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# Assessing the risk of pelvic and para-aortic nodal involvement in apparent early-stage ovarian cancer: A predictors- and nomogram-based analyses

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## HIGHLIGHTS

- About 15% of early-stage ovarian cancer (EOC) are diagnosed with positive nodes.
- High-grade serous and bilateral EOC are associated with occult nodal involvement.
- Pelvic node involvement is more frequently detected in stage II ovarian cancer.

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## ABSTRACT

*Objective.* To estimate the prevalence of lymph node involvement in early-stage epithelial ovarian cancer in order to assess the prognostic value of lymph node dissection.

*Methods.* Data of consecutive patients undergoing staging for early-stage epithelial ovarian cancer were retrospectively evaluated. Logistic regression and a nomogram-based analysis were used to assess the risk of lymph node involvement.

*Results.* Overall, 290 patients were included. All patients had lymph node dissection including pelvic and para-aortic lymphadenectomy. Forty-two (14.5%) patients were upstaged due to lymph node metastatic disease. Pelvic and para-aortic nodal metastases were observed in 22 (7.6%) and 42 (14.5%) patients. Lymph node involvement was observed in 18/95 (18.9%), 1/37 (2.7%), 4/29 (13.8%), 11/63 (17.4%), 3/41 (7.3%) and 5/24 (20.8%) patients with high-grade serous, low-grade-serous, endometrioid G1, endometrioid G2&3, clear cell and undifferentiated, histology, respectively ($p = 0.12$, Chi-square test). We observed that high-grade serous histology was associated with an increased risk of pelvic node involvement; while, histology rather than low-grade serous and bilateral tumors were independently associated with para-aortic lymph node involvement ($p < 0.05$). Nomograms displaying the risk of nodal involvement in the pelvic and para-aortic areas were built. High-grade serous histology and bilateral tumors are the main characteristics suggesting lymph node positivity.

*Conclusions.* Our data suggested that high-grade serous and bilateral early-stage epithelial ovarian cancer are at high risk of having disease harboring in the lymphatic tissues of both pelvic and para-aortic area. After receiving external validation, our data will help to identify patients deserving comprehensive retroperitoneal staging.



## 1. Introduction

Ovarian cancer is one of the most common gynecological malignancies in developed countries [1]. In the United States, >22,400 newly diagnosed cases and 14,000 cancer-related deaths are estimated, every year [1]. The majority of the patients affected are diagnosed with

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advanced stage of disease (stage III and IV according to the International Federation of Obstetrics and Gynecologists, FIGO, staging system). It is estimated that only one patient out of five is diagnosed with an early-stage of disease (FIGO stage I and II) [2].

The mainstay of treatment for patients affected by apparent epithelial early-stage ovarian cancer includes the following procedures: hysterectomy, bilateral salpingo-oophorectomy, peritoneal (including peritoneal washing, omentectomy, random peritoneal biopsies with or without appendectomy) and retroperitoneal staging (including pelvic and para-aortic lymph node (LN) dissection) [3]. In particular, retroperitoneal staging allows surgeons to identify macroscopic disease harboring in the pelvic and para-aortic area; this is extremely helpful in order to identify patients who will benefit from adjuvant treatments. Moreover, the cumulative results of the ICON1-ACTION trials demonstrated that retroperitoneal staging was associated to improved outcomes in patients with apparent early-stage ovarian cancer, and that the benefit from adjuvant chemotherapy appeared to be restricted to patients with non-optimal surgical staging [4].

However, systematic pelvic and para-aortic lymphadenectomy (LND) is challenging and might be associated with high risk of both intraoperative and postoperative events, including the occurrence of severe complications and *sequelae*, thus impacting on patients 'quality of life and potentially on oncologic outcomes (due to the delay planned chemotherapy, when needed) [5]. The decision of performing or not systematic lymphadenectomy could be sometimes challenging, especially for patients who had had surgery for apparent unsuspicious masses. In fact, it is estimated that only 7–20% of patients with early-stage epithelial ovarian cancer had LN involvement, thus resulting in at least 80% of over-treatment [6,7].

The present study aimed to assess the prevalence of lymphatic spread in a large series of apparent early-stage epithelial ovarian cancer undergoing pelvic - and para-aortic -LND. Based on disease characteristics, we sought to identify patients at high risk of LN metastasis in order to tailor the need of retroperitoneal staging.

## 2. Methods

### *2.1. Study population*

This is a retrospective study involving patients undergoing surgery for apparent early-stage epithelial ovarian cancer between January 1975 and January 2016, at IRCCS Foundation - National Cancer Institute of Milan - ITALY. After approval from Institutional Review Board (IRB), we retrospectively searched medical records of all women undergoing staging surgery for apparent early-stage epithelial ovarian cancer, from January 1975 to December 2010. From January 2011, records of all early-stage epithelial ovarian cancer patients have been included in a prospectively collected database. All patients gave written informed consent for data collection for research purpose. Data have been obtained from the computerized surgical database of our Institution. This database is meticulously updated by trained residents and nurses; individual patient's records were reviewed by the authors.

Inclusion criteria were: (a) age ≥ 18 years; (b) primary or restaging surgery for apparent early-stage epithelial ovarian cancer; (c) histological diagnosis of invasive ovarian cancer; (d) execution of LN dissection (including pelvic and para-aortic -LND). Patients affected by mucinous ovarian cancer were excluded from the present analysis, due to the negligible risk of nodal metastases for this cluster of patients [5]. Staging system and architectural grade were reported in accord to the FIGO statements [5]. The World Health Organization (WHO) taxonomy was used in order to classify histological subtypes [5,8].

The primary endpoint measure was to evaluate the prevalence of LN metastasis in patients submitted to LND. Stratification for pelvic and para-aortic areas has been subsequently performed.

During the study period surgical staging generally consisted in hysterectomy, bilateral salpingo-oophorectomy, peritoneal (washing, random peritoneal biopsies; omentectomy) and retroperitoneal (pelvic- and para-aortic-LND) staging. Retroperitoneal staging was usually omitted in patients diagnosed with FIGO grade 1 mucinous tumor at intra-operative frozen section. These patients were excluded from the present study. Women aged 40 years or younger, who were willing to preserve their potential childbearing, were enrolled for fertility sparing surgery. Details of our fertility sparing protocol (basically consisting in the preservation of the uterus and at least one tube and the contra-lateral ovary) are reported elsewhere [8].

Pelvic -LND consisted in the en bloc removal of all lymphatic tissue from the external and internal iliac regions and from the obturator fossa. The borders of the dissection were: psoas muscle laterally, hypogastric artery medially, obturator fossa posteriorly, origin of the epigastric artery caudally, at the level of the circumflex vein, and bifurcation of the common iliac artery cranially. During para-aortic LND the upper limit of dissection was represented by the renal vessels. The medial surgical margin was the prevertebral fascia; while the psoas muscles were the lateral margin. During para-aortic LND all LN closed to the aorta, the cava and between these two vessels were dissected. Surgical approach included standard open abdominal and laparoscopic surgery [8,9]. Details regarding surgical staging are reported elsewhere [8,9]. Over the study period a comprehensive process of health quality improvement have been noted at our institution, thus potentially positively impacting on the overall perioperative care. However, no substantial differences regarding the surgical treatments were observed. Adjuvant treatments were limited to patients considered at high risk of developing recurrence (patients with FIGO grade 3 tumors and patients affected by stage II and III ovarian carcinoma). Different adjuvant strategies varied over the whole study period, as previously reported. Basically, adjuvant chemotherapy consisted in six cycles of platinum based chemotherapy (with or without cyclophosfamide, epirubicin, and/or paclitaxel, according to various protocols used in the wide study period). Follow-up were scheduled every three months during the first year, every four months during the second year, every six months within the first 5 years after surgery and annually thereafter. During follow-up examination, clinical examination was carried out. Additionally, almost all patients had periodic radiological evaluations and serum markers tests, on the basis of patients and diseases' characteristics. Recurrences were recorded at the time of regular follow-up visits and confirmed by histological examination or imaging evaluation, when possible.

### *2.2. Statistical analysis*

Data were summarized using standard descriptive statistics. Since all patients with positive LN involvement had para-aortic nodes, statistical analysis was performed stratifying for pelvic nodes and para-aortic nodes, the last of which represent also the overall positive patients. Predicting variables were evaluated for their association with lymph node involvement (pelvic and para-aortic nodes) based on fitting univariate logistic regression model. A multivariate model was applied to all variables with a $p$-value <0.10. Associations were estimated using odds ratio (OR) and corresponding 95% confidence intervals (CIs). For multivariable analysis, statistical significance was set at the conventional $p \leq 0.05$ level for two-sided tests.

Nomograms were built for estimating the probability of nodal involvement according to different characteristics (FIGO stage, tumor histology and side). Performance testing of the two nomograms developed here was assessed in terms of discrimination (Harrell's c-index). C-index provides an estimate of the probability that the model will correctly identify patients who had LN involvement. A nomogram is a graphical calculating device, a two-dimensional diagram designed to allow the approximate graphical computation of a mathematical function. A nomogram consists of a set of n scales, one for each variable in an equation. Knowing the values of n-1 variables, the value of the unknown variable can be found, or by fixing the values of some variables, the relationship between the unfixed ones can be studied. Statistical

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