Role of hysterectomy and lymphadenectomy in the management of early-stage borderline ovarian tumors

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HIGHLIGHTS

- Cancer-specific survival was examined in stage T1 borderline ovarian tumors (BOTs).
- Hysterectomy and lymphadenectomy were not associated with survival in stage T1 BOTs.
- Among staged patients, nodal metastasis was seen with 1.1% of stage T1 BOTs.

ARTICLE INFO

ABSTRACT

Objective. To examine survival of women with stage T1 borderline ovarian tumors (BOTs) stratified by hysterectomy and lymphadenectomy status at surgery.

Methods. This is a retrospective study examining The Surveillance, Epidemiology, and End Results Program to identify surgically-treated stage T1 BOTs between 1988 and 2003 (n = 4943). Association of surgery patterns and cause-specific survival (CSS) was examined in multivariable analysis.

Results. Mean age was 48.7. The majority had stage T1a disease (75.3%). Median follow-up was 15.6 years and 159 (3.2%) women died of BOTs. Hysterectomy and lymphadenectomy were performed in 1909 (38.6%) and 1295 (26.2%) cases, respectively. Most commonly, neither procedure was performed (46.5%), followed by hysterectomy alone (27.3%), lymphadenectomy alone (14.9%), and both procedures (11.3%). Surgery patterns for hysterectomy and lymphadenectomy significantly differed across age, ethnicity, marital status, registry area, year at diagnosis, histology type, sub-stage, and tumor size (all, $P < 0.001$). On multivariable analysis, surgery patterns for hysterectomy and lymphadenectomy were not associated with CSS: 20-year rates for neither hysterectomy and lymphadenectomy 96.7%, hysterectomy alone 94.5%, lymphadenectomy alone 95.7%, and both procedures 95.2% (adjusted-$P > 0.05$). Age ≥ 50, T1b-c stages, and mucinous histology remained independent prognostic factors for decreased CSS (all, $P < 0.05$). Among 3723 women with stage T1a disease, hysterectomy and lymphadenectomy patterns were not associated with CSS in 2115 women aged <50 ($P = 0.14$) and 1608 women aged ≥50 ($P = 0.48$).

Conclusion. Our study suggests that both hysterectomy and lymphadenectomy may be omitted in the surgical management of women with stage T1 BOTs, especially for those with T1a disease regardless of age.

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1. Introduction

Borderline ovarian tumors have histologic features and biological behavior between benign and frankly malignant epithelial ovarian neoplasms [1]. These tumors were included as a separate entity in its classification and staging system of gynecologic malignancies approximately four decades ago [2]. The majority of women with borderline ovarian tumors have the disease confined in the ovary resulting in good prognosis.

The mainstay of the management for borderline ovarian tumors remains surgery with removal of affected organs and anatomical sites [3]. Women with borderline ovarian tumors who have completed

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childbearing are recommended to undergo bilateral salpingo-oophorectomy and hysterectomy, similar to invasive epithelial ovarian cancer [4]. Conversely, young reproductive age women with early-stage disease commonly undergo fertility sparing surgery, with preservation of the unaffected ovary and the uterus. In addition, women with early-stage borderline ovarian tumors often have undergone surgical treatment by gynecologists for presumed benign ovarian disease, and lack of surgical staging is not uncommon [5].

Prior studies have been inconsistent in support of the benefits of staging surgery, and a recent systematic literature review found that staging surgery, including hysterectomy and lymphadenectomy, for borderline ovarian tumors is not supported by the best evidence [6–8]. As the chances of uterine or nodal metastasis are generally considered low in apparent early-stage borderline ovarian tumors [6,7, 9–11], risks of surgical mortality and benefits for staging information need to be weighed carefully. The objective of our study was to examine survival of women with early-stage borderline ovarian tumors who underwent hysterectomy and lymphadenectomy at surgical treatment.

2. Materials and methods

The Surveillance, Epidemiology, and End Results Program is a population-based tumor registry launched in 1973, supported and managed by the National Cancer Institute in the United States [12]. This database covers approximately 28% of the US population from 11 States and 7 areas. This database is publicly available and deidentified, and the University of Southern California Institutional Review Board exempts the use of the said database. The STROBE guidelines were used to outline this observational study [13].

SEER*Stat 8.3.2. was used to extract the dataset from SEER18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases. Borderline ovarian tumors were first recorded in this tumor registry in 1988 [14]. Histopathology codes were used to identify borderline ovarian tumors based on prior studies (serous 8442-1, 8451-1, and 8462-1; and mucinous 8472-1, 8473-1) [14,15]. Within the extracted dataset, cases with stage T1 borderline ovarian tumors with known hysterectomy and lymphadenectomy status between 1988 and 2003 were included in the study. Women who had stage T2-3 or unknown stage, who received radiotherapy, and who had unknown hysterectomy/lymphadenectomy status were excluded. Variables ascertained from the database were patient demographics, tumor information, treatment pattern, and survival outcome.

Patient demographics included age at diagnosis (<50 versus ≥50 years), calendar year at hysterectomy (1995 or earlier versus later than 1995), ethnicity (White, Black, Hispanic, Asian, and others), marital status (single, married, and others), and registered area (West, Central, and East). Tumor information included histologic subtype (serous versus mucinous), cancer sub-stage (T1a, T1b, T1c, and T1NOS), tumor size (<5 cm versus ≥5 cm), and regional lymph node status (positive, negative, or not examined). Treatment patterns included use of hysterectomy, lymphadenectomy, and ovarian removal. For survival outcome, cause-specific survival was collected.

Recorded cancer T stages were based on the American Joint Committee on Cancer 3rd staging classification schema that was performed between 1988 and 2003 in this database [16]. T1a stage refers to the tumor limited to one ovary, capsule intact, and no tumor on the ovarian surface; T1b refers to the tumor limited to both ovaries, capsules intact, and no tumor on the ovarian surface; and T1c refers to the tumor limited to one or both ovaries with any of the following three (ruptured capsule, ovarian surface tumor involvement, malignant cells in peritoneal washing or ascites) [17].

ICD-O-3 SEER site/histology validation list and World Health Organization histological classification were used for histologic coding as above [18]. Lymphadenectomy performance was based on the coding for the Regional Nodes that was introduced in 1988 in the database. The number of resected regional lymph nodes and positive lymph nodes were abstracted (1–9, 10–19, and ≥20). Recorded cancer M stages were based on the American Joint Committee on Cancer 3rd staging classification schema [16]. Surgical codes including hysterectomy were considered for hysterectomy procedure. If the surgical codes did not include hysterectomy, the cases were considered as no hysterectomy performed. Cause-specific survival was defined the time interval between the date of borderline ovarian tumor diagnosis and the date of death due to borderline ovarian tumor. Patients who were alive at the last follow-up or died of other causes were censored.

The primary interest of analysis was to compare cause-specific survival of women with stage T1 borderline ovarian tumors based on the patterns of hysterectomy and lymphadenectomy at surgical treatment. The secondary interest of analysis was to examine cause-specific survival of women with stage T1a borderline ovarian tumors based on the patterns of hysterectomy and lymphadenectomy as stratified by the patient age (cutoff age, 50 years). This age cutoff was chosen due to general consensus for the reproductive age limit being younger than 50 years of age per the World Health Organization definition [19]. In addition, risk factors for regional lymph node metastasis were examined for women with stage T1 borderline ovarian tumors.

On univariable analysis, Student t-test, Mann-Whitney U test, or Kruskal-Wallis test for continuous variables and chi-square test for ordinal/categorical variables were used as appropriate in a comparison of demographics. For evaluating survival outcome, the Kaplan-Meier method was used to construct survival curves [20], and statistical significance between the curves were assessed with log-rank test in univariable analysis. Cox proportional hazard regression models for multivariable analysis were performed to identify the independent prognostic factors [21]. Covariates entered in the final model were patient demographics, tumor characteristics, and treatment patterns. Magnitude of statistical significance was expressed with hazard ratio [HR] and 95% confidence interval [CI].

In the multivariable model, the ratio of events of interest per the entered variables were assessed for over-adjustment (cutoff level < 10) [22,23]. The variance inflation factor was determined among covariates in multivariable analysis, and a value of ≥2.0 was interpreted as multicollinearity in this study [24]. All statistical analyses were two-tailed and a P-value of <0.05 was considered statistical significant. Statistical Package for Social Sciences (version 12.0, Chicago, IL, USA) was used for the analysis.

3. Results

There were 6379 cases of borderline ovarian tumors initially identified in the database. Of those, there were 490 cases with unknown hysterectomy and/or lymphadenectomy status as well as 30 cases who received radiotherapy that were removed from the study. Among 5859 cases with known surgical procedures, 315 cases with T2 stage, 357 cases with T3 stage, and 244 cases with unknown T stage were removed from the study. The remaining 4943 cases of stage T1 borderline ovarian tumors with known hysterectomy and lymphadenectomy status comprised the study population for analysis.

Patient demographics are shown in Table 1. Mean age was 48.7. The majority of women were White (73.3%), married (53.8%), and Western residents in the United States (63.6%). The majority of borderline ovarian tumors were stage T1a disease (75.3%) with serous histology (58.6%). Hysterectomy and lymphadenectomy were performed in 1909 (38.6%) and 1295 (26.2%) cases, respectively. Among the women who had regional lymphadenectomy, the majority of these women had fewer than 10 resected lymph nodes (57.5%) resected.

Difference in characteristics across the tumor stages were examined (Table S1). Black ethnicity, serous histology, node-positive disease were less likely to be associated with stage T1a disease (all, P < 0.05). Cases with serous histology were compared to those with mucinous histology (Table S2). Women with stage T1 serous borderline tumors were slightly older, less likely to be White, and had single marital status as