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DIAGNOSTIC PITFALLS AND THERAPEUTIC CHALLENGES

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PRIMARY EXTRANODAL VAGINAL NON-HODGKIN LYMPHOMA:

DIAGNOSTIC PITFALLS AND THERAPEUTIC CHALLENGES

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5Hygiene and Preventive Medicine, Department of Medical, Surgical and Experimental Sciences, University of Sassari, Sassari, Italy.

Running title: primary extranodal vaginal non-hodgkin lymphoma

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SUMMARY

Introduction: primary extranodal non-hodgkin vaginal lymphoma (PeNHVL) represents a rare entity, with few data published until now. We present here a series of patients with PeNHVL, analyzing our data as part of a detailed review of the available literature.

Methods: the study included a consecutive series of 6 patients with final diagnosis of PeNHVL admitted at our Institution between January 2000 and December 2017. The systematic review was conducted according to PRISMA guidelines. A literature search of the PubMed, MEDLINE and EMBASE electronic databases was performed using the following terms: ‘vaginal lymphoma’. Relevant data were collected and analyzed for the purposes of this study, reporting results through a narrative approach.

Results: in our series discomfort and vaginal pain, refractory to medical treatments represent the symptoms of disease presentation, and the presence of localized/diffused anelastic area in the vaginal wall with tactile sensation of cork emerges as diagnostic sign (Cork Wall sign). The literature revision included 41 studies, with an overall population of 74 patients. The vast majority of women were diagnosed as early stage disease (93.6%) and received chemotherapy (74.6%) with a very high response rate (96%). Death from disease occurred in 5 women (6.7%).

Conclusions: localized or diffused hard-ligneous vaginal areas with Cork Wall sign represent the typical sign of disease presentation. PeNHVL is characterized by a very high sensitivity to chemotherapy and very favourable prognosis; therefore, radical surgery is not indicated. Histotype characterization is crucial to identify those uncommon variants associated with a less favorable clinical outcome.
INTRODUCTION

Around 25% of non-Hodgkin's lymphomas (NHL) arise from tissue other than lymph nodes, being therefore defined as primary extranodal non-Hodgkin lymphoma (NHL) (Zucca and Cavalli, 2000). This uncommon presentation has been described in almost every organ, and relevant differences, also in term of prognosis, have been described according to primary anatomic site (Krol et al., 2003).

In this context, the female genital tract is a well-known unusual site in which NHL may occur, with ovary, cervix, and uterus as the most commonly involved organs (Krol et al., 2003). On the other hand, the observation of primary extranodal NHL arising in the vagina represents a very rare event with only 68 cases described in the literature until now (Bickel and Bennet, 1954; Weseley and Berrigan, 1958; Butchler and Kline, 1972; Chorlton et al., 1974; Harris and Scully, 1984; Bagella et al., 1989; Liang et al., 1990; Perren et al., 1992; Prevot et al., 1992; Lonardi et al., 1994; Hoffkes, et al., 1995; Jenkins et al., 1997; Guarini et al., 1999; Harris et al., 1999; Perin et al., 2000; Raspagliesi et al., 2000; Vang et al., 2000; Vang et al., 2000; Hayama et al., 2001; Nakamura et al., 2001; Domingo et al., 2004; Engin et al., 2004; Yoshinaga et al., 2004; Garavaglia et al., 2005; Kosari et al., 2005; Carbone et al., 2006; Zafar et al., 2006; Cohn et al., 2007; Hussein et al., 2007; Signorelli et al., 2007; Akbayir et al., 2008; Mahedran 2008; Ikuta et al., 2010; Komine et al., 2011; Guastafierro et al., 2012; Nasu et al., 2012; Cao et al., 2014; Herraiz et al., 2015; Silva et al., 2015; Nohuz et al., 2016; Wang et al., 2018).

Therefore, as for other unusual malignancies, the achievement of a correct diagnosis, as well as the definition of an appropriate therapy is often very challenging given the relevant potential diagnostic pitfalls, and the lack of data regarding prognosis.

Furthermore, the first observation of female genital tract malignancies is carried out by gynecologists, and also for primary extranodal non-hodgkin vaginal lymphoma (PeNHVL) the most common
Symptom at diagnosis involves the gynecological field with the vast majority of women complaining of vaginal discomfort and pain. Therefore, a close cooperation between gynecologists, histopathologists, and onco-hematologists is mandatory to properly manage this uncommon disease avoiding inappropriate therapeutic strategies.

For these reasons, it is crucial to carefully analyze evidence, trying to address the needs of both physicians, and patients facing this challenging entity.

In this context, with the aim of addressing the above-mentioned issues, we present here a series of women who received both diagnosis, and treatment for PeNHVL at our Institution, analyzing our data as part of a detailed revision of the available literature.

MATERIALS AND METHODS

Study Patients

The study included a consecutive series of patients showing a final histological diagnosis of PeNHVL admitted to the Unit of Obstetrics and Gynecology of the University of Sassari between January 2000 and December 2017. All women were submitted to gynecological examination, pelvic ultrasound, colposcopy with biopsy of the vaginal lesion, blood tests, bone marrow biopsy, CT and PET scan in order to achieve the final staging.

Data were collected on: patients' age at the time of diagnosis, initial symptoms, location and morphological features of the lesion, histological type and tumor stage, as well as immunohistochemistry analysis, treatment details, follow-up and prognosis. All women signed informed consents for their data to be collected and analyzed for scientific purpose, and the retrospective study was approved by the Institutional Review Board.
**Histological and immunohistochemical analysis**

All histological specimens were taken from the wall of the vagina, and evaluated by the Histopathology Unit of the Department of Surgical Pathology of the University of Sassari. All specimens were fixed in 10% buffered formalin and embedded in paraffin. Sections 3 µm thick were stained with hematoxillin and eosin (H&E), Periodic Acid of Schiff (PAS), Giemsa and Grocott according to the usual histopathologic techniques. Immunohistochemical investigations were used to characterize the lymphoid cell proliferation. The following antibodies have been investigated by immunohistochemistry: CD45, CD20, CD79a, CD3, CD4, CD30, CD10, BCL1, BCL2, BCL6, MUM1, MYC, CK, IRTA. Polymerase chain reaction (PCR), Immunohistochemistry and fluorescent in situ hybridization techniques (FISH) were performed to investigate for t(14/18) translocation, for Human papilloma virus (HPV), Epstein Barr Virus (EBV) and Cytomegalovirus (CMV) according to the usual techniques. The lymphoid neoplasm was classified according to WHO classification of non-Hodgkin's lymphomas (NHL) identifying both histotype, and immunohistochemical profiles (Swerdlow et al., 2016).

**Treatment**

The patients with PeNHVL received chemotherapy according to the CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) regimen for a total of 4-6 cycles. Also radiation therapy, for a total dose of 50Gy, has been administered in selected cases as summarized in Table 1. The treatment choice was mainly based on tumor stage, and histotype. Patients were evaluated for clinical response to chemotherapy according to RECIST criteria (Eisenhauer, et al., 2009).
Literature Review

The systematic review was conducted according to the preferred reporting items for systematic reviews and metaanalyses (PRISMA) guidelines (Liberati et al., 2009). A literature search of the PubMed, MEDLINE and EMBASE electronic databases was performed using the following terms: ‘vaginal lymphoma’. All types of articles reporting clinical data regarding PeNHVL were included in the systematic reviews. After study selection, relevant data were collected and analyzed for the purposes of this study, reporting results through a narrative approach.

RESULTS

Our series

Between January 2000 and December 2017, 6 women with proven histological diagnosis of PeNHVL were admitted at our Institution, thus representing one of the largest series published until now (Table 1). All women underwent a gynecological examination due to the presence of persistent symptoms of discomfort and severe vaginal pain, refractory to medical treatments, which represent the symptoms of disease presentation. At vaginal examination, we observed a change in vaginal consistency with loss of elasticity, and the presence of a localized or diffused anelastic area in the vaginal wall with the typical tactile sensation of cork, thus identifying the so-called Cork Wall diagnostic sign of PeNHVL. Blood examination at the time of diagnosis did not reveal changes in the normal white blood cells count showing just mild anemia only in 2 women affected by LBCNHL, LDH was within normal limits in all cases, and no evidence of lymphadenopathy at clinical and CT scan investigations. Medical history and serological investigations were within normal limits; immunohistochemical and molecular investigations confirmed the absence of active infections from Hepatitis, Herpes, Human papilloma,
Cytomegalovirus and Epstein-Barr virus. All cases according to the Lugano Classification for staging the non-Hodgkin lymphomas were classified as stage IE (Cheson et al., 2014).

From a diagnostic point of view, in 3 patients (50.0%) first biopsy performed with traditional cervical forceps resulted negative for malignancy, requiring a further conic sampling performed deeply in the vaginal wall using cold knife. Median age at diagnosis was 52 years old (42-69 years), and histopathological diagnosis documented a diffuse large B-cell NHL (DLBCL) with positive staining for CD20 (Figure 1D) in 5 patients (83.4%), and follicular lymphoma (FL) in one woman (16.6%). In the vast majority of patients PeNHVL was diagnosed as early stage (Stage IEA=66.7%, Table 1) thus further supporting the excellent prognosis. All women received chemotherapy according to the recommended R-CHOP regimen, and in 4 patients also radiation therapy was administered. Complete response was achieved in all cases, and with a medium follow-up time of 54 months no recurrences or systemic diffusion were observed.

**Histological findings**

Four cases were characterized by a diffuse proliferation of large atypical lymphoid cells, centroblastic like (Figure 1C), positive for B-cell markers such as CD20 (Figure 1D), and CD79a, intermingled with small T lymphocytes positive for CD3, indicative of DLBCL. One case with Follicular Lymphoma (FL) showed a nodular structure with a large amount of centroblasts like cells. Three cases of DLBCL were negative for CD10 and positive for BCL6 and BCL2. One case of DLBCL as well the FL was positive for CD10, BCL6 and BCL2; All cases were negative for MUM1, CD30, BCL1 and MYC. All cases were CD45 positive. On the basis of these findings the 4 cases of DLBCL according to the Hans (Hans CP et al 2004) criteria, were diagnosed as NH, DLBC, GCB type. The FL according to the WHO classification, on the basis of the number of centroblasts more than 15 per high power field (HPF) and
presence of centrocytes have been diagnosed as follicular lymphoma grade 3a. None of the cases had a blastoid appearance. The bone marrow biopsies performed in all cases showed no involvement by lymphoma. All cases showed a characteristic subepithelium “normal free” zone separating the epithelium from neoplastic lymphoid infiltration (Figure 1A) mostly localized deeply in vaginal stromal tissue. Some cases also showed lymphoid infiltration just beneath the epithelium (Figure 1B) but none of the cases showed epithelium infiltration or ulceration. These findings give evidence that superficial biopsies were not adequate for diagnosis as actually happened in some of our cases (see above), but deep biopsies were required to achieve histological diagnosis.

**Literature review**

As described in material and methods section all case reports, and case series published until now reporting clinical data of patients with diagnosis of PeNHVL have been retrieved and analyzed for study purposes (Figure 2). In particular, 398 studies were retrieved from the electronic databases, with 237 (59.5%) case series being excluded since they did not report data on primary PeNHVL, and 121 (30.4%) studies removed from final analysis for lack of data regarding diagnosis, therapy, and follow up. As a consequence, 41 studies (10.3%, including the present study) were included in final literature review, with an overall population of 74 patients affected by PeNHVL (including our series).

Focusing on tumor histotype, around 66% of women with PeNHVL showed DLBCL, while FL occurred in 10 women (13% of the overall series). Finally, reticulum cell sarcoma (so-called according to previous NHL classification), and lymphocytic lymphoma accounted for around 5% of PeNHVL, respectively (Table 2). Median age at diagnosis was 48 years (19-82 years), with women showing reticulum cell sarcoma being around one-decade younger compared with the overall population.
The vast majority of patients were diagnosed with early stage of disease (Stage IIE = 93.6%, Table 2). Regarding treatment strategies, chemotherapy, and radiation therapy were administered in 74.6%, and 42.9% of patients with PeNHVL, respectively. In particular, in women with DLBCL, and FL, R-CHOP regimen was administered in 92.7%, and 66.7% of cases. On the other hand, all patients showing reticulum cell sarcoma, and lymphocytic lymphoma did not receive chemotherapy, being submitted to radiation therapy alone, and in one case with reticulum cell sarcoma radical surgery alone. Overall, PeNHVL showed a very high sensitivity to treatments with a 96% rate of complete/partial response to chemotherapy/radiation therapy. Progressive disease was observed in just one woman with reticulum cell sarcoma. Focusing on prognosis, only one death from disease was documented in patients with DLBCL (2.7%), with the remaining 4 deaths from disease occurring in the group of reticulum cell sarcoma, lymphocytic lymphoma, and other histotypes. No recurrences, or death from disease were observed in patients with FL (Table 2).

DISCUSSION

PeNHVL represents a very rare malignancy, with unique biological and clinical behaviors, raising several diagnostic, and therapeutic challenges.

For instance, disease presentation in our series, as well as in the reported literature, is very unusual with the absence of “B symptoms” (i.e. fever, night sweats, and weight loss), no enlarged lymph nodes elsewhere, no bone marrow involvement and the presence of the typical gynecological symptoms represented by vaginal discomfort and pain (Bickel and Bennet, 1954; Weseley and Berrigan, 1958; Butchler and Kline, 1972; Chorlton et al., 1974; Harris and Scully, 1984; Bagella et al., 1989; Liang et al., 1990; Perren et al., 1992; Prevot et al., 1992; Lonardi et al., 1994; Hoffkes, et al., 1995; Jenkins et al., 1997; Guarini et al., 1999; Harris et al., 1999; Perin et al., 2000; Raspagliesi et al., 2000; Vang et
al., 2000; Vang et al., 2000; Hayama et al., 2001; Nakamura et al., 2001; Domingo et al., 2004; Engin et al., 2004; Yoshinaga et al., 2004; Garavaglia et al., 2005; Kosari et al., 2005; Carbone et al., 2006; Zafar et al., 2006; Cohn et al., 2007; Hussein et al., 2007; Signorelli et al., 2007; Akbayir et al., 2008; Mahedran 2008; Ikuta et al., 2010; Komine et al., 2011; Guastafierro et al., 2012; Nasu et al., 2012; Cao et al., 2014; Herraiz et al., 2015; Silva et al., 2015; Nohuz et al., 2016; Wang et al., 2018).

Therefore, PeNHVL even representing a hematologic disease is always firstly identified by gynecologists, with pathologists playing the crucial role of linking between the above-mentioned specialists. From the gynecologic point of view our series, representing one of the largest published until now, emphasizes some crucial points. First of all, compared with vaginal epithelial malignancies, PeNHVL does not present as an ulcerated bleeding lesion, but as a diffuse infiltration of the vaginal wall. As a consequence, the typical soft aspect of vaginal tissue is replaced by a cork like hard-ligneous consistence. This finding is related to a deep, thick infiltration of the wall by the lymphoid proliferation and represents the most suspicious sign of disease. Another crucial point emerging from our series is the need to perform repeated biopsies with cold knife excision of a deep portion of vaginal wall in one half of patients. Superficial biopsies in our cases were often devoid of lesion, since it was possible to see the tumour only in the deep portion of the vaginal wall. Focusing on this point, it appears obvious that compared with epithelial malignancies always showing a superficial neoplastic erosion, PeNHVL requires to sample an adequate portion of vaginal wall to allow pathologists to safely identify the lymphocytic infiltration in the mucosal and submucosal layers. Therefore, in patients complaining of a long-lasting vaginal pain and discomfort without bleeding, and the sign of Cork Wall we suggest to always perform biopsies deeply in the vaginal wall to avoid diagnostic delay. Recently, a new technique by FNAC (Fine Needle Aspiration Cytology) (Zeppa, et al., 2010) has been suggested to characterize lymphoid proliferation either benign or malignant by cytologic criteria supported by flow
cytometry. This procedure has been used with good results mostly to investigate lymph nodes but also extra nodal lymphoid proliferation. However since in our cases the nature of the lesions was unexpected and characterized by absence of a mass, the procedure above mentioned has not been taken into consideration, also because histological specimens taken were enough to characterize completely the lymphoid proliferation. However, on the basis of these observations, gynecologists, if able to identify the sign of Cork Wall, should suspect a lymphoid proliferation and in this case such a procedure should be taken into consideration to avoid deep biopsies.

In this context, in accordance with the results of the available literature, also in our series, around 90% of PeNHVL have been diagnosed at early stage, without differences among tumor histotypes (Table 2). Moreover, clinical behavior appears very favorable with an incidence of death from disease accounting for 8.7% (5 women) in the overall population (Table 2). Therefore, PeNHVL appears as a very peculiar hematological entity characterized by a low proliferation rate with a favorable natural history, which appears significantly different from patients with classical nodal lymphomas but similar to other extra nodal NHLs (Zucca and Cavalli, 2000; Krol et al., 2003).

As reported in Table 2, histopathological examination should drive therapeutic choices also providing a characterization of PeNHVL. In fact, this malignancy should not be considered as a unique disease, since at least 4 major types of PeNHVL can be identified: DLBCL which represents the most common variant accounting for 67.6% of the PeNHVL, followed by FL (12.2%), reticulum cell sarcoma (5.4%), (old terminology, currently more properly called DLBC NHL) and lymphocytic lymphoma (4.0%).

In this context, our literature revision focuses for the first time the clinical differences among tumor histotypes providing, in an overall population of 74 patients (including our cohort), useful data to properly face this challenging disease (Table 2). In particular, women with vaginal so-called reticulum cell sarcoma appeared around a decade younger compared with the other groups. Furthermore, the 7
patients with so-called reticulum cell sarcoma and lymphocytic lymphoma chemotherapy received surgery and radiation therapy as primary treatment, with no women receiving chemotherapy and 2 deaths from disease were observed (28.5%) due to early disease progression. On the other hand, among the 59 patients with DLBCL and FL almost all women experienced complete response to chemotherapy (R-CHOP regimen) with only 1 woman (2.7%) showing partial response. Therefore, even if the overall behavior of PeNHVL appears very favorable, the two variants of so-called reticulum cell sarcoma and lymphocytic lymphoma seem to be characterized by a more unfavourable clinical outcome due to the development of systemic disease. Furthermore, in the last decade the successful results achieved with the use of chemotherapy alone have progressively reduced the use of radiation therapy in this clinical setting.

Regarding the potential role of viral infections in the development of PeNHVL our data did not show the presence of HPV, Hepatitis, Herpes, Cytomegalovirus and Epstein-Barr virus and, in line with available literature, this intriguing hypothesis cannot be definitively supported, since a clear correlation remains to be demonstrated in future studies.

In conclusion, PeNHVL appears a very rare entity which requires a careful diagnostic approach by gynecologists to achieve a proper sampling trying to reduce as much as possible therapeutic delays. The presence of localized or diffused hard-ligneous vaginal areas with the Cork Wall sign represent the typical disease presentation. PeNHVL is characterized by a very high sensitivity to chemotherapy with a very favourable prognosis (overall survival approaching 95%); therefore, radical surgery is not indicated in this clinical setting. Finally, histotype characterization is always required to identify those uncommon variants associated with a less favorable clinical outcome. As for other rare orphan malignancies, also for PeNHVL a close cooperation among Institutions with the development of worldwide registries is urgently needed to improve disease knowledge, and therapeutic approaches.
ACKNOWLEDGMENTS

None to be acknowledged.
REFERENCES


Harris N.L. and Scully R.E. (1984). Malignant lymphoma and granulocytic sarcoma of the uterus and


Hodgkin’s lymphoma of the vaginal wall in a hemodialysis patient with hepatocellular carcinoma. J. UOEH. 33, 139-146.


Figure 1: A. All cases showed a characteristic subepithelium “normal free” zone separating the normal epithelium from the neoplastic lymphoid infiltration mostly localized deeply in vaginal stromal tissue (H&E X20; Scale Bar=1mm). B. Some cases showed also lymphoid infiltration just beneath the normal epithelium (H&E X100; Scale Bar=500µm). C Diffuse proliferation of large atypical lymphoid cells (H&E X200; Scale Bar=100µm). D. The large lymphoid cells are strongly CD20 positive (IHC X300; Scale Bar=50µm).

Figure 2. CONSORT diagram describing the studies identified and included in the systematic review.
Table 1. Clinico-pathological characteristics of the study population.

<table>
<thead>
<tr>
<th>YEAR</th>
<th>AGE</th>
<th>SYMPTOMS AT DISEASE PRESENTATION</th>
<th>STAGE</th>
<th>HISTOLOGY</th>
<th>TREATMENT</th>
<th>FOLLOW-UP TIME (Months)</th>
<th>RESPONSE TO TREATMENT</th>
<th>SURVIVAL STATUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>52</td>
<td>vaginal discomfort, vaginal pain, vaginal bleeding,</td>
<td>IEA</td>
<td>DLBLC</td>
<td>Chemotherapy-RT (50 Gy)</td>
<td>216</td>
<td>CR</td>
<td>NED</td>
</tr>
<tr>
<td>2010</td>
<td>60</td>
<td>vaginal discomfort, vaginal pain, vaginal bleeding, dyspareunia</td>
<td>IEA</td>
<td>DLBLC</td>
<td>Chemotherapy-RT (50 Gy)</td>
<td>72</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td>2012</td>
<td>47</td>
<td>vaginal discomfort, vaginal pain</td>
<td>IIEA</td>
<td>DLBLC</td>
<td>Chemotherapy-RT (50 Gy)</td>
<td>72</td>
<td>CR</td>
<td>NED</td>
</tr>
<tr>
<td>2014</td>
<td>52</td>
<td>vaginal discomfort, vaginal pain</td>
<td>IEA</td>
<td>DLBLC</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td>2015</td>
<td>69</td>
<td>vaginal discomfort, vaginal pain, weight loss</td>
<td>IEA</td>
<td>DLBLC</td>
<td>Chemotherapy alone</td>
<td>36</td>
<td>CR</td>
<td>NED</td>
</tr>
<tr>
<td>2017</td>
<td>42</td>
<td>vaginal discomfort, vaginal pain</td>
<td>IIEA</td>
<td>FL</td>
<td>Chemotherapy alone</td>
<td>3</td>
<td>CR</td>
<td>NED</td>
</tr>
</tbody>
</table>

DLBLC= diffuse large B-cell lymphoma; FL= follicular lymphoma; CR=complete response; NED= alive, with not evidence of disease
n.a. not available
### Table 2. Clinico-pathological characteristics, and treatment details of the published cases according to tumor histotype.

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>TYPE OF VAGINAL LYMPHOMA</th>
<th>(n)</th>
<th>%</th>
<th>(n)</th>
<th>%</th>
<th>(n)</th>
<th>%</th>
<th>(n)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N^o) of patients</td>
<td>ALL</td>
<td>74</td>
<td></td>
<td>49</td>
<td>66.2%</td>
<td>10</td>
<td>13.6%</td>
<td>4</td>
<td>5.4%</td>
</tr>
<tr>
<td>Median Age (years, range)</td>
<td>ALL</td>
<td>48.8 (19-82)</td>
<td>48.1 (19-79)</td>
<td>46.7 (25-71)</td>
<td>35.2 (20-47)</td>
<td>54 (31-79)</td>
<td>62.2 (52-82)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage</td>
<td>IEA-IIE</td>
<td>59</td>
<td>93.6%</td>
<td>38</td>
<td>92.7%</td>
<td>10</td>
<td>100%</td>
<td>4</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>IIIE-IVA</td>
<td>4</td>
<td>6.4%</td>
<td>3</td>
<td>7.3%</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>n.a.</td>
<td>11</td>
<td></td>
<td>8</td>
<td></td>
<td>0</td>
<td></td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>Yes</td>
<td>47</td>
<td>74.6%</td>
<td>38</td>
<td>92.7%</td>
<td>6</td>
<td>66.7%</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>16</td>
<td>25.4%</td>
<td>3</td>
<td>7.3%</td>
<td>3</td>
<td>33.3%</td>
<td>4</td>
<td>100%</td>
</tr>
<tr>
<td>Radiation therapy</td>
<td>Yes</td>
<td>36</td>
<td>57.1%</td>
<td>25</td>
<td>61%</td>
<td>4</td>
<td>44.4%</td>
<td>3</td>
<td>75%</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>27</td>
<td>42.9%</td>
<td>16</td>
<td>39%</td>
<td>5</td>
<td>55.6%</td>
<td>1</td>
<td>25%</td>
</tr>
<tr>
<td></td>
<td>n.a.</td>
<td>11</td>
<td></td>
<td>8</td>
<td></td>
<td>1</td>
<td></td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Response to treatment</td>
<td>CR</td>
<td>47</td>
<td>88.7%</td>
<td>35</td>
<td>97.2%</td>
<td>9</td>
<td>100%</td>
<td>1</td>
<td>33.3%</td>
</tr>
<tr>
<td></td>
<td>PR</td>
<td>3</td>
<td>5.6%</td>
<td>1</td>
<td>2.8%</td>
<td>0</td>
<td></td>
<td>1</td>
<td>33.3%</td>
</tr>
<tr>
<td></td>
<td>PD</td>
<td>3</td>
<td>5.6%</td>
<td>0</td>
<td></td>
<td>0</td>
<td></td>
<td>1</td>
<td>33.3%</td>
</tr>
<tr>
<td></td>
<td>n.a.</td>
<td>21</td>
<td></td>
<td>13</td>
<td></td>
<td>1</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Follow-up n°</td>
<td>Death from disease</td>
<td>5</td>
<td>8.7%</td>
<td>1</td>
<td>2.7%</td>
<td>0</td>
<td></td>
<td>1</td>
<td>25%</td>
</tr>
<tr>
<td></td>
<td>Death from other causes</td>
<td>2</td>
<td>3.5%</td>
<td>0</td>
<td></td>
<td>0</td>
<td></td>
<td>1</td>
<td>25%</td>
</tr>
<tr>
<td></td>
<td>n.a.</td>
<td>17</td>
<td></td>
<td>13</td>
<td></td>
<td>1</td>
<td></td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>
DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; CR = complete response; PR = partial response; PD = progressive disease; n.a. = not available. Percentages have been calculated excluding cases with n.a. data.
Studies retrieved on electronic databases, keyword: vaginal lymphoma (n=398)

Studies excluded: no primary vaginal lymphoma (n=237)

Eligible studies evaluated for study analysis (n=161)

Studies not included in final analysis: no mention of diagnosis, therapy and prognosis. (n=121)

Studies included in final narrative analysis (n=41)