaluation

introduction

Hodgkin lymphoma (HL) is a rare but one of the best curable malignancies. With a median age at diagnosis of 30–35 years, the majority of patients will have a long life expectancy, which could be affected by long-term therapy-related complications. Fifteen to twenty years after treatment second malignancies (e.g. breast or lung cancer) and cardiovascular diseases overtake the risk of mortality due to treatment-refractory HL [1–4]. The main challenge faced by physicians treating patients with HL is to cure their patients with the minimal risk for long-term complications [5]. Standard chemotherapy has switched from the mitoxin, vincristin, procarbazin and prednisone (MOPP) schedule or MOPP-like variants to adriamycin, bleomycin, vinblastin and dacarbazin (ABVD) or its variants, thereby reducing the risk of secondary leukaemias and infertility [6–8]. ABVD may induce anthracycline-related cardiotoxicity and bleomycin-induced lung damage. On the other hand, the successful introduction of bleomycin, etoposide, Adriamycin, cyclophosphamide, vincristin, procarbazin and prednisone (BEACOPP) escalated indeed increased efficacy in terms of progression-free and overall survival for patients with advanced disease, but at the cost of the increased toxicity as seen in the historical MOPP/MOPP-like schedules [9, 10].

Reduction of the total number of required cycles of chemotherapy may decrease the risk of toxicity but cure rates should not come down. Reduction, or even omittance of radiotherapy, will certainly abolish certain serious late effects such as infield malignancies (breast and lung cancer) or premature cardiovascular disease, but has to be balanced...
against the potential higher risk of relapse. In advanced
disease, radiotherapy (RT) can be restricted to 15%–20% of
patients after BEACOPP escalated, using very careful post-
chemotherapy restaging including 18F-fluorodeoxyglucose
positron emission tomography (FDG-PET) scan [11]. The
European Organisation for Research and Treatment of Cancer
(EORTC) Lymphoma group is pioneering the involved node
RT principle in the combined modality treatment in early-
stage disease, to further reduce the radiation fields [12].
Evidently, these newer approaches ask for a meticulous staging
procedure, reliable and reproducible identification of involved
nodes and extranodal sites and a precise classification in the
various predefined risk groups (Ann Arbor stage, EORTC stage
I/II risk criteria and the International Prognostic Score for
advanced stage disease). Preferably, this is done by experienced
specialists in clinical haematology, radiation oncology,
pathology, radiology and nuclear medicine [11, 13, 14].
Therefore, it seems rational to have a centralised review of the
diagnostic procedures, because it is known that the reliability
of pathology and imaging is not optimal in centres with a low
volume of specific forms of cancer.

In The Netherlands, patients with HL are treated in
university medical centres as well as in community hospitals.
Community hospitals diagnose and treat between 1 and 10
new patients with HL yearly. Although the consultation of
specialist expertise is well organised within the framework of
our Dutch Comprehensive Cancer Centre consultation
network, the given advice is based upon written or verbal
information often without a structured review of all available
diagnostic data. Therefore, we decided to offer our affiliated
community hospitals, a centralised review for all newly
diagnosed patients with HL to optimise diagnosis and
treatment while maintaining the infrastructure of having
patients being treated in their immediate vicinity. In close
cooperation with the participating regional hospitals started in
2006, our HL joint outpatient clinic were all new patients with
HL were seen by one haematologist and one radiation
oncologist of the Radboud University Nijmegen Medical
Centre (RUN MC). In this report, we review our experience on
the joint HL outpatient clinic by a team consisting of a haematologist and a radiation oncologist, for medical
history and physical examination. Two days after the HL outpatient clinic visit all available data were centrally reviewed during the weekly
multidisciplinary conference attended by haematologists, radiation
oncologists, pathologists, radiologists and nuclear medicine physicians. The final diagnosis, stage attribution and treatment advice were defined and the
same day communicated to the referring physician.

The conclusions on pathology, staging and treatment advice were
categorised as either concordant or discordant with that of the referring
hospital. Concordance implies that the RUN MC experts agreed with the
clinician, pathologist, radiologist and nuclear medicine physician of the
referring hospital. Discordance means that there was a difference of
opinion between the referring specialist and the RUN MC. The
discordances were categorised as minor, when the difference did not
change the treatment advice, and major when the change in the pathology
or staging resulted in a treatment adjustment.

Statistical analysis was performed using SPSS 16.0.01, release 16.0.2,
10-april-2008. Descriptive techniques were used for specifying the
population and observed discordances.

results

A total of 125 patients visited the HL outpatient clinic between
January 2006 and May 2010. Their clinical data are
summarized in Table 1. The median age at first visit was 37
years (range 16–83) and 52% were male. The median age and
male/female distribution is as expected.

<table>
<thead>
<tr>
<th>Table 1. Patient characteristics</th>
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<tbody>
<tr>
<td>Value</td>
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<tr>
<td>Median age, years (range)</td>
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<tr>
<td>Sex</td>
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<tr>
<td>Referring hospital</td>
</tr>
<tr>
<td>Canisius Wilhelmina Hospital,</td>
</tr>
<tr>
<td>Nijmegen, n (%)</td>
</tr>
<tr>
<td>Rijnstate Hospital, Arnhem, n</td>
</tr>
<tr>
<td>(n = 124)</td>
</tr>
<tr>
<td>Hospital De Gelderse Vallei,</td>
</tr>
<tr>
<td>Ede, n (%)</td>
</tr>
<tr>
<td>Slingeland Hospital, Doetinchem, n (%) 16 (13)</td>
</tr>
<tr>
<td>VieCuri Medical Centre Noord-Limburg, Venlo, n (%)</td>
</tr>
<tr>
<td>St. Jansdal, Harderwijk, n (%)</td>
</tr>
<tr>
<td>Streekziekenhuis, Zevenaar, n (%)</td>
</tr>
<tr>
<td>Laboratory results</td>
</tr>
<tr>
<td>Mean ESR, mm/h (range) (n = 124)</td>
</tr>
<tr>
<td>Male: 8.1–10.7</td>
</tr>
<tr>
<td>Female: 7.3–9.7</td>
</tr>
<tr>
<td>Mean haemoglobin, mmol/L (range) (n = 124)</td>
</tr>
<tr>
<td>Male: 8.1–10.7</td>
</tr>
<tr>
<td>Female: 7.3–9.7</td>
</tr>
<tr>
<td>Mean leucocyte count, ×10⁹ (range) (n = 116)</td>
</tr>
<tr>
<td>2–4</td>
</tr>
<tr>
<td>Mean lymphocyte count, ×10⁹ (range) (n = 116)</td>
</tr>
<tr>
<td>Mean albumin, g/L (range) (n = 112)</td>
</tr>
<tr>
<td>35–50</td>
</tr>
</tbody>
</table>
pathology

Agreement between the pathologists from the referring hospital and the RUN MC was reached in 108/125 cases (86%) (Table 2). Minor discordances in the sub-typing of HL concerned a change between the mixed cellularity (MCcHL) and nodular sclerosing (NScHL) sub-type \( (n = 5) \) and between not otherwise specified (NOS) and MCcHL or NScHL \( (n = 7) \) (Table 2).

Major discordance was established in 5/125 cases (4%). All of these were lymphocyte rich lesions and the well-known difficult differential diagnosis between lymphocyte-rich classical HL (LRcHL), nodular lymphocyte predominant HL (NLPHL) and diffuse large B-cell NHL (DLBCL) was the problem in four cases. In one case, the diagnosis was changed from LRcHL to methotrexate (MTX)-related Epstein–Barr positive Hodgkin-like lymphoproliferation due to the clinical presentation.

staging

The Ann Arbor stage could be attributed to 123/125 (98%) patients at the central review. In one patient, FDG-PET-CT scan could not be timely retrieved and, in one, the diagnosis changed to DLBCL (Table 3). There were 113 FDG-PET scans with a diagnostic CT scan reviewed and 11 FDG-PET scans with a low-dose CT scan.

Of the 123 cases, which could be compared, 95 (77%) were concordant (Table 3). A total of 28 patients (23%) had a discordant stage after revision, 10 were minor discordant and in 18 a major discordance was revealed (Table 3). Details of the 18 major discordant cases include:

- **Downscaling after centralised revision**
  - Clinical stage (CS) III to stage CS II due to negative FDG-PET scan on doubtful infra-diaphragmatic lymph node \( n = 1 \)
  - CS II unfavourable to CS II favourable due to negative FDG-PET scan on one suspected lymph node area \( n = 1 \)

- **Upscaling after centralised revision**
  - CS I/II to CS III/IV due to FDG-PET driven revision of CT scan with suspected infra-diaphragmatic nodes \( n = 8 \)
  - CS I/II favourable to CS I/II unfavourable due to abnormal nodes on FDG-PET scan correlating with revised CT scan findings \( n = 3 \)
  - CS I/II favourable to CS I/II unfavourable due to elevated ESR and/or B symptoms \( n = 3 \)

### Table 2. Comparison in histopathology between the referring hospital and centralised revision

<table>
<thead>
<tr>
<th>Histopathology referring hospital</th>
<th>NScHL</th>
<th>MCcHL</th>
<th>LRcHL</th>
<th>NLPcHL</th>
<th>NOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>NScHL</td>
<td>75</td>
<td>3</td>
<td>5</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>MCcHL</td>
<td>2</td>
<td>10</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>LRcHL</td>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>NLPcHL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NOS</td>
<td>1</td>
<td>1</td>
<td></td>
<td>8</td>
<td></td>
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<tr>
<td>Others</td>
<td></td>
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</tbody>
</table>

\( ^a \)Diffuse large B-cell lymphoma.

\( ^b \)EBV positive lymphoproliferative Hodgkin-like lymphoproliferation.

NScHL, nodular sclerosis; MCcHL, mixed cellularity; LRcHL, lymphocyte rich; NLPcHL, nodular lymphocyte predominant; NOS, not otherwise specified.

### Table 3. Differences in staging between the referring hospital and centralised revision

<table>
<thead>
<tr>
<th>Ann Arbor referring hospital</th>
<th>Stage I favourable</th>
<th>Stage I unfavourable</th>
<th>Stage II favourable</th>
<th>Stage II unfavourable</th>
<th>Stage III good risk</th>
<th>Stage III poor risk</th>
<th>Stage IV good risk</th>
<th>Stage IV poor risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I favourable</td>
<td>9</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Stage I unfavourable</td>
<td>4</td>
<td>1</td>
<td>6</td>
<td>26</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Stage II favourable</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>6</td>
<td>5</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Stage III good risk</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Stage III poor risk</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>6</td>
<td>5</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Stage IV good risk</td>
<td></td>
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<tr>
<td>Stage IV poor risk</td>
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<tr>
<td>Missing data/other</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
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</tbody>
</table>

\( ^a \)CT and FDG-PET scan could not be timely retrieved.

\( ^b \)DLBCL.
- CS II favourable to CS IV good risk due to bone lesions on revised FDG-PET scan \( n = 1 \)
- CS III to CS IV because of suspected liver lesion on revised FDG-PET scan \( n = 1 \)

**Therapy**

In 124/125 patients, a central treatment advice could be given. In the group of 124 patients, the referral hospital had already specified the treatment advice in 104 while, in 20 patients, the treatment was not yet defined.

The treatment advice was concordant in 84/104 (81%) cases. In 20 patients (19%), the central revision process led to a change in treatment advice based on changes in the pathology and/or staging results (Table 4).

Changes in RT fields occurred in four patients:
- Involved field radiotherapy (IF-RT) changed to ABVD + IN-RT due to change in diagnosis from NLPHL to LRcHL \( n = 1 \) or CS I favourable to CS II favourable \( n = 1 \)
- ABVD × 3 + involved node radiotherapy (IN-RT) changed to IF-RT due to change in diagnosis from LRcHL to NLPHL \( n = 1 \)
- IF-RT changed other chemotherapy due to change in histological diagnosis from NLPHL to DLBCL \( n = 1 \)

Combined changes in the number of ABVD cycles and involved nodes for the IN-RT in 12 patients:
- CS II favourable changed to CS II unfavourable resulting in ABVD × 4 instead of × 3 + IN-RT \( n = 5 \)
- CS II unfavourable changed to CS II favourable resulting in ABVD × 3 instead of × 4 + IN-RT \( n = 1 \)
- CS I/II change to CS III/IV resulted in change from ABVD × 3/4 + IN-RT to ABVD × 6/8 \( n = 5 \)
- CS III/IV change to CS I/II resulting in change from ABVD × 6 to ABVD × 3 + IN-RT \( n = 1 \)

Other changes in four patients:
- Change type of chemotherapy ABVD to other schedule due to co-morbidity \( n = 2 \)
- Change ABVD + IN-RT to stop MTX in MTX related Hodgkin-like lymphoma \( n = 1 \)
- Change ABVD + IN-RT in close observation in unconfirmed HL diagnosis \( n = 1 \)

**Discussion**

In this report, we evaluated our experience with a centralised diagnostic review process for 125 previously untreated patients with HL, initially diagnosed in one of the cooperating neighbouring community hospitals. Our results indicate that this representative group of patients with HL a 20% change in treatment advice was given upon revision of the diagnostic procedures.

In the past, some series have addressed the significance of a centralised pathology panel or FDG-PET scan panel [15–22]. This is the first series to combine a review of pathology, imaging and treatment advice in one process. Our results indicate that an experienced panel for diagnosis, imaging and treatment advice is needed because treatment is increasingly tailored to individual patient characteristics including meticulous staging, to prevent under- or over-treatment.

The inter-observer concordance in pathology of HL varies between 49% and 96% [15–18, 23]. We observed a high concordant pathology rate of 86% in our central review. The high agreement percentage is probably attributable to the regional lymphoma panel, in which all newly diagnosed malignant lymphomas are centrally reviewed. Evaluation of this panel is in progress, but preliminary data indicate that about 50% of all new lymphomas are actually referred to the panel. Recently, the surplus value of central review was highlighted by Proctor et al. [23]. In our review, only 4% of cases had major discordant histopathology leading to a treatment adjustment. The majority of this major discordant histopathology was due to NLPHL changed into LRcHL or DLBCL or vice versa a well-known pitfall [24, 25]. In fact, LRcHL was only relatively recently identified among NLPHL cases which were centrally reviewed in the framework of a

**Table 4. Differences in treatment proposal between the referring hospital and centralised revision**

<table>
<thead>
<tr>
<th>Treatment proposal referring hospital</th>
<th>IF-RT</th>
<th>ABVD × 6</th>
<th>ABVD × 8</th>
<th>ChlVPP × 6-8</th>
<th>Other chemo</th>
<th>ABVD × 3 + IN-RT</th>
<th>ABVD × 4 + IN-RT</th>
<th>Missing data</th>
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<tbody>
<tr>
<td>IF-RT</td>
<td>8</td>
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<td></td>
<td></td>
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<td>ABVD × 6</td>
<td></td>
<td>1</td>
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<td>ABVD × 8</td>
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<td>ChlVPP × 6-8</td>
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<td>1</td>
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<td>2</td>
<td>3</td>
<td>6</td>
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<tr>
<td>Other chemo</td>
<td>1</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Treatment proposal centralised revision</td>
<td></td>
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<td>2</td>
<td>3</td>
<td>6</td>
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<tr>
<td>ABVD × 3 + IN-RT</td>
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<tr>
<td>ABVD × 4 + IN-RT</td>
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<tr>
<td>Other chemo + RT</td>
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<tr>
<td>Other treatment</td>
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*3 × MOPP with IN-RT.
*bChlVPP with IN-RT.
*cWatchful waiting.
clinical trial. The European task force on lymphoma project reviewed 388 samples of NLPHL; 56% were concordant and of the discordant 30% was changed into newly created subgroup LrCHL [24]. We only changed 8% of the NLPHL into LrCHL, since this category is now well recognised in the WHO 2008 classification. The importance of correct clinical data when pathology is performed was illustrated by a case that was morphologically and phenotypically HL, but appeared to be a MTX-related Epstein–Barr positive Hodgkin-like lymphoproliferation. This is a well-known pitfall which can only be avoided by proper clinical information. Obviously, this is a very relevant change, since this patient does not need treatment for HL.

The reduction of radiation fields from involved field to involved node enhances the risk of under treatment if the involved nodes are not correctly determined [12]. As most relapses occur in the initially involved lymph node(s) in patients with early-stage HL treated with only chemotherapy, accurate staging is indispensable [26–29]. The increasing use of FDG-PET scanning not only in response to therapy evaluation but also in primary staging, asks for standardization of interpretation of the scans. There is less discordance between experienced nuclear physicians than between less experienced and expert readers [19, 20, 22]. Pre-therapy FDG-PET scan is not mandatory but strongly advised and widely used for baseline scans being concordant with the expert opinion [19].

Anticipated inter-observer disagreement, only 56% of the involved nodes are not correctly determined [12]. As most involved node enhances the risk of under treatment if the accurate staging is indispensable [26]. Patients with early-stage HL treated with only chemotherapy, relapses occur in the initially involved lymph node(s) in PET negative baseline scans were only concordant in 45% [19]. Agreement of the overall Ann Arbor stages of 0.71 confidence interval [20]. This high concordance is probably due to the fact that their observers were experienced reviewers of FDG-PET-CT scans. In our series, we observe a discordance of 77%, which is in agreement to the literature. Most of our discordance was due to the fact that the nodes or lesions were missed by the first nuclear medicine physicians (n = 16), other reasons were a very low threshold for positive nodes (n = 6) which let to downscaling and upscaling after correlating the FDG-PET scan with the CT scan (n = 3). Two-thirds of the discordance was in patients who were seen during the first 2 years of our HL out-patients clinic. The reason the discordance is not as high as mentioned in Hofman et al. is due to the fact that we have a greater variation in inter-observer FDG-PET scan experience. Standardization of interpretation methods and improvement of the technology results in better concordance than mentioned by Zijlstra et al. This emphasises the fact that nuclear medical physicians need learning sessions and that interpretation should be standardized.

RT fields were changed in our review in 10/104 patients with early-stage HL based on the centralised expert review of the imaging results. It is self-evident that a change from an early stage to an advanced stage as encountered in 9.6% of our patients has even more clinical impact. The literature emphasises that more experienced interpreters have fewer false-positives results and that standardization of FDG-PET-scan protocols is necessary [19, 20].

The centralised review process on pathology and staging resulted in an overall change in treatment advice for 19% of newly diagnosed patients with HL in our region. Whether this adaptation of treatment actually improves the outcome of the patients cannot be answered by this prospective observational study. However, our findings highlight the heterogeneity in interpretation of diagnostic tests. As modern treatment approaches rely on correct initial diagnosis and staging using modern pathologic classification and imaging techniques, we strongly advocate a centralised review process for all newly diagnosed patients with such a rare disease as HL.

disclosure
The authors have declared no conflicts of interest.

references
Circulating activin-A is elevated in patients with advanced multiple myeloma and correlates with extensive bone involvement and inferior survival; no alterations post-lenalidomide and dexamethasone therapy


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**Background:** Activin-A is a transforming growth factor-β superfamily member, which seems to be implicated in the biology of osteolytic disease in multiple myeloma.

**Design and methods:** Circulating activin-A was evaluated in 98 newly diagnosed myeloma patients (85 with symptomatic disease), in 40 patients with relapsed myeloma before and after four cycles of lenalidomide and dexamethasone (RD), in 27 healthy controls and in 10 monoclonal gammopathy of undetermined significance (MGUS) patients at diagnosis and in 40 patients with relapsed myeloma before and after four cycles of lenalidomide and dexamethasone therapy.

**Results:** Patients with newly diagnosed symptomatic myeloma had increased circulating activin-A compared with controls (P < 0.001), while patients with relapsed disease had elevated activin-A even compared with symptomatic patients at diagnosis (P < 0.001). High activin-A correlated with advanced International Staging System stage.

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