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Title:
Nodular lymphocyte predominant Hodgkin lymphoma behaves as a distinct clinical entity with good outcome: Evidence from 14 year follow-up in the West of Scotland Cancer Network

Running Title:
West Scotland NLPHL outcome study

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ABSTRACT
Clinically and biologically, nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) has much more in common with germinal-centre derived B-cell NHL than classical HL. Management of NLPHL remains controversial. In a 14-year multi-centre series, 69 cases were analysed; median follow-up was 53 months (range 11-165.) B symptoms were present in only 4.3% of patients. 81.1% of patients had stage I/II disease. Treatment was with radiotherapy (53.6 %), chemotherapy (21.7%), combined modality (17.4%) and observation (7.2%.) 10.1% of patients relapsed and 2.9% of patients developed high-grade transformation to DLBCL. All relapses and transformations were salvageable. No patient died of their disease. The 5 yr relapse-free survival was 96.7%, transformation-free survival 98.4% and overall survival 100%. We conclude that NLPHL behaves as a distinct clinical entity, often presenting at early stage without risk factors. It has an excellent outcome. It may be possible to reduce intensity of therapy in NLPHL without affecting OS.

Word Count: 148 words
INTRODUCTION

Nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) comprises ~5% of all Hodgkin lymphoma. Clinically and biologically, NLPHL has more in common with germinal-centre derived B-cell non-Hodgkin lymphomas (NHLs) than classical Hodgkin Lymphoma (cHL) and clinically is characterised by male predominance, early stage disease, excellent response to treatment and good outcome. Late relapses and transformation to high-grade non-Hodgkin lymphoma (NHL) are recognised. Classical HL is characterised by a loss of the B-cell programme and expression patterns. In contrast, the cancer cell in NLPHL, the LP cell (formerly known as the "popcorn" or lymphocytic & histiocytic cell) expresses B cell markers, more in keeping with NHL, including CD20, CD79, PAX5, OCT2 and BOB1. Gene expression profiling demonstrates a striking similarity to the patterns of expression seen in T-cell rich B-NHL. There is a recognised risk of transformation from NLPHL to high-grade NHL, particularly diffuse large B-cell NHL (DLBCL). This risk of transformation, often long after the initial diagnosis, has been confirmed in previous studies.

Previous retrospective studies have examined the presentation of NLPHL, however, due to its rarity and low incidence of events, there have been no published prospective randomised controlled trials in this area, outwith the context of NLPHL cases included in larger cHL trials. As a result, there is widespread variation worldwide in treatment of this condition. Such variation makes comparison of outcome data between studies challenging. On the basis of this work, however, there is a growing feeling that NLPHL, particularly limited stage (IA) disease, may be treated less intensively than cHL. For the substantial remainder of patients, many current treatment protocols recommend management as for cHL (with chemotherapy and/or radiotherapy). It is being increasingly recognised that late toxicity with such treatments is substantial; excess risk of second cancers and cardiovascular disease continues to rise long after treatment and even 30 years after diagnosis, HL patients continue to have an elevated risk of death from all causes. In spite of this, some groups argue for treatment intensification reporting improved responses, without improvements in overall survival.

The aim of this study is firstly to examine the clinical features at presentation of this disease, to observe whether NLPHL represents a distinct group. Secondly, the outcome of patients will be examined to assess optimal approaches to management.
MATERIALS AND METHODS

Case Ascertainment

Cases were identified through registration with the West of Scotland Cancer Network lymphoma database. The population of the area covered in the study is 2.6 million. A diagnosis of NLPHL was made in 71 patients (adults and children) between 01/01/97 – 31/10/10. Diagnosis was confirmed by cross-referencing with pathology reports in all cases. Most cases had pathology reviewed in the context of reference review to an expert haemato-pathologist and discussion at regional pathology team meetings. On pathological review, two patients were found to have T-cell rich DLBCL at time of initial diagnosis, and were excluded from the analysis. Thus, a total of 69 patients were included in the analysis. Eight of a total of nine re-presentations were biopsied (88%). Cases were censored as of 31/10/10. Eight patients (11.2%) were unavailable for analysis at the census date ("lost to follow up"). As this was a retrospective non-interventional study, complete case analysis was used and these patients were censored at the date when last seen. The median follow-up time was 53 months (range 11-165 months).

Clinical Characteristics, Management And Outcomes

Data was obtained using direct case-note review, using a standard form. The following baseline clinical variables were recorded: sex, age at diagnosis, date of diagnosis, co-morbidity, duration of symptoms, presence or absence of B-symptoms, Ann Arbor Stage, involved nodal sites, other site of disease (pulmonary, spleen, bone marrow, other extranodal), the presence or absence of EORTC risk-factors for early stage disease: (mediastinal disease > 0.33 intra-thoracic diameter at T5/6, age ≥ 50 years, ESR > 50mm/h, ≥ 4 nodal areas), Hasenclever score for advanced stage disease (serum albumin <4g/dl, haemoglobin <10.5g/dl, male sex, stage IV disease, age ≥ 45, white cell count ≥ 15000/mm3, lymphocyte count <600/mm3 or 8% of total white count), supra-diaphragmatic disease only, axial disease only. Staging at diagnosis employed computed tomography (CT) scanning, and, when it became available, positron emission tomography-computed tomography (PET-CT) scanning. PET-CT scanning was in routine use in the region after 2008. All patients with advanced disease underwent bone marrow examination. The decision to examine bone marrow in early stage disease was at the discretion of the individual clinician. All patients were managed by individual consultant
haemato-oncologists who chose the treatment. All had access to a regional multi-disciplinary team meeting by video-conference, where cases could be discussed. From 2005, all had access to the local Clinical Management Guideline which recommended involved field radiotherapy only for stage IA NLPHL, and standard treatment as per classical HL for all other cases. Management of disease was recorded as excision only (observation only or “watch and wait”), chemotherapy, radiotherapy or combined modality (chemotherapy and radiotherapy.) For those patients who received chemotherapy, the regime used and number of cycles given was recorded. For those patients who received radiotherapy, the site irradiated, dose and fractionation were recorded. Any toxicity or complication of therapy was recorded. Clinical response to therapy was assessed at end of treatment using CT scanning, and, when it became available and was appropriate, PET-CT scanning. For those patients who re-presented, progressions were classed as either relapse of NLPHL or transformation to high-grade non-Hodgkin lymphoma. Subsequent therapy was recorded, as was response. For those patients who died, cause of death was recorded.

Definitions
Responses were classified according to the criteria of Cheson et al. Complete response (CR) was defined as complete disappearance of all detectable clinical evidence of disease and disease-related symptoms if present before therapy, or, in the case of patients in whom the PET scan was positive before therapy, a post-treatment residual mass of any size was permitted as long as it was PET negative. Partial response (PR) was defined as at least a 50\% decrease in sum of the product of the diameters (SPD) of up to six of the largest dominant nodes or nodal masses, with the additional criteria as defined above. Stable disease was defined as when a patient failed to attain the criteria needed for a CR or PR, but did not fulfil those for progressive disease. Progressive disease (PD) was defined as any new lesion or increase in SPD by> 50\% of previously involved sites from the nadir. Overall survival (OS) was measured from the date of diagnosis to date of last follow-up or death. Relapse-free survival (RFS) is defined as time from date of diagnosis to either progression, relapse of the initial NLPHL diagnosis only, or death from any cause. Transformation-free survival (TFS) was defined as time from date of diagnosis to transformation to high-grade NHL, or death from any cause. Event-free survival (EFS) is defined as time of diagnosis to progression, relapse or high-grade transformation, or death from any cause. Survival from relapse and progression were defined as from
date of diagnosis of the relapse or transformation to date of last follow-up or death. Patients who died with no evidence of progression or event as defined above were censored at date of death. Early stage disease was defined as clinical stage I and IIA, and no bulky disease (see below.) Advanced stage disease was defined as clinical stage IIB, III and IV or any with bulk disease. Bulk disease was defined as nodal mass>10cm or mediastinal mass>0.33 of intra-thoracic diameter at T5/6. Comparing tumour volume in this cohort is impossible due to the differences in radiological reporting and volume measurements not becoming standard until more recently. For those patients without bulk disease by the conventional definition above, we took any nodal mass >2cm as an arbitrary surrogate of higher volume disease, to allow comparison of outcome by tumour bulk between patients.

Statistics
Data was analysed using SPSS software, version 15.0 (IBM Corporation, Somers, NY USA.) Standard descriptive statistical analysis was performed. For crude-association analysis, data were analysed using the chi-square test. Survival analyses were calculated according using the Kaplan-Meier method, and presented as either survival curves or hazard curves. Analyses of OS, RFS, TFS and EFS using Cox regression were performed to assess any factors associated with these measures. Binary logistic regression was used to perform multivariate analysis of the same.
RESULTS

Patient Characteristics

The main characteristics of the 69 patients are given in table I. The median age of patients was 39.0 years (range 11-79) and the majority (69.6%) were male. Three children were included in the cohort, diagnosed at ages 11, 12 and 14 years. Eighty-one percent of patients presented with stage I or II disease. Most patients presented with localised peripheral lymphadenopathy. Lymphadenopathy had been present for a median of 6 months prior to diagnosis, and this did not correlate with disease stage at presentation. Only 3 patients (4.3%) presented with B-symptoms (one clinical stage II, two stage III.) The distribution of patients’ disease is given in table II. Of note, in 50 patients (72.5%) disease was confined supra-diaphragmatically. Only 14 patients (20.3%) had axial disease (mediastinal or abdominal.) Fifty-five patients (79.7 %) had early stage disease (stage IA or IIA) and of these, none had risk factors as defined by the EORTC (see methods, above.) Fourteen patients (20.3 %) had advanced stage disease (Stage IB, IIB, III or IV.) There was a trend to an increased proportion of older patients presenting with advanced stage disease (28% of patients >45 years with advanced stage disease as compared with 15.8% of patients under the age of 45 years with advanced stage disease, although this did not reach statistical significance (p=0.18 by Chi-square test.) The mean Hasenclever score for patients with advanced stage disease was 1.57 (range 1-2); age and male sex being the most common risk factors present. No patients had bulk disease as per the accepted definitions (see methods.) A majority of patients had disease where at least one of their nodal areas was >2cm (55.1%, n=38.) PET-CT scans were performed as part of disease staging in 10 patients. No patient was up-staged as a result of this, or necessitated a change in therapy. One patient was confirmed to have stage IV disease on the PET-CT scan.

Management

Patients were managed by 46 haemato-oncologists working in the region. Management was decided by the treating physician. The first-line management strategy used is given in table III. The most frequent strategy was radiotherapy only employed in 37 patients (53.6%). Forty-nine patients (71.0%) received radiotherapy as part of their treatment. The mean radiotherapy dose was 30Gy (range 20-40Gy) delivered most commonly in 15 or 20 fractions. Radiotherapy was delivered as involved field radiotherapy in 45/50 cases. Five cases received mantle radiotherapy (four stage II, one stage I); no
patient received mantle radiotherapy after the year 2000. Twenty-seven patients (39.1%) received chemotherapy, for 15 of whom, it was sole therapy. The chemotherapies employed in first line treatment varied. The most frequent chemotherapeutic regimen employed was doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD) (in 25 patients.) Number of cycles varied (median 4, range 1.5-6.) Eight of the twelve patients who received ABVD as sole therapy received six cycles. Other chemotherapeutic regimens employed included: chlorambucil, vincristine, procarbazine, etoposide, prednisolone, doxorubicin, vinblastine (ChlVPP/EVA) in two patients and ChlVPP/ABVD x 3 in one patient being treated on the paediatric UKCCSG HD 2000/02 protocol, which, at the time, did not differentiate NLPHL from cHL.

Five patients were managed by observation only following involved node excision; two with stage I disease, two with stage II disease and one with stage III disease. Other than lymphadenopathy, all in this group were asymptomatic. The presence of significant co-morbidity in two of these patients (chronic renal failure in one, and CNS tuberculosis in the other) may have impacted on the decision to manage expectantly. In total, 25 of the 69 patients (36.2 %) had some sort of co-morbidity, which may have impacted on ability to deliver therapy. The commonest co-morbidities seen were asthma, seen in 6%, and hypertension seen in 6%. Other co-morbidities which may have potentially affected therapeutic choices included Wolff-Parkinson-White syndrome, alcohol excess, diabetes, ischaemic heart disease, aortic incompetence and renal dysfunction.

Response
Sixty-three of the sixty-four treated patients obtained a CR with first line treatment (98.4%), the other one patient obtaining a PR, which remains stable. No patient failed to respond to first line treatment. No patient in our cohort had primary progressive disease. Of the five patients managed by observation, one developed a transformation to DLBCL at 16 months. The other developed progression of his primary disease (asymptomatic increase in size of lymph nodes) at 85 months, but is still not requiring therapy, and continues to be managed expectantly. The other three continued to have stable disease at a median of 57.0 months from diagnosis.
Complications of therapy

One of the compelling arguments for treatment reduction in this group of patients is the toxicity of therapy. Complications of first line treatment were seen in eighteen patients (28.1% of treated patients.) For patients receiving radiotherapy as sole treatment modality, 27 of 37 patients tolerated this with no complications. Four patients became hypothyroid. Other toxicities of radiotherapy were xerostomia, local discomfort over biopsy/irradiated area, infertility and oesophagitis. For the 29 patients who received chemotherapy, 18 tolerated it with no complications. Three of the 27 patients developed infection, which was the commonest toxicity of chemotherapy. Two patients developed respiratory toxicity, both of whom had received bleomycin. Of particular note, one of the paediatric patients, a male treated at age 12 with ChlVPP/ABVD x 3, has since been found to be infertile, confirmed on sperm analysis. Multivariate analysis by age, treatment modality, clinical stage and co-morbidity failed to predict who would suffer from treatment associated toxicity.

Outcomes

Seven patients (10.1%) relapsed (histopathologically confirmed NLPHL in 6 cases) at a mean of 57.7 months (range 13-121 months.) These relapses occurred in 3 patients with stage I disease, 2 with stage II disease, and 1 each with stage III and IV disease. The treatment of the primary disease in these cases varied (1 observation only, 3 radiotherapy only, 2 chemotherapy only & 1 combined modality therapy.) The majority of relapses were treated with chemotherapy, including one patient who received an autologous PBSCT. The treatments of the relapses included: ABVD (for 2 patients who had not received chemotherapy before, and 1 who had received 2 cycles as part of combined modality first line treatment), splenectomy, IVE and BEAM Auto-PBSCT, and ChlVPP PA(BL)OE (all one patient each.) One patient remains asymptomatic and has not yet commenced treatment. One of the patients is currently receiving treatment for relapse, but the other 5 are in CR at a median follow-up of 44.5 months (range 13-121.) In all cases, these relapses were salvageable and there were no deaths resulting from relapsed disease. The 2-year relapse-free survival was 96.7%. The 5-year relapse free survival was 92%.
Two patients (2.9%) went on to develop high grade transformation to DLBCL at 2 and 81 months. One patient was treated with 6xR-CHOP whilst the other patient received 3xR-CHOP prior to consolidation with DHAPx3, IVEx1 and a BEAM autologous PBSCT. Both patients treated for their high grade transformations achieved a CR with treatment. The median survival from transformation was 61.5 (range 40-83) months. Both high-grade transformations were salvageable and there were no deaths resulting from transformed disease. The 2-year and 5-year transformation-free survival was 98.4%. When relapses and transformations are taken together, this gives an overall event free survival at 2 years of 93.3% and 90.5% at 5 years. Figure 1 demonstrates the Kaplan-Meier plots for event-free survival.

In order to assess the efficacy of less-intensive treatment in early stage disease, we analysed the outcomes in the 37 (53.6%) of stage I and II patients treated with single-modality radiotherapy. In this group, outcomes were excellent with relapse-free survival of 93.9% at 5-years, transformation-free survival of 100% at 5 years and overall survival of 100% at 5 years (demonstrated in Figure 2).

Cox regression modelling of relapse-free and transformation free survival by age at diagnosis, clinical stage, treatment modality, presence of B symptoms, axial disease or Hasenclever score failed to give a model for predicting those patients more likely to relapse.

There were two deaths in this cohort, neither of which was related to the diagnosis of NLPHL, its transformation, relapse or treatment (the causes of death for the two patients being trauma in one case, and confirmed lung carcinoma 7.5 years after diagnosis in one of the patients who was managed by observation only.) The 5-year OS was 100% and disease specific survival was 100%. The Kaplan-Meier plot for overall survival is given in Figure 3.
DISCUSSION

Our study adds to the current literature in this area. Accepting the potential limitations of a retrospective cohort analysis, we suggest that the strengths of our study are its applicability to current oncology practice. As a multi-centre study with management strategies decided by individual physicians, this study is representative of practice in many settings. In contrast to recent single centre-studies,\textsuperscript{5,19} our cohort is restricted to cases diagnosed since 1997 which will have been managed with modern, accepted diagnostic techniques, treatments and response definitions.

We confirm that NLPHL behaves clinically as a distinct clinical entity. The majority of patients present with early stage disease, with localised peripheral lymphadenopathy. The presence of B-symptoms was unusual, and most patients had no other risk factors. All patients responded well to primary therapy, most attaining a CR.

In our study, there was a 10.1% relapse rate. Relapses and progressive disease continued to occur late in the natural history of the disease, with relapses in particular, occurring steadily to more than 10 years post first-treatment, with no sign in a plateau in the curve. This is in contrast to cHL, where much of the relapse risk is early and can be predicted in higher-risk groups of patients. Cox regression modelling of relapse-free and transformation free survival in this study failed to give a model for predicting those patients more likely to relapse. This is in itself significant, as it suggests that the natural history of this disease proceeds regardless at which stage the patient is at when diagnosed, or indeed whichever management strategy is taken. Whilst underpowered to detect equivalence, there is no evidence in our study to support the proposal that early, more intensive therapy, particularly in the form of chemotherapy will be beneficial, as has been suggested by other studies.\textsuperscript{13} Instead, we would argue, that as relapse risk exists is unmodified by stage or first-line treatment, a strategy of minimal therapy as and when required will achieve disease control with fewer toxicities. In our study, all relapses responded fully to therapy, suggesting no advantage in earlier intensification.

Particularly striking in our cohort is the 7.2% of patients managed by observation only (“watch & wait”) in whom there was no detectable difference in survival compared with the treated patients. We note
that the numbers managed by observation alone are too small to demonstrate statistical significance, but our outcomes are in agreement with other studies suggesting that management by resection only may be appropriate in selected groups of limited stage patients.20

The majority of patients were able to be treated by involved-field radiotherapy (IFRT) alone, avoiding many of the toxicities of extended field radiotherapy or chemotherapy. Previous published studies have suggested that for early stage patients, radiotherapy alone may be potentially curative.21 The OS of 100% and EFS of 93.9% at 5 years in the stage I and II patients treated with single modality radiotherapy in our study would certainly support this approach; although we noted an ongoing risk of late relapse in this group.

As has been described in other studies8-10, we found an ongoing risk of evolution to high-grade NHL. However, the risk of this was comparatively low (2.9%) and, in contrast to de novo high-grade NHL, all cases were salvageable to sustained CRs with therapy. Overall, in our study, NLPHL has an excellent outcome and there were no deaths due to lymphoma.

Some large co-operative study groups are beginning to introduce reduced-intensity treatment options for NLPHL. The EURONET paediatric protocol for NLPHL22 is randomising between excision and observation in PET negative patients versus low intensity regimens omitting anthracycline. It is certainly interesting that the three children treated in our study received what would now be regarded as intensive therapy, with significant late toxicity (infertility) in at least one case. Current large multi-centre studies ongoing in the United Kingdom (e.g. NCRI RATHL) specifically exclude NLPHL. Given the CD20 positivity of this disease, recent commentators23,24 have suggested the addition of rituximab to chemotherapeutic regimes for NLPHL. The rationale for this is logical, the outcomes are good, and the suggestion that a putative HL stem cell may be CD20 positive supports this.25 However, in the case of NLPHL, the natural history of the disease would support reserving this for those patients with relapsed disease, even as an alternative to chemo/radiotherapy.

Our local policy now recommends a first-line “watch and wait” strategy for those stage IA patients who are PET negative after excision biopsy, IFRT alone for stage IA and IIA patients, and six cycles of
ABVD chemotherapy for patients with stage III and IV disease. Data will continue to be collected. We suggest that it may be possible to reduce intensity of therapy in NLPHL without affecting OS, whilst substantially reducing the risk of late toxicities of treatment. We would support the development of multi-centre randomised controlled studies in this condition to address this hypothesis.
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DECLARATION OF INTERESTS

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The authors declare no other conflict of interest.
Reference List


(13) Savage KJ, Skinnider B, Al Mansour M et al. Incorporation of ABVD increased cure rates of patients with limited stage nodular lymphocyte predominant Hodgkin lymphoma [abstract]. Presented at the 52nd ASH meeting, Orlando, USA. 2010;3887.


Table I: Clinical characteristics of the 69 cases of NLPHL included in the study (note, where percentages do not come to 100%, this is due to rounding)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number of Patients (%)</th>
</tr>
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<tbody>
<tr>
<td>Male sex</td>
<td>48 (69.6)</td>
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<tr>
<td>Age Group</td>
<td></td>
</tr>
<tr>
<td>&lt;16</td>
<td>3 (4.3)</td>
</tr>
<tr>
<td>17-29</td>
<td>18 (26.1)</td>
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<tr>
<td>30-45</td>
<td>23 (33.3)</td>
</tr>
<tr>
<td>45-60</td>
<td>15 (21.7)</td>
</tr>
<tr>
<td>&gt;61</td>
<td>10 (14.5)</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>35 (50.7)</td>
</tr>
<tr>
<td>II</td>
<td>21 (30.4)</td>
</tr>
<tr>
<td>III</td>
<td>9 (13.0)</td>
</tr>
<tr>
<td>IV</td>
<td>4 (5.8)</td>
</tr>
</tbody>
</table>
Table II: Distribution of disease by involved region. Note, nodal involvement is not isolated unless otherwise specified.

<table>
<thead>
<tr>
<th>Region Involved</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parotid</td>
<td>3 (4.3)</td>
</tr>
<tr>
<td>Sub-mandibular</td>
<td>4 (5.8)</td>
</tr>
<tr>
<td>Cervical</td>
<td>44 (63.8)</td>
</tr>
<tr>
<td>of which, number with isolated cervical disease only</td>
<td>25 (36.2)</td>
</tr>
<tr>
<td>Axillary</td>
<td>23 (33.3)</td>
</tr>
<tr>
<td>of which, number with isolated axillary disease only</td>
<td>10 (14.5)</td>
</tr>
<tr>
<td>Mediastinal</td>
<td>6 (8.7)</td>
</tr>
<tr>
<td>Inguinal</td>
<td>10 (14.5)</td>
</tr>
<tr>
<td>Abdominal</td>
<td>11 (15.9)</td>
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<tr>
<td>Bone marrow</td>
<td>3 (4.3)</td>
</tr>
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</table>
Table III: First-line treatment of patients by clinical stage (number of patients)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Observation (%)</th>
<th>Radiotherapy Only</th>
<th>Chemotherapy only</th>
<th>Combined Modality</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>50.7</td>
<td>2</td>
<td>26</td>
<td>1</td>
</tr>
<tr>
<td>II</td>
<td>30.4</td>
<td>2</td>
<td>11</td>
<td>3</td>
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<tr>
<td>III</td>
<td>13.0</td>
<td>1</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>IV</td>
<td>5.8</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
</tbody>
</table>
Figures – please see separate bitmap files

Figure Legends

Figure 1: Kaplan-Meier plot of event-free survival (months) by type of progression

Figure 2: Kaplan-Meier plot of event-free survival (months) in all stage I & II patients treated by single modality radiotherapy as first-line treatment

Figure 3: Kaplan-Meier plot of overall survival (months)