Gynecologic Oncology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Primary lymphoma of the female genital tract: An analysis of 697 cases

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HIGHLIGHTS

- Primary lymphoma of the female genital tract is a rare and most commonly arises from the ovary and cervix.
- The most prevalent histologic subtypes are diffuse large B-cell and follicular lymphoma.
- Localized disease, premenopausal age, and follicular histology are associated with better outcomes.

ARTICLE INFO

Article history:
Received 3 January 2017
Received in revised form 27 February 2017
Accepted 28 February 2017
Available online xxxx

Keywords:
Lymphoma
B-cell lymphoma
Extranodal lymphoma
Uterus
Ovary
Cervix

ABSTRACT

Objective. Primary lymphoma of the female genital tract (PLFGT) is a rare entity. The aim of this population-based study was to elucidate the clinico-pathological, demographic characteristics and survival of women with PLFGT.

Materials and methods. The Surveillance, Epidemiology, and End Results database was accessed and cases of PLFGT diagnosed between 1988 and 2012 were identified. Five-year overall (OS) and cancer-specific (CSS) survival rates were calculated with the Kaplan-Meier method. The influence of demographic and clinical parameters on survival was examined with the log-rank test. Factors independently associated with cancer-specific mortality were evaluated with a Cox proportional hazard model.

Results. A total of 697 women with PLFGT were identified with a median age of 54 years. The most prevalent histological subtypes were diffuse large B-cell (59.8%) and follicular (11.9%) lymphoma. Tumors were most commonly located in the ovary (37%), cervix (21.4%), and uterus (16.5%). According to the Ann Arbor staging system, 42.6% and 17.9% of cases had stage I and stage II disease, respectively. Cancer-directed surgery (CDS) was performed in the majority of cases (62.8%). Five-year OS and CSS were 70.2% and 75.2% respectively. Localized disease, premenopausal age and follicular histology were associated with superior cancer-specific mortality while CDS did not confer any mortality benefit.

Conclusions. This is the largest cohort of PLFGT presented in literature. While in our study surgical treatment was not associated with improved outcomes, larger multi-institutional studies should address the optimal management of women with PLFGT.

1. Introduction

Primary non-Hodgkin's lymphoma (NHL) can arise from lymph nodes (nodal) or lymphatic cells located in solid organs (extranodal) [1]. Extranodal lymphoma is regarded as a distinct entity with unique epidemiological features and prognosis [2,3]. It accounts for approximately 25–35% of all NHL cases and its incidence is currently rising [1–4]. Extranodal NHL most commonly involves the gastrointestinal tract and central nervous system however occasionally can arise from other sites such as the adrenal glands, breast, thyroid, bone, prostate and female genital tract [4–7].

Primary lymphoma of the female genital tract (PLFGT) is an extremely rare entity, comprising 0.2–1.1% of all cases of extra-nodal lymphoma. In the U.S there are an estimated 165 new cases of PLFGT annually [8]. The female genital tract and particularly the ovaries are, however, commonly involved in disseminated lymphoma (7–30%) [8]. Differentiation between secondary and primary lymphoma is challenging especially in the presence of both nodal and extranodal disease but pivotal in terms of treatment and prognosis [9,10]. Certain authors

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http://dx.doi.org/10.1016/j.ygyno.2017.02.043
0090-8258/

suggest that if an extranodal lesion clinically predominates, the lymphoma can be characterized as primary extranodal [2,3,10]. Management of PLFGT remains unclear and standardized guidelines do not exist [8,9,11]. Given the rarity of PLFGT, information on its epidemiology and prognosis is scarce and derived from case reports and small case-series [9,11–15]. The aim of this population-based study is to investigate the demographic, clinico-pathological characteristics and survival of women with PLFGT using a multi-institutional database.

2. Material methods

A cohort of women was selected from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database, which incorporates high quality data on primary malignant tumor cases. In the present study, data from 18 cancer registries were included (Detroit, Iowa, Kentucky, Louisiana, Utah, Connecticut, New Jersey, Atlanta, Rural and Greater Georgia, Alaska, California, Hawaii, Los Angeles, New Mexico, San Francisco, San Jose, Seattle), as released on April 2014 . These cancer registries cover approximately 27.8% of the total US population based on the 2010 census [16]. Patient data drawn from the SEER database are de-identified and available to the public for research purposes. The present study was also deemed exempt from IRB review.

ICD-O-3 histological (9590/3–9729/3) and topographical (C.51–C.57) codes were employed to identify cases of primary lymphoma arising from the female genital tract [17]. Cases without active follow-up (diagnosed from autopsy or death records) and those without histological and/or cytological confirmation were excluded. In addition, cases diagnosed prior to 1983 were excluded due to unavailability of staging information according to the Ann Arbor system currently employed for staging extranodal lymphoma [10]. Using the "case-listing" option demographic and clinico-pathological parameters and survival data were extracted from the database. No information on the administration of chemotherapy is available in the SEER database. Given that following the introduction of rituximab in 1997, the management of NHL of B-cell subtype changed drastically, year of diagnosis was dichotomized as following (<1997, ≥1997) [18]. Based on the ICD-O-3 topographic codes, tumor location was grouped as following: 1) vulva (labium majus, labium minus, clitoris, overlapping lesion of vulva and vulva NOS), 2) vagina, 3) cervix uteri (endocervix, exocervix, overlapping lesion of cervix uteri, and cervix uteri NOS), 4) ovary, 5) uterus (corpus uterus and uterus NOS) and 6) other location (fallopian tube, broad ligament, round ligament, parametrium, uterine adnexa, other parts, female genital tract NOS, overlapping lesion of female genital tract).

In the SEER database survival is calculated as the number of months from cancer diagnosis to the date of death. For the estimation of cancer-specific survival (CSS) women who died from causes other than primary lymphoma were censored. Given the indolent course of lymphoma, we opted to exclude from the survival analysis women with a diagnosis of another primary tumor in a different location. In order to determine median and 5-year overall and cancer-specific survival, Kaplan-Meier curves were generated and the log-rank test was employed to perform comparisons between different groups. Cox proportional hazard model was constructed to determine independent predictors of cancer-specific mortality. Cases with unavailable information for one or more variables were excluded from the multivariate analysis. Statistical analysis was performed with the SPSS v.24 statistical package. The alpha level of statistical significance was set at 0.05 and all p-values were two-sided.

3. Results

In total, 697 women with PLFGT who met the inclusion criteria were identified. Key demographic and clinico-pathological characteristics of the study population are summarized in Table 1. The median age of women with PLFGT was 54 years (range 1–94). The majority were of White race (81.8%) and diagnosed in the years following the introduction of rituximab (78.9%) (≥1997). The most common location of PLFGT was ovary (37%, median age 48 years) followed by cervix (21.4%, median age 49 years), uterus (16.5%, median age 67 years), vagina (11.8%, median age 57 years) and vulva (8.8%, median age 69 years).

Women with PLFGT frequently presented with early stage diseased based on the Ann Arbor staging system; 42.6% and 17.9% had stage I and stage II, respectively. The most prevalent tumor histological subtype

Table 1
Demographic and clinical characteristics of women with Primary Lymphoma of the Female Genital Tract.

Variable	n (%)
Age	
<54	336 (48.2%)
≥54	361 (51.8%)
Race	
White	570 (81.8%)
Black	63 (9%)
Other/unknown	64 (9.2%)
Marital status	
Married	359 (51.5%)
Single	307 (44%)
Unknown	31 (4.4%)
Year of diagnosis	
<1997	147 (21.1%)
≥1997	550 (78.9%)
Site	
Ovary	258 (37%)
Uterus	115 (16.5%)
Cervix	149 (21.4%)
Vulva	57 (8.2%)
Vagina	82 (11.8%)
Other	36 (5.2%)
Stage (Ann Arbor)	
Stage I	297 (42.6%)
Stage II	125 (17.9%)
Stage III	38 (5.5%)
Stage IV	211 (30.3%)
Unknown	26 (3.7%)
Surgery	
Yes	438 (62.8%)
No	252 (36.2%)
Unknown	7 (1%)
Radiation	
Yes	133 (19.1%)
No	553 (79.3%)
Unknown	11 (1.6%)
Treatment	
No surgery or radiation	174 (25%)
Surgery only	375 (53.8%)
Radiation only	75 (10.8%)
Surgery and radiation	57 (8.2%)
Unknown	16 (2.3%)

Table 2
Histological subtypes of Primary Lymphoma of the Female Genital Tract.

Histology	n (%)
Diffuse large B-cell lymphoma	417 (59.8%)
Follicular lymphoma	83 (11.9%)
Burkitt lymphoma	39 (5.6%)
Mucosal-associated-lymphoid tissue lymphoma	32 (4.6%)
Non-Hodgkin's lymphoma, T-cell	17 (2.4%)
Non-Hodgkin's lymphoma, B-cell NOS	37 (5.3%)
Other Non-Hodgkin's lymphoma, B-cell	6 (0.9%)
Non-Hodgkin's lymphoma, NOS	28 (4%)
Chronic/small lymphocytic leukemia	9 (1.3%)
Hodgkin's lymphoma	1 (0.1%)
Lymphoma, NOS	28 (4%)

NOS: not otherwise specified.

Please cite this article as: D. Nasioudis, et al., Primary lymphoma of the female genital tract: An analysis of 697 cases, Gynecol Oncol (2017), http://dx.doi.org/10.1016/j.ygyno.2017.02.043