Bone marrow infiltration was associated with a greater chance of relapse (P=0.04, odds ratio 2.747; CI95% 1.897 to 7.603). Also, relapse rate was strongly associated with death rate (P<0.0001; odds ratio 38.25; CI95% 7.716 to 189.5). Histological subtype did not influence DFS. Regarding laboratory parameters, only lactate dehydrogenase serum levels were associated with relapse (P=0.016).

**Discussion**

We demonstrated that there was no difference between MOPP/ABV and ABVD protocols in our patients regarding CR, OS, and DFS rates, the results being comparable to those described elsewhere [9, 11]. The most relevant comparative study was carried out by the cooperative group CALGB in which 856 patients were included with advanced-stage disease (stages III and IV) [9]. CR rates were 76.4% and 80.4% (P=0.16), OS 82% versus 81% (P=0.82), and DFS 63% versus 61% (P=0.42) for ABVD and MOPP/ABV, respectively. Interestingly, OS in our study was 93.8% and 89.6% and DFS 85.6% and 81.6% for ABVD and MOPP/ABV, respectively. This difference compared to CALGB results probably reflects the inclusion of patients with localized disease in our studied population (37.4% in the ABVD group and 39.5% in the MOPP/ABV group).

Few studies were done for Brazilian patients and there are none that had compared the two mentioned protocols. We acknowledge the fact that the incidence of HL in developing countries is different from developed ones as well as the severity of the disease. Therefore, we highlight the importance of studying the Brazilian population from the largest city of South America. In 1993, Spector et al. published results obtained after treating 59 patients with the COPP–ABV hybrid protocol in two public hospitals from Rio de Janeiro City, Brazil. The CR rate was 85%, a result similar to that observed in our study. However, we observed OS and DFS values of 89.6% and 81.6%, respectively, which were higher than those observed by Spector et al. (OS 78% and DFS 69%) for a similar observation period. The discrepancies observed between our study and the study conducted by Spector et al. point toward two interpretations: first, our sample size, which was larger than theirs and, second, differences in economical status observed between these two states (Sao Paulo State and Rio de Janeiro State), reflecting differences in health care.

Considering that IPRT was more frequently used during the ABVD period and that a greater proportion of patients were treated with IPRT during the MOPP/ABV period, we confirm the present tendency in using combined chemotherapy and RT, reducing the intensity and radiation field as well as the number of chemotherapy cycles, in an attempt to reduce long-term toxicity in these patients [20].

The mortality rate was similar for both protocols, and a large percentage was due to active disease. However, we point out that the mean observation period for ABVD (50 months) was inferior to that for MOPP/ABV (112 months). There were three cases of secondary malignancies in the MOPP/ABV group. Interestingly, we observed an absolute risk for secondary neoplasms of 27/10,000 per year, lower than the data published with 89.3/10,000 per year [18] or 47.2/10,000 per year [8], perhaps due to our shorter follow-up period.

Hasenclever and Diehl [13] identified seven prognostic factors strong enough to predict FFS in advanced disease: albumin < 4 g/l, hemoglobin < 10.5 g/dl, male gender, age > 45 years old, stage IV disease, white blood cell count (WBC) > 15 x 10^9 per liter, and lymphopenia (< 0.6 x 10^9 per liter or 8% of the number of WBC). In our study, we did not identify any of these factors as predictor of poorer prognosis. Again, the inclusion of patients with localized disease probably is responsible for this difference.

This study covered a 14-year period in two public hospitals in Sao Paulo city. It is noteworthy that there was practically no change in clinical presentation in our midst. Seventy-two out of 115 patients treated with ABVD (62.6%) and 43 out of 71 with MOPP/ABV (60.5%) had advanced stage at diagnosis. These data differ from those published in developed countries, where the incidence of advanced cancer is around 43% [10]. This fact brings to our attention the need for greater efforts regarding public health policies in our country, allowing earlier diagnosis in order to achieve better therapeutic results.

We carried out a retrospective study comparing ABVD and MOPP/ABV hybrid protocols and demonstrated that OS and DFS in these protocols are similar and that secondary cancer is probably more related to MOPP/ABV. We conclude that, between these two protocols, ABVD could be considered as the protocol of choice for patients with Hodgkin’s lymphoma in our population.

**References**

A pêndice


disease with MOPP, ABVD, or MOPP alternating with ABVD. N Engl J Med 327:1474–1484
5. Carbonette PF, Kaplan HS, Matushof K (1971) Report of the committee on
vinblastine and dacarbazine) chemotherapy protocols and had locally extensive or advanced stage disease at diagnosis. Locally extensive disease was defined by clinical stages I-II A/B (Ann Arbor Staging System) with massive mediastinal adenopathy (mass ≥1/3 maximum intrathoracic diameter on standing postero-anterior chest X-rays), and advanced disease defined as stages III-IV. Between 1994 and 1999, the standard treatment approach in both institutions was MOPPABV hybrid regimen, and after 1999, ABVD has been used. This research was submitted to the Brazilian Research Council and approved by the ethical review committee of both Hospitals according to the Declaration of Helsinki.

Statistical analysis

Data were analysed using SPSS version 16 software (Chicago, IL, USA). Differences in baseline patients and disease characteristics between EBV-positive and EBV-negative cHL cases were compared using either χ²-test or Fisher’s exact test. The association between EBV status and clinical parameters was analysed using logistic regression with results expressed as odds ratios (ORs) and 95% confidence intervals (CIs). Actuarial survival curves were compiled using the Kaplan-Meier method, and log-rank tests were used to compare curves. Overall survival (OS) was calculated from the date of diagnosis to the date of death or the last follow-up. Event-free survival (EFS) was calculated from the start of treatment to the date of progression, death or last follow-up. To evaluate the impact of EBV status on survival controlling for other prognostic factors, we used Cox proportional hazards regression to determine hazard ratios, which estimate the instantaneous relative risk of death averaged over the entire time period.

Results and discussion

This study included 97 patients with cHL diagnosed between 1994 and 2000. The median age was 30 years old (range from 18 to 75), and 58 patients (59.7%) were male. According to WHO classification, nodular sclerosis (NS) histologic subtype was found in 68 patients (70.2%), mixed cellularity (MC) in 27 (27.8%), lymphocyte depletion (LD) in 1 and lymphocyte predominant in 1. The majority of patients presented with advanced disease (stages III and IV) at diagnosis (61, 63%) and (71, 73%) presented with B symptoms. The median follow-up period was 80 months (range from 8 to 174 months).

EBV in RS cells was detected in 52.5% of all cases (51/97). All EBV-related cases were positive for EBER-ISH and 8% (4/51) of our cases had negative LMP1 IHC. We did not evaluate the intensity of LMP1 positivity in our cases as did the study by Vasalos et al. (6) and due to the few discrepancies observed between the two techniques we did not address them separately. The patient’s characteristics according to EBV status in RS cells are summarized in Table 1. There was no difference in age, gender, presence of B symptoms and stage at diagnosis between patients with EBV-related and non-related cHL. NS subtype was far more common in the EBV negative than in EBV positive tumour (p < 0.001) and the MC subtype was more common in EBV positive than in EBV negative (p < 0.005). Response to treatment, either complete response (CR) or partial response (PR) was observed in 89 patients (91.7%), while seven had refractory disease and one was not evaluated due to early death. There was no difference between EBV-related and non-related groups regarding CR and PR. When stratified according to the chemotherapy protocol used (MOPPABV or ABVD) or disease stage (localized or advanced), we still did not find any difference. OS and EFS curves according to EBV status showed no statistical difference between the two groups (Figure 1).

In Table 2, we showed the results of a MEDLINE/PubMed search for population-based and clinical studies for the last 10 years considering the influence of EBV in Hodgkin’s lymphoma prognosis. To build a search strategy, we used the MeSH database to find medical subject heading terms (see Table 2). Some studies have shown a worse prognosis in the EBV-related cHL (13, 14, 18, 19, 23), some reported that EBV in cHL has a positive prognostic impact (6, 10, 11, 17), while others suggest that the presence of EBV in RS cells does not influence OS (9, 15, 16, 20–22).

The discrepancies observed in these studies reflect differences in patient populations, highlighting the importance of studying different populations from different countries, limited statistical power due to small sample sizes and differences in patient recruitment and treatment used. In our study, we selected 97 HBV negative patients with cHL treated either with MOPPABV or ABVD. Our group has recently shown no difference in OS and EFS between patients with cHL treated with MOPPABV or ABVD (24). Additionally, we used two different tech-
Epstein-Barr virus related Hodgkin lymphoma prognosis

Figure 1. (A) Overall survival and (B) event-free survival curves according to EBV status in 97 patients with classical Hodgkin lymphoma from São Paulo city, Brazil.

Different techniques make our data reliable and unique for the Brazilian population. It is well known that the incidence of EBV-related cHL in developing countries is different from that in developed countries, and the severity...
Table 2. Population-based and clinical studies considering the influence of EBV presence in Hodgkin’s lymphoma for the last 10 years

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Sample size</th>
<th>EBV+ cases (%)</th>
<th>Prognostic value of EBV on cHL survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axdorph, et al. [7]</td>
<td>1999</td>
<td>92</td>
<td>33</td>
<td>Not significant</td>
</tr>
<tr>
<td>Enblad, et al. [8]</td>
<td>1999</td>
<td>117</td>
<td>27</td>
<td>Not significant</td>
</tr>
<tr>
<td>Murphy, et al. [9]</td>
<td>1999</td>
<td>190</td>
<td>27</td>
<td>Not significant</td>
</tr>
<tr>
<td>Gervais-Duarto, et al. [12]</td>
<td>2001</td>
<td>100</td>
<td>26</td>
<td>EBV+ associated with longer DFS in &lt;30 years</td>
</tr>
<tr>
<td>Clarke, et al. [13]</td>
<td>2001</td>
<td>311</td>
<td>17</td>
<td>Negative DFS only in women &gt;45 years old</td>
</tr>
<tr>
<td>Vassallo, et al. [16]</td>
<td>2003</td>
<td>78</td>
<td>64</td>
<td>Positive only LMP-1 positive cases</td>
</tr>
<tr>
<td>Stark, et al. [14]</td>
<td>2003</td>
<td>102</td>
<td>34</td>
<td>Negative</td>
</tr>
<tr>
<td>Herling, et al. [16]</td>
<td>2003</td>
<td>577</td>
<td>64</td>
<td>Not significant</td>
</tr>
<tr>
<td>Jarrett, et al. [18]</td>
<td>2005</td>
<td>437</td>
<td>33</td>
<td>Negative</td>
</tr>
<tr>
<td>Keegan, et al. [19]</td>
<td>2005</td>
<td>922</td>
<td>27</td>
<td>EBV+ associated with better survival in young patients and poorer survival in older patients with NS cHL</td>
</tr>
<tr>
<td>Kwon, et al. [20]</td>
<td>2006</td>
<td>36</td>
<td>41</td>
<td>EBV+ associated with longer DFS in &lt;25 years and shorter DFS in &gt;25 years</td>
</tr>
<tr>
<td>Kenesszies, et al. [21]</td>
<td>2006</td>
<td>109</td>
<td>43</td>
<td>Not significant</td>
</tr>
<tr>
<td>Dandri, et al. [22]</td>
<td>2007</td>
<td>118</td>
<td>97</td>
<td>Not significant</td>
</tr>
<tr>
<td>Depretis, et al. [23]</td>
<td>2009</td>
<td>412</td>
<td>34</td>
<td>EBV+ associated with shorter DFS in older patients</td>
</tr>
</tbody>
</table>

EBV, Epstein-Barr virus; cHL, classical Hodgkin’s lymphoma; OS, overall survival; LMP1, latent membrane protein 1; NS, nodular sclerosis; DFS, disease-free survival.

*DFS generally measures the time from diagnosis to primary treatment failure or relapse.

of the disease at presentation is typically more advanced, as we can see in our study, in which the majority of cases had advanced disease at diagnosis (63%). Therefore, we emphasize the importance of studying the Brazilian population from the largest city of South America.

Recently, Keegan et al. [19] and Depretis et al. [23] studied the impact of EBV tumour status in patients with cHL according to certain age groups and observed a poorer disease-free survival in older patients with EBV-related cHL. To address this question, we separately analysed patients with more than 55 years old (1497, 14.4%). Nine patients had EBV-related and five EBV non-related cHL (p = 0.07) and we did not find any difference in OS and EFS in this specific group. We acknowledge the fact that our small sample size in this age group may have influenced our results, and larger studies are warranted. Noteworthy, we are carrying a multi-centric prospective study in Brazil addressing the role of regulatory T-lymphocytes and EBV-related HL in elderly patients, and hopefully we will be able to draw more conclusive results.

We carried out a retrospective study demonstrating that EBV is present in 52.5% of patients with cHL, in Brazil, and there was no difference in the clinical evolution of these patients.

Acknowledgements

This study was supported by the São Paulo Research Council (FAPESP. 02/0290-1 and 02/09994-4).

References


Authorship and disclosures

EMS was the principal investigator and takes primary responsibility for the paper. OCGGB, MAZ, MGA recruited the patients. ACA reviewed all cases included in this study. EMS and CD performed the laboratory work for this study. DPE participated in the statistical analyses.
Epstein-Barr virus related Hodgkin's lymphoma prognosis

Matrix metalloproteinase-9 is consistently expressed in Hodgkin-Reed-Sternberg cells and has no impact on survival in patients with Epstein-Barr virus (EBV) related and non-related Hodgkin lymphoma in Brazil.

Eni M. Souza; Otávio C. G. Baiocchi; Maria A. Zanichelli; Antonio C. Alves; Marianne G. Assis; Joyce M. K. Silva; Cristine Dobo; José S. R. Oliveira

1- Federal University of São Paulo (UNIFESP), Hematology and Transfusion Service, São Paulo, SP, Brazil

2- Brigadeiro State Hospital, Oncology and Hematology Division, São Paulo, SP, Brazil

3- Federal University of São Paulo (UNIFESP), Pathology Departament, São Paulo, SP, Brazil.

Corresponding author: Otavio C. G. Baiocchi, MD, PhD.
Address: Rua Botucatu 740, Disciplina de Hematologia e Hemoterapia, Vila Clementino, São Paulo, SP, Brazil. CEP: 04023-060.
Phone: (5511) 5576-4240
Fax: (5511) 5571-8806
baiocchi@hemato.epm.br

Running title: MMP-9 expression in Hodgkin-Reed-Sternberg cells

ABSTRACT

Clinical and histological features of classical Hodgkin lymphoma (cHL) are primarily due to the effects of cytokines, enzymes and chemokines produced by Hodgkin-Reed-Sternberg (HRS) cells and their surrounding inflammatory cells in response to signals triggered by etiological factors such as Epstein-Barr virus (EBV). Matrix metalloproteinase-9 (MMP-9) has been associated with poorer survival in patients with aggressive non-Hodgkin lymphomas. In EBV-related cancers the expression of viral latent membrane protein 1 (LMP1) correlates with an increased MMP-9 expression. In this study, we evaluated the prognostic relevance of MMP-9 expression and EBV status in HRS cells in patients with cHL in Brazil. Material and Methods: We selected 97 patients with cHL. Patients were included if they had: 1) > 18 years, 2) Undergone similar chemotherapy protocols, 3) Paraffin blocks available for review and for EBV and MMP-9 detection and 4) Clinical, epidemiological and laboratorial parameters available. Results: EBV was detected in 52.5% of all cases. MMP-9 expression positivity was found in 87.6% of all cases. There was no correlation between MMP-9 expression and EBV status. Response to treatment and relapse rate were independent of MMP-9 expression and EBV status. When stratified according to chemotherapy protocol used or disease stage, we still did not find any difference. MMP-9 positivity did not influence overall survival and event free survival. Conclusion: MMP-9 are expressed in the majority of HRS cells and did not correlated with EBV status or survival. The consistent MMP-9 expression in HRS cells makes this enzyme a potential target for therapy.

Key words: Hodgkin lymphoma, metalloproteinase-9, Epstein-Barr virus, prognostic, survival
INTRODUCTION

Classical Hodgkin lymphoma (cHL) is a B cell malignancy most commonly affecting young adults (1). Unlike most other human malignancies, the malignant cells of cHL, the so-called Hodgkin-Reed-Sternberg (HRS) cells, are vastly outnumbered by the surrounding nonmalignant inflammatory cells (1-3). It is now widely believed that the clinical and histological features of cHL are primarily due to the effects of a plethora of cytokines, enzymes and chemokines produced by HRS cells and their surrounding cells in response to inflammatory signals triggered by etiological factors such as Epstein-Barr virus (EBV) (3). Latent EBV genomes are found in HRS cells of approximately one-third of cHL cases, although the rate of involvement is as high as 100% in developing countries (4).

The matrix metalloproteinases (MMPs) are a family of zinc- and calcium-dependent proteolytic enzymes capable of degrading most extracellular matrix (ECM) components (5). MMP-9 is a member of this family and has a role in degrading denatured collagens, native Type IV and Type V collagens, and elastin (5, 6). Because Type IV collagen is one of the integral components of the basement membrane (BM), the uncontrolled expression of MMP-9 is believed to play a critical role in the invasion of the BM by tumor cells (5). MMP-9 has been implicated in tumor invasion and metastasis in several solid tumors (6-8). In one study by Sakata et al. (9) MMP-9 expression was associated with poorer survival in patients with aggressive non-Hodgkin lymphomas. In EBV-related cancers and in vitro studies the expression of viral latent membrane protein 1 (LMP1) seems to correlate with an increased expression of MMP-9, but its prognostic relevance remains controversial (8, 10, 11).

In this study, we evaluated the prognostic relevance of matrix metalloproteinase-9 expression and EBV status in HRS cells in patients with cHL in Brazil.
MATERIAL AND METHODS

A total 97 cases of cHL with sufficient paraffin wax embedded tissue was selected for this study. All cases were diagnosed between 1994 and 2004 at the University Hospital São Paulo and the Hospital Brigadeiro, both of which are located in the city of São Paulo, Brazil. The two selected hospitals are public hospitals and responsible for the assistance of nearly six million people. All cases were subjected to hemopathologist re-review and subtyped according to the W.H.O classification system. Patients with positive HIV serology were excluded from this study. Determination of EBV association in tumor biopsies was done by \textit{in situ} hybridization (HIS) for EBV-encoded RNA (EBER) and immunohistochemistry (IHC) for LMP-1 following previously established procedures (12, 13). Cases with positive results on one or both tests were defined as EBV-related cHL. All assays were done in duplicate, and when discrepancies occurred, both techniques were repeated. For MMP-9 detection, immunohistochemical staining with a mouse monoclonal antibody to MMP-9 (dilution 1:200) (Lab Vision Corp, Freemont, California, USA) was performed using the avidin–biotin–peroxidase complex method as previously described (14). One section known to give strong staining was included in each subsequent run as a positive control. Negative controls consisted of the substitution of the MMP-9 antibody with non-immune serum. For the evaluation of immunohistochemical staining, intensity of staining was considered negative when less than 10% of the HRS cells demonstrated expression for MMP-9; positive (+) when positivity ranged from 11 to 50% of HRS cells and positive (++) when more than 50% of HRS cells was involved. Visualization of these reactions was done by peroxidase–antiperoxidase method with diaminobenzidine as a substrate.

All patients received either MOPP/ABV (mechlorethamine, vincristine, procarbazine, prednisone, doxorubicin, bleomycin and vinblastine) or ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) chemotherapy protocols and had locally extensive or advanced stage disease at diagnosis. Locally extensive disease was defined by clinical stages I-II-A/B (Ann Arbor Staging System) with massive mediastinal adenopathy (mass \( \geq 1/3 \) maximum intrathoracic diameter on standing postero-anterior chest x-rays), and advanced disease
defined as stages III-IV. Between 1994 and 1999 the standard treatment applied in both institutions was MOPP/ABV hybrid regimen, and after 1999, ABVD has been used. The Cancer and Leukemia Group B (CALGB) published in 2003 (15) that there was no difference in EFS and OS comparing MOPP/ABV and ABVD in patients with cHL, a study published by our group also showed the same results (16). This research was submitted to the Brazilian Research Council and approved by the ethical review committee of both Hospitals according to the Declaration of Helsinki.

STATISTICAL ANALYSIS

Data were analyzed using SPSS version 16 software (Chicago, IL, USA). Differences in baseline patients and disease characteristics between MMP-9 expression and EBV-related and non-related cHL were compared using either chi-square test or Fisher's exact test. The association between EBV status and MMP-9 expression was analyzed using logistic regression with results expressed as odds ratios (ORs) and 95% confidence intervals (CIs). Actuarial survival curves were compiled using the Kaplan-Meier method, and log-rank tests were used to compare curves. Overall survival (OS) was calculated from the date of diagnosis to the date of death or the last follow-up. Event free survival (EFS) was calculated from the start of treatment to the date of progression, death or last follow-up.
RESULTS AND DISCUSSION

This study included 97 patients with cHL diagnosed between 1994 and 2004. The median age was 30 years old (ranging from 18 to 75), and 58 patients (59.7%) were male. According to W.H.O. classification, nodular sclerosis (NS) histological subtype was found in 68 patients (70.2%), mixed cellularity (MC) in 27 (27.8%), lymphocyte depletion (LD) in 1 and lymphocyte predominant in 1. The majority of patients presented with advanced disease (stages III and IV) at diagnosis (61, 63%) and (71, 73%) presented with B symptoms. The median follow-up was 84 months ranging from 20 to 194 months. EBV in HRS cells was detected in 52.5% of all cases (51/97). All EBV-related cases were positive for EBER-HIS and 8% (4/51) of our cases had negative LMP-1 IHQ. Nodular sclerosis (NS) subtype was far more common in the EBV negative than in EBV positive tumor (P<0.001) and the mixed cellularity (MC) subtype was more common in EBV positive than in EBV negative (P=0.005).

MMP-9 expression positivity was found in 85/97 patients (87.6%), 35 positive (+) and 50 positive (++). Only 12 patients (12.4%) had less than 10% of HRS cells with positive expression and were considered negative. There was no difference in age, gender, histological subtype, presence of B symptoms and stage at diagnosis in relation to MMP-9 expression. There was no correlation between MMP-9 expression and the intensity of expression with EBV status in HRS cells. Response to treatment, either complete response (CR) or partial response (PR), and relapse rate were independent of MMP-9 expression and EBV status. When stratified according to the chemotherapy protocol used (MOPPABV or ABVD) or disease stage (localized or advanced), we still did not find any difference. MMP-9 positivity did not influence overall survival (OS) and event free survival (EFS) (P=0.60 and P=0.19, respectively) (Figure 1) in this group of patients.

The complex process of tumor invasion and metastasis include the degradation of the ECM and BM by several enzymes (5, 17, 18). MMP-9 is believed to be one of the critical enzymes required for tumor metastasis (17). In EBV-related cHL, the HRS cells have a restricted set of viral proteins expression (3, 4). LMP-1 is always expressed in this context and is critical for EBV survival and latency maintenance (3, 19). Some studies have shown that LMP-1 increases MMP-9 expression (8, 10,
11). Given that the incidence of EBV-related cHL and also disease presentation and severity are different in developing countries than in developed ones, we examined the relevance of MMP-9 in a series of cHL cases treated in two public Hospitals in Brazil.

In this study, we demonstrated that MMP-9 is expressed in the majority of HRS cells in cHL cases and did not correlate with EBV status in the tumor. Additionally, MMP-9 expression had no impact on relapse rate and survival. Flavell et al. (14) also showed that MMP-9 expression was not related either to LMP-1 values or to survival. Although presenting similar results, in the study conducted by Flavell et al. (14) important clinical and epidemiological data were omitted. In our study, information regarding patient’s characteristics, treatment used, response to treatment and follow-up were gathered together enabling us to perform a more detailed analysis.

MMP-9 over-expression is found in aggressive B and T cell lymphomas and is associated with poorer prognosis (9). Similar findings were demonstrated in nasopharyngeal carcinoma (8). Noteworthy, in this EBV-related cancer the expression of MMP-9 had a significant positive correlation with the expression of LMP-1 (8). In colon-rectal and pancreatic cancers MMP-9 expression was a significant independent prognostic factor for patient’s survival (6, 7). We acknowledge the fact that our small sample size and the predominance of advanced disease at diagnosis may be responsible for the lack of association between EBV and MMP-9 expression and further investigations are warranted. Interestingly, the consistent and increased intensity of MMP-9 expression in HRS cells make this enzyme a potential target for therapy.
REFERENCES


Authorship and Disclosures

EMS was the principal investigator and takes primary responsibility for the paper. EMS, OCCGB, MAZ, MGA recruited the patients. ACA reviewed all cases included in this study. EMS and CD performed the laboratory work for this study. JMKS participated in the statistical analysis and recruited the patients. EMS, OCCGB, JR SO co-ordinated the research. EMS, OCCGB, DPE, JR SO wrote the paper. JR SO critically revised the paper. The authors reported no potential conflicts of interest.
Figure 1. A) Event free survival and B) Overall survival curves according to MMP-9 positivity in 97 patients with classical Hodgkin’s lymphoma. Negative when less than 10% of the HRS cells demonstrated expression for MMP-9; positive (+) when positivity ranged from 11 to 50% of HRS cells and positive (++) when more than 50% of HRS cells was involved.
BIBLIOGRAFIA CONSULTADA