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Trends in the use of neoadjuvant chemotherapy for advanced ovarian cancer in the United States

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HIGHLIGHTS

- Treatment of advanced ovarian cancer with neoadjuvant chemotherapy became more frequent between 2004 and 2013
- Utilization of neoadjuvant chemotherapy began to increase in 2007
- Neoadjuvant chemotherapy was adopted most rapidly among elderly women, and those with stage IV ovarian cancer

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ABSTRACT

Objective. Neoadjuvant chemotherapy and interval debulking surgery for the treatment of advanced ovarian cancer has remained controversial, despite the publication of two randomized trials comparing this modality with primary cytoreductive surgery. This study describes temporal trends in the utilization of neoadjuvant chemotherapy and interval debulking surgery in clinical practice in the United States.

Methods. We completed a time trend analysis of the National Cancer Data Base. We identified women with stage IIIC and IV epithelial ovarian cancer diagnosed between 2004 and 2013. We categorized subjects as having undergone one of four treatment modalities: primary cytoreductive surgery followed by adjuvant chemotherapy, neoadjuvant chemotherapy followed by interval debulking surgery, surgery only, and chemotherapy only. Temporal trends in the frequency of treatment modalities were evaluated using Joinpoint regression, and χ^2 tests.

Results. We identified 40,694 women meeting inclusion criteria, of whom 27,032 (66.4%) underwent primary cytoreductive surgery and adjuvant chemotherapy, 5429 (13.3%) received neoadjuvant chemotherapy and interval surgery, 5844 (15.4%) had surgery only, and 2389 (5.9%) received chemotherapy only. The proportion of women receiving neoadjuvant chemotherapy and surgery increased from 8.6% to 22.6% between 2004 and 2013 ($p < 0.001$), and adoption of this treatment modality occurred primarily after 2007 (95%CI 2006–2009; $p = 0.001$). During this period, the proportion of women who received primary cytoreductive surgery and chemotherapy declined from 68.1% to 60.8% ($p < 0.001$), and the proportion who underwent surgery only declined from 17.8% to 9.9% ($p < 0.001$).

Conclusion. Between 2004 and 2013 the frequency of neoadjuvant chemotherapy and interval surgery increased significantly in the United States.

1. Introduction

Primary cytoreductive surgery followed by adjuvant chemotherapy has historically been the standard of care for women with advanced ovarian cancer; however, treatment with neoadjuvant chemotherapy followed by interval debulking surgery has emerged as an alternative treatment modality. Two phase III trials have compared neoadjuvant chemotherapy followed by interval cytoreductive surgery to primary

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cytoreductive surgery followed by adjuvant chemotherapy in women with advanced stage ovarian cancer [1–2]. In both trials survival was equivalent between the treatment groups, leading the authors to conclude that neoadjuvant chemotherapy was an acceptable alternative for patients with advanced ovarian cancer [1–2]. Nonetheless, some experts, particularly in the United States, have remained skeptical about the equivalence of these treatment modalities [3–5]. The Vergote et al. trial is limited by the short overall survival and low proportion of patient who were optimally cytoreduced to <1 cm of residual disease (41.6%). The median overall survival of patients randomized to primary cytoreductive surgery was only 29 months and 30 months in the neoadjuvant chemotherapy group. [2] Similarly, in the CHemotherapy OR Upfront Surgery (CHORUS) trial the median overall survival of patients randomized to primary cytoreductive surgery was 23 months vs. 24 months in the neoadjuvant chemotherapy group, and only 41% of the patients in the PCS arm were optimally cytoreduced to <1 cm of residual disease. [1].

Clinical societies have cautiously weighed in on the debate. The European Society for Medical Oncology released guidelines in 2010 in which neoadjuvant chemotherapy with interval cytoreductive surgery was described as a viable alternative to primary cytoreductive surgery among patients considered to be not optimally resectable at initial presentation [6]. Similarly, the National Comprehensive Cancer Network guidelines from 2011 state that neoadjuvant chemotherapy followed by interval debulking surgery can be considered for patients with bulky stage III and IV disease who are poor surgical candidates or have unresectable disease [7]. Most recently, guidelines from the American Society for Clinical Oncology, and the Society for Gynecologic Oncology, have recommended neoadjuvant chemotherapy and interval surgery for women with high perioperative risk, or low likelihood of achieving optimal cytoreduction [8].

The goal of the current study was to describe temporal trends in the adoption of neoadjuvant chemotherapy followed by interval cytoreductive surgery as a treatment modality in women with advanced stage ovarian cancer in the United States, and to assess how emerging evidence has influence clinical practice.

2. Materials and methods

We conducted a time-trend analysis utilizing the National Cancer Data Base. The National Cancer Data Base is a nationwide comprehensive clinical surveillance oncology system established by the American Cancer Society and the Commission on Cancer of the American College of Surgeons. Currently, this database captures 70% of newly diagnosed malignancies in the United States, and receives over one million case reports from over 1500 hospitals annually [9]. The National Cancer Data Base aggregates information about patient demographics, tumor characteristics, cancer-directed therapies, treating facility, and overall survival. This study was exempt from Intuitional Review Board oversight.

We identified all women with invasive ovarian cancer diagnosed from 2004 through 2013 in the National Cancer Data Base 2013 public use file. We used International Classification of Disease for Oncology, 3rd Edition (ICD-O-3) codes to identify women with epithelial ovarian histologies (Appendix 1) [10]. Only women with pathologically confirmed American Joint Committee on Cancer 7th edition stage IIIC or stage IV epithelial ovarian cancer were included [11]. We excluded women who had a cancer other than ovarian cancer, those with borderline malignancies, and those diagnosed at autopsy. Women under 40 years old were also excluded because data about the treating facility is suppressed among such patients.

We categorized subjects as having undergone one of four mutually exclusive primary treatment modalities: primary cytoreductive surgery followed by adjuvant chemotherapy, neoadjuvant chemotherapy followed by interval debluking surgery, surgery only, and chemotherapy only. Surgery was defined as the most definitive surgical procedure performed. The annual proportion of patients who underwent each treatment modality was calculated among all patients, and among subgroups stratified by stage (IIIC or IV), and age group (40–49 years, 50–59 years, 60–69 years, or 70 years and older).

We classified region using United States Census Bureau definitions [12]. Race and ethnicity were used to construct a single mutually exclusive race-ethnicity variables (non-Hispanic white, black, white-Hispanic, or other and unknown). The treating facility was categorized according to the Commission on Cancer accreditation program as a community cancer program, comprehensive community cancer program, academic/research program, integrated network cancer program, or other.

We calculated descriptive statistics including mean, medians, and proportions. We compared categorical variables using the χ^2 test and continuous variables using the independent sample *t*-test. Temporal trends in the frequency of treatment modalities were evaluated using a piecewise regression approach implemented in Joinpoint Regression Program 4.1.1.5 (National Cancer Institute, Bethesda MD) [13].. This methodology, developed by the National Cancer Institute, has been utilized to identify temporal trends in the epidemiology of a variety of malignancies, and by our group to evaluate trends in cancer directed therapy in endometrial cancer [14–17]. The annual frequency of each treatment modality was modeled using a linear segmented regression function, with a log-transformed dependant variable, and inflection points corresponding to changes of slope. We allowed up to one inflection point, and the permutation test was used to identify the most parsimonious model [13]. We set the overall significance for model selection to 0.05, and adjusted for heteroscedasticity of errors using regression coefficients that were calculated by weighted least squares, where the weight at each point was the inverse of the standard error. The presence of an inflection point was interpreted as a change in temporal trend. Temporal trends from joinpoint regression are reported in terms of annual percentage change when a change of trend was detected during the study period, and as average annual percentage change when discussing trends over the entire period. To evaluate the magnitude of change in the proportion of patients receiving a given treatment over the study period, we compared the proportion of subjects receiving this treatment in the first and last year of the study using the χ^2square. Statistical analysis was performed using SAS 9.3, R 3.0.3, and Joinpoint Regression Program 4.1.1.5.

3. Results

We identified 40,694 women with stage IIIC and IV epithelial ovarian cancer who received treatment at a facility participating in the National Cancer Data Base between 2004 and 2013, and met inclusion criteria. Demographic and tumor characteristics of women included in the study are reported in Table 1. The median age at diagnosis was 63 years [intraquartile rage (IQR) 55–71]. Among patients with known tumor grade, 85.9% had grade 3 disease. Serous adenocarcinoma was the most common histology, and was identified in 74.2% of the patients. During the study period, primary cytoreductive surgery followed by adjuvant chemotherapy was the most common treatment, and was the primary therapeutic modality for 27,032 women (66.4%). Neoadjuvant chemotherapy followed by interval debulking surgery was the primary treatment for 5429 (13.3%) women. We found 5844 (15.4%) subjects who underwent surgery but did not receive chemotherapy, and 2389 (5.9%) who received chemotherapy but did not undergo surgery.

The proportion of patients treated with neoadjuvant chemotherapy and interval cytoreductive surgery increased significantly over the study period (Fig. 1). While in 2004 only 8.6% of patients received neoadjuvant chemotherapy, by 2013 this proportion increased to 22.6% ($p < 0.001$). Analysis of temporal trends demonstrated that growth in the utilization of neoadjuvant chemotherapy occurred after 2007 (95% CI 2006–2009, p for change of trend $p = 0.001$). While the proportion of women who received neoadjuvant chemotherapy and surgery remained constant between 2004 and 2007, after 2007 the proportion

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