Gynecologic Oncology xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Gynecologic Oncology

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

Prognostic significance of lymphadenectomy and prevalence of lymph node metastasis in clinically-apparent stage I endometrioid and mucinous ovarian carcinoma

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HIGHLIGHTS

- Rate of lymph node metastasis for stage I ovarian mucinous carcinoma is 1.7%.
- Rate of lymph node metastasis for stage I ovarian endometrioid carcinoma is 2.1%.
- Lymphadenectomy is associated with a survival benefit for women with endometrioid carcinoma.
- Lymphadenectomy could be omitted when staging stage I ovarian mucinous carcinoma.

ARTICLE INFO

Article history:
Received 7 September 2016
Received in revised form 7 November 2016
Accepted 21 November 2016
Available online xxxx

Keywords:
Ovarian neoplasms
Lymphadenectomy
Serous adenocarcinoma
Mucinous adenocarcinoma
Ovary

ABSTRACT

Objective. The aim of the present study was to investigate the prevalence of lymph node (LN) metastasis in women with apparent stage I ovarian carcinoma of endometrioid or mucinous histology and to examine the prognostic significance of LN sampling/dissection (LND) on patient survival.

Methods. The National Cancer Institute's Surveillance, Epidemiology, and End Results database was accessed and a cohort of surgically-staged women, diagnosed between 1988 and 2013, with apparent stage I ovarian carcinoma of mucinous or endometrioid histology was selected. Information derived from the histopathology report was employed to determine whether LND was performed and the status of harvested LNs. Five-year cancer-specific survival (CSS) rate was calculated following generation of Kaplan-Meier curves. Comparisons were made using the log-rank test. Cox proportional hazard models were constructed to evaluate the effect of LND on survival.

Results. A total of 3354 and 2855 women with endometrioid and mucinous tumors who met the inclusion criteria were identified. LND was performed in 2307 (68.8%) and 1602 (56.1%) of them ($p < 0.001$), respectively. The rate of histopathologically confirmed LN metastasis was 2.1% and 1.7%, respectively. By multivariate analysis LND was associated with superior cancer-specific mortality only for women with endometrioid carcinoma.

Conclusions. Lymph node involvement in women with mucinous and endometrioid ovarian carcinoma grossly confined to the ovary is infrequent. LND is associated with a survival advantage for those with endometrioid carcinoma.

1. Introduction

Ovarian cancer accounts for 3% of all malignancies in women, with an annual incidence of 12.1 cases per 100,000 in the United States [1]. However, ovarian cancer is a heterogeneous group of tumors each characterized by unique histopathological and clinical features [2]. The majority of ovarian epithelial tumors are of high-grade serous histology (also known as type II); these tumors usually present at advanced stages and are characterized by genetic instability and a poor prognosis. Conversely, type I tumors (which include endometrioid, mucinous, low-grade serous and clear cell tumors) are genetically stable and tend to be localized to the ovary at presentation [2,3]. However, the incidence of type I tumors is low and single institutional cohort studies usually include a small number of cases.

According to FIGO guidelines every patient diagnosed with ovarian cancer should undergo a complete staging procedure to adequately assess tumor spread and guide adjuvant chemotherapy recommendations. A complete staging procedure should include omentectomy,

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http://dx.doi.org/10.1016/j.ygyno.2016.11.038
0090-8258/

biopsy of all suspicious lesions, peritoneal washings and lymph node sampling/dissection (LND) [4].

Two large population-based studies have investigated the prognostic significance of LND on the survival of women with ovarian cancer. Chan et al.examined 6686 women with clinical stage I ovarian cancer and concluded that LND improved survival in non-clear cell epithelial tumors [5]. In another study that included 30,836 women with epithelial ovarian cancer, the benefit of LND on cause-specific survival, regardless of disease stage and extent of surgical staging, was demonstrated [6]. However, both studies failed to discriminate between the different histological subtypes of epithelial ovarian cancer, with the exception of clear cell carcinoma. Another recent report, focusing on clear cell tumors grossly confined to the ovary, concluded that lymph node metastasis was relative infrequent (4.5%) [7].

Given the paucity of evidence, the aim of the present study was to investigate the prevalence of LN metastasis and the prognostic significance of LND on the survival of women with clinically apparent stage I mucinous or endometrioid ovarian carcinoma, the two most common histotypes of type I ovarian tumors, using a multi-institutional database.

2. Materials and methods

The National Cancer Institute's SEER database was accessed and a cohort of women with primary ovarian (ICD-O-3/WHO 2008 site code "C.569/ovary") carcinoma was selected. In the present study, data from 18 cancer registries were included as released on November 2015, covering approximately 27.8% of the total US population based on the 2010 census [8]. All patient data are de-identified and available to the public for research purposes; an exemption was also granted from obtaining institutional review board approval.

ICD-O-3 morphology codes "8470–8490, 9015" and "8380–8381, 8560, 8570" as grouped by the International Agency for Research on Cancer (IARC) were used to identify cases of mucinous and endometrioid ovarian tumors, respectively, diagnosed between 1988 and 2013 [9]. Based on information deriving from the T and M codes available at the Collaborative staging (CS) and Extent of Disease (EOD)-10 fields, women with apparent Stage I (T1a, T1b, T1c, T1NOS) and documented absence of metastasis to distant sites (M0)(T1/Nx/M0) were selected for further analysis. Staging information was converted to the most recent schema. Those who did not undergo cancer-directed surgery (as assessed from the site-specific surgery codes) as well as cases without microscopic confirmation and active follow-up (diagnosis obtained from death certificate) were excluded. Moreover, we opted not to include women with a history of a prior primary tumor or a subsequent primary tumor in another location. Tumor grade when available was recoded into a 3-tier system; grade I (well differentiated), grade II (moderate differentiated) and grade III (poorly differentiated and undifferentiated) and further classified for analysis purposes into low grade (grade I) and high grade (grade II–III) as in previous reports [10]. In order to control for any advances in surgical techniques and adjuvant treatment, year of diagnosis was dichotomized into <2003 and ≥2003, based on the date of publication of the results of the ICON1 and ACTION controlled randomized trials on the use of adjuvant chemotherapy for stage I ovarian cancer [11,12].

Information derived from the histopathology report available in the "regional nodes examined" and "regional nodes positive" fields was employed to determine whether LN sampling/dissection (LND) was performed. Women with missing or unknown histopathological information were excluded as well as those with an unknown number of harvested LNs. The number of harvested and examined LNs was also used as a surrogate marker to determine the extent of LND as in previous studies [5–7]. Extent of LND was further categorized into no LND (LND0 group), LND1 group (1–10 LNs removed), LND2 group (11–20 LNs removed) and LND3 group (>20 LNs removed).

Five-year cancer-specific survival (CSS) rate was estimated following generation of Kaplan-Meier curves. Cases who were alive or died from causes other than malignant ovarian tumor were censored. Possible "follow-up discard" cases were excluded from the survival analysis. Univariate comparisons of survival between different groups were made with the log-rank test. In addition a multivariate Cox proportional regression analysis was performed to investigate the effect of LND on cancer-specific mortality. Given that women with occult LN metastasis would be inadvertently included in the LND− group, we opted to include all women who underwent LND in the LND+, irrespective of the LN status of examined LNs when comparing survival and mortality.

Frequency distribution of categorical and continuous variables was compared with the chi-square test and Mann-Whitney *U* test, respectively. Statistical analysis was performed with the SPSS v.24 statistical package and the alpha level of statistical significance was set at 0.05.

3. Results

A total of 6209 women who met the inclusion criteria were identified; 3354 (54%) with endometrioid and 2855 (46%) with mucinous carcinoma. Five-year CSS for women diagnosed before 2003 was 91% compared to 92.7% for those diagnosed at or after 2003 ($p = 0.003$). Compared to women with endometrioid those with mucinous carcinoma were younger (median age, 50 vs 54 years, $p < 0.001$), less likely to present with apparent stage IC disease (23.1% vs 34.2%, $p < 0.001$), more likely to be of Non-white race (19.2% vs 15.3%, $p < 0.001$) and have a preoperative CA-125 value within the normal range (40.3% vs 25.4%, $p < 0.001$).

In our cohort, based on the histopathology report, a total of 3909 (63%) women underwent LND; 56.1% and 68.8% of those with mucinous and endometrioid carcinoma, respectively ($p < 0.001$). Women who underwent LND were younger (median age, 52 vs 54 years, $p < 0.001$). A significant increase in the percentage of cases undergoing LND was noted per study period (71.5% of women diagnosed after 2003 underwent LND while only 50.7% of those diagnosed before 2003, $p < 0.001$). Moreover, more extensive LND procedures were performed for women diagnosed after 2003; 24.9% and 30.7% had 11–20 and >20 LNs removed compared to 16.9% and 25.6% of those diagnosed before 2003, respectively ($p < 0.001$). No statistically significant differences in LND rates were noted based on race. Women with endometrioid carcinoma were more likely to undergo more extensive LND compared to those with mucinous carcinoma; 30.4% and 23.8% had 11–20 or >20 LNs removed compared to 26.9% and 19.9% respectively ($p < 0.001$). Using the reverse Kaplan-Meier method, median follow-up of women with endometrioid and mucinous carcinoma was 98 months and 110 months, respectively.

Supplemental Table 1 summarizes demographic and clinicopathological characteristics of our cohort.

3.1. Endometrioid histology

A total of 2307 (68.8%) women underwent LND (66.5% and 74%, of those with IA/IB and IC apparent stage disease, respectively, $p < 0.001$). There was no difference in LND rates based on tumor grade (68.6% for grade I and 70.8% for grade II/III tumors, $p = 0.191$). However, based on available information, women who underwent LND had larger tumors (median size 10.2 cm vs 8.5 cm, $p < 0.001$) and were younger (median age 53 vs 56 years, $p < 0.001$). From those who underwent LND, 45.8%, 30.4% and 23.8% were included in the LND1, LND2 and LND3 groups respectively. Extent of LND did not differ according to grade ($p = 0.61$) or apparent stage ($p = 0.42$). However women >65 years were less likely to be in the LND2 (27.3%) and LND3 group (18.7%) compared to those aged 50–65 years (32.2% and 23.9%) or <50 (30% and 26.2%) ($p = 0.002$). The median number of removed LN was 12 (range 1–84) and a total of 48 (2.1%) women had LNs positive for metastasis. Rate of LN metastasis was similar between women who were in the LND1 group (2.3%), LND2 group (2%) and LND3 group (1.8%) LND ($p = 0.82$). Rate of LN metastasis was 1.6% and 3%

Please cite this article as: D. Nasioudis, et al., Prognostic significance of lymphadenectomy and prevalence of lymph node metastasis in clinically-apparent stage I endometrioid and..., Gynecol Oncol (2016), http://dx.doi.org/10.1016/j.ygyno.2016.11.038