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Adjuvant chemotherapy for stage I ovarian clear cell carcinoma: Patterns of use and outcomes

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HIGHLIGHTS

- In a large cohort, rate of adjuvant chemotherapy use for stage I ovarian clear cell carcinoma was 79.1%.
- Type of facility, location, age, substage and year of diagnosis were associated with its administration.
- Adjuvant chemotherapy was associated with better survival for stage IA disease.

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ABSTRACT

Objective. The aim of this study was to investigate the patterns of use and outcomes of adjuvant chemotherapy for patients diagnosed with FIGO stage I ovarian clear cell carcinoma (OCCC).

Methods. A cohort of patients diagnosed between 2004 and 2015 with OCCC was drawn from the National Cancer Database. Those with stage I disease who had primary surgery and underwent systematic lymphadenectomy (defined as at least 10 lymph nodes removed) were selected for further analysis. Factors associated with the administration of adjuvant chemotherapy were investigated with multivariate logistic regression. Overall survival (OS) was evaluated using Kaplan-Meier curves for patients diagnosed between 2004 and 2014, while comparisons were made with the log-rank test. Multivariate Cox analysis was performed to control for possible confounders.

Results. A total of 2325 patients met the inclusion criteria. Median age was 55 years. The majority were White (86.6%). Adjuvant chemotherapy was administered to 1839 (79.1%) patients. Hospital type and location, patient age, disease sub-stage, and year of diagnosis were independently associated with the administration of chemotherapy. Patients who received adjuvant chemotherapy ($n = 1629$) had better OS than those who did not ($n = 443$), (5-year OS rates 89.2% vs 82.6%, $p < 0.001$). After controlling for disease sub-stage, age, race, hospital type and medical comorbidities, adjuvant chemotherapy was associated with better overall survival (HR: 0.59, 95% CI: 0.45, 0.78).

Conclusions. Adjuvant chemotherapy could be associated with a survival benefit for patients with stage I OCCC.

1. Introduction

Ovarian cancer is a heterogeneous group of tumors; each is associated with unique clinico-pathological characteristics [1]. OCCC is the third most prevalent histologic subtype of epithelial ovarian carcinoma accounting for approximately 5–25% of all newly diagnosed ovarian cancer cases [2]. Compared to patients with serous tumors, those with OCCC are younger, more likely to be of Asian ancestry, and more commonly present with early stage disease [2,3]. OCCC has unique molecular characteristics such as frequent mutations of the ARID1A gene and is relative resistant to first line platinum chemotherapy [4]. The reported response rates to chemotherapy range from 22% to 56%. Currently, the National Comprehensive Cancer Network (NCCN) and the European Society of Medical Oncology (ESMO) practice guidelines recommend the administration of adjuvant chemotherapy to women with stage I disease regardless of disease sub-stage, since clear cell histology is regarded as a high-risk characteristic for tumor relapse [2,5,6]. However, its utility has yet to be established, especially for patients with stage IA disease. A recent large population-based study revealed that

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patients who received chemotherapy did not have a superior OS even after controlling for disease sub-stage [7]. On the other hand, two small retrospective studies have demonstrated a possible improvement in progression free survival (PFS) in patients with OCCC who received chemotherapy [8,9].

Since it remains unclear whether these patients with OCCC may truly benefit from adjuvant chemotherapy, the aim of this study is to investigate patterns of adjuvant chemotherapy use in the United States and further elucidate the role of adjuvant chemotherapy in the treatment of stage I ovarian clear cell carcinoma using a national hospital-derived database that covers approximately 70% of all patients with newly diagnosed malignancy in the United States.

2. Materials and methods

We identified patients with histologically confirmed malignant ovarian tumor in the National Cancer Data Base (NCDB) diagnosed between 2004 and 2015. The NCDB, has been established jointly by the American Cancer Society and Commission on Cancer of the American College of Surgeons, as a hospital-based database capturing data of patients with newly diagnosed cancer in the United States. Patient data is prospectively collected from participating commission-accredited cancer programs and is regularly audited [10]. All data are de-identified and available for research purposes. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytical or statistical methodology employed, or the conclusions drawn from these data.

Patients with OCCC based on histology codes (8310/3–8313/3, 9110/3) as grouped by the International Agency for Research on Cancer were identified [11]. Patients with stage I disease who underwent primary surgery and had systematic lymphadenectomy (defined as at least 10 lymph nodes (LN) removed and examined) were selected for further analysis. Given the lack of specific data on surgical staging in the NCDB, performance of systematic lymphadenectomy was used as a surrogate marker for adequate staging. Interval between primary surgery and chemotherapy administration was calculated. Similar to previous studies [12], we opted to exclude women who received adjuvant chemotherapy >6 months following primary surgery given the possibility that it was used in the recurrent setting. In addition, cases without available information on the administration of chemotherapy, those who received neoadjuvant chemotherapy, and those with unknown surgery-chemotherapy interval were excluded from the present study.

Demographic and clinico-pathological information was extracted from the de-identified NCDB dataset. For the purpose of analysis, reporting facility location was grouped as Northeast (New England, Mid-Atlantic), Midwest (East North Central, West North Central), South (South Atlantic, East South Central, West South Central) and West (Mountain, Pacific). Reporting facility type was divided into Academic and non-academic. Patient race was recoded as White and non-White/Unknown and age was dichotomized into <65 and ≥65 yrs. Using the collaborative staging schema, cases were assigned to sub-stage IA, IB, IC, INOS (not otherwise specified). Year of diagnosis was mathematically categorized into 2004–2006, 2007–2009, 2010–2012 and 2013–2015.

Chi-square and Mann-Witney *U* tests were used to evaluate categorical and continuous variables, respectively. A multivariate binary logistic regression was performed to identify clinical variables independently associated with the administration of chemotherapy. Overall survival (OS) was defined as the number of months elapsed from tumor diagnosis to the date of death or last-follow up. Kaplan-Meier curves were generated to determine 5-year OS rates while univariate analysis was performed with the log-rank test. Vital status and months from tumor diagnosis to the date of last contact or death are suppressed for cases diagnosed in 2015, as such survival analyses were restricted to cases diagnosed in 2014 and earlier. A Cox multivariate model was used to evaluate mortality after controlling for possible confounders. For the survival analysis, a minimum of 1 month of follow-up was required. All statistical analysis was performed with the SPSS v.24 statistical package (IBM Corp. Armonk, NY), and the alpha level of statistical significance was set at 0.05.

3. Results

A total of 2325 patients met the inclusion criteria. Median age was 55 years (range 23–89 years). The majority were White (86.6%, n = 2014), followed by Asian/Native American/Pacific Islander (8.4%%, n = 196), Black (3.1%, n = 73) and Other/Unknown (1.8%, n = 42). Median number of LN removed and examined was 19 (range 10–88). A total of 1298 women (55.8%) had stage IA/IB disease (including 35 patients with stage IB), 1007 women (43.3%) had stage IC disease and 20 (0.9%) had stage I NOS. In our cohort, only 29 patients received radiation therapy. Adjuvant chemotherapy was administered to 1839 (79.1%) women. More specifically, a multi-agent regimen was used for the majority of patients (94.5%), while 1.8% of patients received single agent chemotherapy and 3.7% of patients had no information on the number of agents were used.

Table 1 summarizes the demographic and clinico-pathological characteristics of patients who did and did not receive adjuvant chemotherapy. An increase in the rate of chemotherapy use was noted during the study period; 73.2% and 71.5% for those diagnosed between 2004–2006 and 2007–2009 compared to 82.4% and 84.9% for those diagnosed between 2010–2012 and 2013–2015 respectively ($p < 0.001$). Chemotherapy administration rate was higher in academic programs (82.9%) compared to non-academic programs (74.5%) ($p < 0.001$). In addition, higher chemotherapy use was observed in facilities located in the Midwest (83.7%) and the East (83.3%) compared to the South (74.8%) and the West (70.7%) ($p < 0.001$). Women who received chemotherapy were younger ($p = 0.037$), more likely to be of White race ($p = 0.052$), with private insurance ($p = 0.023$) and have stage IC disease ($p < 0.001$). No difference was noted in median income, education status, and presence of medical comorbidities between those who received chemotherapy versus those who did not. The predictors of adjuvant chemotherapy administration in multivariate analysis were year of diagnosis, disease sub-stage, patient age, reporting facility type and location (Table 2). After controlling for other variables, patients with stage IC had higher odds of receiving chemotherapy compared to those with stage IA and IB (OR: 1.75, 95% CI: 1.4, 2.18, $p < 0.001$).

Median follow-up for the chemotherapy and observation groups were 59.1 months (range 1.1, 151.4) and 68.3 months (range 1.7, 151.8) respectively. Patients who received adjuvant chemotherapy (n = 1629) had better OS than those who did not (n = 443) (5-year OS rate was 89.2% vs 82.6%, respectively, $p < 0.001$) (Fig. 1). After stratifying by disease sub-stage, women with stage IA or IB disease who received chemotherapy (n = 873) had better OS than those who did not (n = 290), (5-year OS rate was 92.5% vs. 84% respectively, $p < 0.001$) (Fig. 2). For stage IC, there was a trend towards better OS in patients who received chemotherapy (n = 744) compared to those who did not (n = 145), but this did not achieve statistical significance (5-yr OS rate was 85.1% vs 77.5%, respectively, $p = 0.116$) (Fig. 3). After controlling for disease sub-stage (IA or IB vs IC), patient age (<65 vs ≥65 years) and race (White vs non-White), facility type (academic vs non-academic) and the presence of medical comorbidities, the administration of adjuvant chemotherapy was associated with better OS (HR: 0.59, 95% CI: 0.45, 0.78).

4. Discussion

This is the largest cohort of patients with stage I OCCC with adequate staging presented in the literature. Our study demonstrated a possible survival benefit of using adjuvant chemotherapy in patients with stage I disease. Given the low incidence of OCCC in Western countries, clear cell histology was relatively underrepresented in the major randomized

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