Gynecologic Oncology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Gynecologic Oncology

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

Prevalence of lymph node metastasis and prognostic significance of lymphadenectomy in apparent early-stage malignant ovarian sex cord-stromal tumors

Dimitrios Nasioudis *, Tomi T. Kanninen, Kevin Holcomb, Giovanni Sisti, Steven S. Witkin

Department of Obstetrics and Gynecology, Weill Cornell Medicine, New York, NY, USA

HIGHLIGHTS

- Rate of lymph node metastases in early stage ovarian sex cord-stromal tumors was 3.3%.
- No differences were noted based on stage, histology and extend of lymphadenectomy.
- Lymphadenectomy did not confer a survival benefit in this cohort.
- Routine lymphadenectomy can be omitted when staging SCSTs.

ARTICLE INFO

Article history:
Received 24 January 2017
Received in revised form 2 March 2017
Accepted 6 March 2017
Available online xxxx

Keywords:
Ovarian cancer
Sex cord-stromal tumors
Granulosa cell
Lymphadenectomy

ABSTRACT

Objective. The aim of this retrospective population-based study was to investigate the prevalence of lymph node metastasis in patients with apparent early stage malignant sex cord-stromal tumors (SCSTs) and the effect of regional lymph node sampling/lymphadenectomy (LND) on their survival.

Methods. A cohort of patients diagnosed with malignant SCSTs between 1988 and 2012 was drawn from the National Cancer Institute's Surveillance, Epidemiology, and End Results database. Overall and Cancer Specific Survival, stratified by performance of LND, were calculated following generation of Kaplan-Meier curves. Comparisons were made using the log-rank and Breslow tests. A multivariate Cox proportional analysis was performed to determine the effect of LND on overall mortality.

Results. A total of 1156 patients with SCST met the inclusion criteria; 1000 (86.5%) and 156 (13.5%) patients had apparent stage I and II disease, respectively. LND was performed in 572 (49.5%) patients. Lymph node metastases were pathologically confirmed in 19 patients (3.3%). Five-year cancer specific survival (CSS) was similar, 92.7% and 94.7%, for patients who did or did not undergo LND, respectively. According to multivariate analysis overall mortality did not differ between the two groups after controlling for age, histology and apparent stage.

Conclusions. Regional lymphatic mode metastasis in patients with apparent early stage SCSTs is uncommon and lymphadenectomy did not confer a survival benefit in this cohort.

1. Introduction

Ovarian sex cord-stromal tumors (SCST) are a rare category of non-epithelial tumors accounting for approximately <7% of all malignant ovarian tumors [1,2]. They are characterized by an indolent course and an excellent long-term prognosis [3]. Due to their low incidence, clinical management of patients with SCSTs remains variable and is often based on experience derived from more common epithelial ovarian cancers. Patients with malignant SCSTs most commonly present with disease confined to the ovary and are often initially managed by general gynecologists with a gynecologic oncology referral only in the case of a subsequent recurrence [4]. In addition many women with SCST are at childbearing age and therefore fertility-sparing surgical options are often pursued [2,5]. Given this characteristic presentation, a relatively high number of patients undergo incomplete staging procedures in comparison to patients with epithelial ovarian tumors.

According to FIGO guidelines every patient with a malignant ovarian tumor should be offered a complete staging surgical procedure that includes omental biopsy, peritoneal washings, removal of all suspicious lesions, and pelvic/para-aortic lymphadenectomy to provide an adequate assessment of disease extent [2]. The presence of lymph node metastasis in the absence of peritoneal metastasis upstages a patient with

* Corresponding author at: Department of Obstetrics and Gynecology, Weill Cornell Medicine, 1300 York Avenue, Box 35, New York, NY 10065, USA.
E-mail addresses: din2004@med.cornell.edu, dnasioudis@gmail.com (D. Nasioudis).

http://dx.doi.org/10.1016/j.ygyno.2017.03.005
0090-8258/

apparent stage I or II disease to stage III disease [6]. An adequate staging procedure further guides adjuvant chemotherapy recommendations [7].

For patients with apparent stage I–II epithelial ovarian cancer, the rate of lymph node (LN) involvement is considerable, approaching 14.2% [8]. However, according to a recent systematic review of small-scale retrospective studies, lymph node metastases are extremely uncommon for patients with SCSTs and apparent stage I–II disease [2]. The rarity of LN metastasis has led several authors to suggest that LN dissection can be omitted from the staging procedure of patients with SCSTs [1,2,5,9].

Given the lack of large scale studies, the aim of this retrospective population-based analysis was to evaluate the rate of regional LN involvement in patients with apparent stage I and II ovarian malignant SCSTs and to investigate the prognostic significance of lymphadenectomy.

2. Material/methods

A cohort of patients diagnosed with primary ovarian cancer was drawn from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database. 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), which cover approximately 27.8% of the total US population based on the 2010 census [10]. The SEER database performs vigorous quality control to ensure the robustness of the provided data [11]. All patient data are de-identified; an exemption was also granted from obtaining institutional review board approval.

Using the ICD-O-3/WHO 2008 site code "C.569/ovary" and the ICD-O-3 morphology codes "8590/3-8671/3" as grouped by the International Agency for Research on Cancer (IARC), cases of malignant sex cord-stromal tumors located at the ovary and diagnosed between 1988 and 2012 were identified [12]. For analysis purposes two histology groups were formed; granulosa-cell tumors (including cases of juvenile granulosa cell tumors) and non-granulosa cell tumors (including cases with 8590/3: Sex cord-gonadal stromal tumor, malignant, not otherwise specified NOS). Cases without microscopic confirmation and active follow-up (diagnosis obtained from death certificate) were excluded. In addition, patients that did not undergo cancer-directed surgery as assessed from the site-specific surgery codes were excluded from the present study. Based on the Collaborative staging (CS) and Extent of Disease (EOD)-10" fields, a cohort of patients with apparent Stage I and II (T1–2) with documented absence of distant metastases (M0) (T1–2/Nx/M0) was selected [13]. Information derived from the histopathological report available in the "regional nodes examined/positive" fields was employed to determine whether lymphadenectomy was performed. Cases with missing/unknown histopathological information were excluded. For analysis purposes three LND groups were formed; LND1 (1–9 LNs removed), LND2 (10–20 LNs removed) and LND3 (>20 LNs removed) as previously described [14]. For those patients who undergo lymph node dissection/sampling and histopathological examination confirms the absence of metastatic disease, apparent stage coincides with final FIGO stage [6].

Five year overall survival (OS) and cancer-specific survival (CSS) were estimated following generation of Kaplan-Meier curves. In SEER database, the survival variable represents the number of months from cancer diagnosis to the date of death. For the estimation of CSS, only those with one tumor or the first of multiple primary malignant tumors were included; patients who died from causes other than malignant SCSTs were censored [15,16]. Univariate analysis of survival between different groups was made using the log-rank and Breslow tests. In addition, a multivariate Cox regression analysis was performed to determine the effect of LND on overall mortality after controlling for possible confounders, identified from univariate analysis. Tumor recurrence is not documented in the SEER database precluding us from investigating progression free survival. Moreover, information on the administration and composition of adjuvant chemotherapy is not captured in the SEER database.

Frequency distribution of categorical variables was compared with the chi-square test or Fisher's exact test when appropriate and that of continuous variables with Mann-Whitney *U* test. All statistical analysis was performed with the SPSS v.22 statistical package. The alpha level of statistical significance was set at 0.05.

3. Results

A total of 1156 patients with malignant SCSTs who met the inclusion criteria were identified. The majority (82.5%) had granulosa cell tumors (including 9 cases of juvenile granulosa cell tumors). Using the reverse Kaplan-Meier method median follow-up of the cohort was 95 months (95% CI: 88.26, 101.74). From these, 1000 (86.5%) patients had apparent stage I (62% IA, 1.2% IB, 18.4% IC, 4.8% INOS) and 156 (13.5%) stage II (2.2% IIA, 7.9% IIB, 2.7% IIC, 0.7% IINOS) disease respectively.

Based on information deriving from the histopathology report, 572 (49.5%) patients underwent regional LN dissection/sampling (LND group). Patients who underwent LND were more likely to present with apparent stage II disease ($p = 0.011$) and have larger tumors ($p = 0.006$). Moreover, for women with apparent stage I disease, rate of LND was 46.6% and 54.2% for those with stage IA and IB/IC respectively ($p = 0.046$). In addition, an increase in the percentage of patients receiving LND per study period was noted (39.3% of patients diagnosed between 1988 and 2000 and 53.7% of those diagnosed between 2001 and 2012 underwent LND respectively) ($p < 0.001$). Table 1 summarizes demographic and clinico-pathological characteristics of patients with SCSTs stratified by performance of LND. The exact number of removed LNs was available for 536 cases with the median number of LN removed being 9 (range 1–61). More specifically, 279 (52.1%) patients were included in the LND1 group, while 172 (32.1%) and 85 (15.9%) in the LND2 and LND3 groups respectively. Based on site-specific surgery codes, the exact nature of cancer-directed surgery (CDS) performed could be assessed for 1147 patients. A total of 58 patients underwent extended surgical procedures documented as tumor debulking or exenteration; 1089 patients underwent unilateral/bilateral total/subtotal salpingoophorectomy. Based on available information, 38% (439/1089) had omentectomy while 64.5% (671/1041) had hysterectomy. For a total of 314 (28.8%) patients there was documented evidence of a staging procedure that included omentectomy and LND.

From the 572 patients who underwent LND, 19 (3.3%) had pathologically confirmed lymph node metastases. Regarding the histological tumor characteristics of patients with positive LNs: 15 had a granulosa cell tumor, one patient had a Sertoli-Leydig tumor, one patient had a Sertoli cell carcinoma and 2 patients had a sex-cord stromal tumor not otherwise specified (NOS). Rate of LN metastasis for patients with granulosa cell and non-granulosa cell tumors were 3.2% and 4% respectively ($p = 0.76$). However when cases of sex cord-gonadal stromal tumors, NOS (ICD-O-3 histology code: 8590/3) were excluded from the non-granulosa cell tumor group, rate of LN metastases was 2.3% ($p = 0.67$). Three (15.8%) patients had apparent stage II disease (1 IIA and 2 IIB) while 16 (84.2%) patients had apparent stage I disease (9 IA, 4 IC and 3 INOS). The rate of lymph node metastasis was identical for patients with apparent stage I and stage II disease (3.3%). The rate of LN metastases was 3.6%, 2.3% and 4.7% in the LND1, LND2 and LND3 groups respectively ($p = 0.58$). No differences in the rate of LN metastasis were noted based on tumor size, patient age, race, or tumor laterality. The exact number of positive LN was available for 18 cases; median number of positive LNs harvested was 1 (range 1–8) while median lymph node ratio (LNR) (number of positive LN divided by number of harvested LN) was 0.17 (range 0.04–1). Table 2 summarizes the distribution of patients with positive LN based on the exact number of LN harvested. The exact location of positive LNs was available for 18 patients;

Please cite this article as: D. Nasioudis, et al., Prevalence of lymph node metastasis and prognostic significance of lymphadenectomy in apparent early-stage malignant ovarian sex c..., Gynecol Oncol (2017), http://dx.doi.org/10.1016/j.ygyno.2017.03.005