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Cost-Effectiveness of Neoadjuvant Chemotherapy versus Primary Surgery in Elderly Patients with Advanced Ovarian Cancer

Insiya B. Poonawalla, MS[1], *David R. Lairson, PhD*[2,*], *Wenyaw Chan, PhD*[3], *Linda B. Piller, MD, MPH*[1], *Xianglin L. Du, MD, PhD*[1]

[1]*Department of Epidemiology, Human Genetics, and Environmental Science, School of Public Health, University of Texas Health Science Center at Houston, Houston, TX, USA;* [2]*Department of Management Policy and Community Health, School of Public Health, University of Texas Health Science Center at Houston, Houston, TX, USA;* [3]*Department of Biostatistics, School of Public Health, University of Texas Health Science Center at Houston, Houston, TX, USA*

ABSTRACT

Background: The use of neoadjuvant chemotherapy (NAC) in the treatment of advanced ovarian cancer has increased in recent years. There is uncertainty about NAC's effectiveness and no study of its cost-effectiveness compared with that of standard primary debulking surgery (PDS). **Objectives:** To seek answers to three important questions: 1) What is the lifetime cost of treating elderly patients with advanced ovarian cancer, based on the primary treatment received? 2) Are the extra costs expended by the NAC group worth any extra survival advantage? 3) Would NAC potentially benefit a particular subgroup and serve as a cost-effective first-line treatment approach? **Methods:** A cohort of elderly women (≥65 years) with stage III/IV ovarian cancer was identified from the Surveillance, Epidemiology and End Results-Medicare linked database from January 1, 2000, to December 31, 2009. Cost analysis was conducted from a payer perspective, and direct medical costs incurred by Medicare were integrated for each patient. Cumulative treatment costs were estimated with a phase-of-care approach, and effectiveness was measured as years of survival. Incremental cost-effectiveness ratio (ICER) and propensity-score–adjusted net monetary benefit regression was used to estimate the cost-effectiveness of NAC per life-year gained. Analyses were further stratified by risk group categorization on the basis of tumor stage, patient age, and comorbidity score. **Results:** Average lifetime cost for treatment with NAC was $17,417 more than with PDS. With only 0.1 incremental life-year gained, the ICER estimate was $174,173. Stratification, however, helped to delineate the treatment effect. Patients in the high-risk subgroup incurred $34,390 and 0.8 life-years more than did patients in the PDS subgroup, with a corresponding ICER of $42,987. In the non–high-risk subgroup, NAC use was dominated by PDS (more costly, less effective). **Conclusions:** Administering NAC before surgery to patients in the high-risk subgroup was cost-effective at "normal" levels of willingness to pay, but not for the overall sample or for patients in the non–high-risk subgroup.

Keywords: cost-effectiveness, neoadjuvant chemotherapy, primary debulking surgery, ovarian cancer.

Introduction

Ovarian cancer accounts for only 3% of all cancers in women in the United States [1], yet it is the leading cause of death from gynecologic malignancies, with elderly women experiencing a significantly greater burden of this disease [2]. Despite a 5-year survival rate of 95% in women with stage I disease, 60% to 75% of the cases are diagnosed at an advanced stage, wherein survival is dramatically reduced to about 30%; a poor prognosis [2,3]. Primary debulking surgery (PDS) followed by adjuvant chemotherapy (AC) has remained the standard approach to treat advanced stage III/IV ovarian cancer for decades. Surgical debulking is the standard treatment for this malignancy, with its success lying in optimally reducing the macroscopic tumor lump to less than 1 cm in size. More recently, experts report that optimal resection entails no macroscopic tumor residue after surgery [4]. Clinical characteristics (e.g., bulky unresectable tumor or poor performance status), however, often present a challenge in performing optimal first-line surgical resection and patients may instead be given neoadjuvant chemotherapy (NAC) before debulking surgery; that is, a few cycles of chemotherapy are followed by delayed debulking surgery [5]. This method helps to overcome the surgical difficulties of treating complex disease and reduces the tumor to a manageable size for optimum cytoreduction.

The effectiveness of NAC versus PDS has been studied over the last two decades. Studies have highlighted the mixed effects

* *Address correspondence to:* David R. Lairson, Division of Management Policy and Community Health, School of Public Health, University of Texas Health Science Center at Houston, 1200 Pressler Street, RAS-E307, Houston, TX 77030.

E-mail: David.R.Lairson@uth.tmc.edu.

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of NAC on survival and perioperative morbidity, but were limited to nonrandomized small sample or retrospective evaluations (see Onda and Yoshikawa [6] for a review). A meta-analysis of 22 cohorts reported that platinum-based NAC was associated with inferior overall survival compared with PDS-AC [7]. In contrast, a subsequent meta-analysis concluded that NAC reduced the risk of suboptimal surgery by half and may also help gynecologic oncologists enhance the rate of optimal cytoreduction [8]. Findings from meta-analyses are dependent on the kind of studies included, as well as different statistical analysis performed. The age of patients included in these studies ranged from 53 to 68 years and may not be generalizable to elderly women (i.e., 65+ years). Of four prospective randomized phase III trials initiated to date [9–12], results from the European Organisation for Research and Treatment of Cancer (EORTC) and Medical Research Council-Chemotherapy or Upfront Surgery in Ovarian Cancer Patients trials have reported noninferior survival with significantly less morbidity in patients with stage IIIc/IV cancer receiving NAC [9,11]. Although other phase III trials are underway, exploratory subgroup findings from the EORTC trial reveal that patients with stage IV cancer and bulky metastatic tumors may have a longer survival from NAC [13]. Although members of the Society of Gynecologic Oncologists in the United States are not fully convinced of NAC as a treatment option [14], population-based evidence has shown that from 1995 to 2005 there has been a small decline in the use of PDS, with a corresponding increase in the odds of use of NAC in elderly patients with ovarian cancer [15]. Almost 14% of advanced cases (n = 6844) received NAC and experienced fewer postsurgical complications than did those receiving PDS [16]. Thus, we anticipate a slow growing use of NAC in routine clinical practice. An aging population and possible change in treatment paradigm over the years can be expected to contribute to the strain on Medicare resources. Because administering chemotherapy before debulking will likely increase health care utilization, concerns about cost-effectiveness will likely arise, despite favorable outcomes for some patients.

Economic evaluations within the realm of ovarian cancer have largely centered on cost-effectiveness studies evaluating various chemotherapeutic agents for de novo [17–24] and recurrent [25–30] cases of cancer or assessing the value of intraperitoneal chemotherapy compared with intravenous administration [31,32]. Most of the cost-effectiveness estimates were based on modeling approaches using several data sources and results from clinical trials. Economic assessment involving the use of NAC in ovarian cancer has not been explored, despite its anticipated increasing use in community practice. We sought answers to three important questions: 1) What is the lifetime cost of treating elderly patients with advanced ovarian cancer, based on the primary treatment received? 2) Are the extra costs expended by the NAC group worth any extra survival advantage? 3) Would NAC potentially benefit a particular subgroup and serve as a cost-effective first-line treatment approach?

Methods

Data Source, Cohort Selection, and Treatment Identification

This was a retrospective cohort study that used data from the Surveillance, Epidemiology and End Results (SEER)-Medicare linked database [33,34]. We included women 65 years or older and newly diagnosed with advanced stage III/IV epithelial ovarian cancer from January 1, 2000, to December 31, 2009, with their Medicare claims through 2010 (n = 8188). For information on SEER-Medicare data and details on the cohort selection, see Appendix A in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2015.01.005. Treatment received was identified on the basis of first claim after ovarian cancer diagnosis from Medicare claims data. Cases with no evidence of surgery or chemotherapy within 12 months of diagnosis were excluded (n = 1810). Patients receiving surgery as first-line treatment within 12 months from diagnosis (may or may not be given AC) were classified as having received PDS and were identified from Medicare claims or from cancer-directed surgery codes in SEER data. Although our PDS definition may be less stringent than that used in trials [10], a frequency distribution for cancer-directed surgery codes showed that most of the patients belonged to code 60 (debulking; cytoreductive surgery, not otherwise specified; n = 1340) or code 61 (with colon [including appendix] and/or small intestine resection [not incidental]; n = 1208). None of the patients in our study had SEER-surgery codes 10-16, 20-22, or 30-32, which may be more characteristic of surgery for early stage ovarian cancer. Hence, our definition for PDS would match closely with that used in clinical trials. Patients receiving chemotherapy as first-line treatment within 12 months of diagnosis and before the date of surgery were classified as having received NAC (see Appendix A, Tables 2–4, in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2015.01.005 for codes used to define PDS and NAC). Patients who did not receive surgery after primary chemotherapy were excluded (n = 1535).

Data Analysis

Patient characteristics were described by primary treatment, with statistically significant differences identified using *t* tests for continuous variables and chi-square tests for categorical variables. Treatment assignment is not randomized in routine clinical care, and there may be baseline differences in patient and clinical characteristics. Traditionally used multivariate-regression methods that adjust for confounding bias pose a threat in situations in which there is lack of overlap between treatment groups. Patients with complete contraindications and those with absolute indications for the treatment are not easily identified with the conventional method, leading to model-misspecification and biased estimates of treatment effects [35,36]. Hence, we used the propensity score (PS) method to adjust for baseline characteristic differences between treatment groups when evaluating cost, effectiveness, and cost-effectiveness measures. PS is the conditional probability of being treated given the observed baseline covariates [37]. Using the logistic regression model, a PS was estimated to predict the probability of treatment assignment (dependent variable) for each patient from covariates listed in Table 1. Quintiles of PS were computed to stratify patients into mutually exclusive groups, so that across strata, patients with either treatment alternative have a similar distribution of measured covariates. This method can eliminate almost 90% of the bias owing to unbalanced treatment groups [38], and hence can provide better control of bias over traditional multivariate regressions. Considerable overlap was seen in plots of PS distribution for both treatment groups, and the last column in Table 1 shows that after adjustment with PS quintiles, balance was achieved in the distribution of covariates between treatment groups. Computer programming and analysis were carried out using SAS version 9.3 (SAS Institute, Inc., Cary, NC).

Estimating Costs

Total treatment costs were estimated starting from the date of diagnosis until death or last available Medicare claims (December 2010), using the phase-of-care approach [39]. This method is popularly used to estimate costs in the presence of censored data [40,41], wherein the period between cancer diagnosis and death was divided into three phases of care—initial, continuing, and terminal—depending on patient survival time (see Appendix A, Table 7, in Supplemental Materials found at http://dx.doi.org/