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Review of methodological challenges in comparing the effectiveness of neoadjuvant chemotherapy versus primary debulking surgery for advanced ovarian cancer in the United States

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ABSTRACT

Randomized trials outside the U.S. have found non-inferior survival for neoadjuvant chemotherapy (NACT) versus primary debulking surgery (PDS) for advanced ovarian cancer (AOC). However, these trials reported lower overall survival and lower rates of optimal debulking than U.S. studies, leading to questions about generalizability to U.S. practice, where aggressive debulking is more common. Consequently, comparative effectiveness in the U.S. remains controversial. We reviewed U.S. comparative effectiveness studies of NACT versus PDS for AOC. Here we describe methodological challenges, compare results to trials outside the U.S., and make suggestions for future research. We identified U.S. studies published in 2010 or later that evaluated the comparative effectiveness of NACT versus PDS on survival in AOC through a PubMed search. Two independent reviewers abstracted data from eligible articles. Nine of 230 articles were eligible for review. Methodological challenges included unmeasured confounders, heterogeneous treatment effects, treatment variations over time, and inconsistent measurement of treatment and survival. Whereas some limitations were unavoidable, several limitations noted across studies were avoidable, including conditioning on mediating factors and immortal time introduced by measuring survival beginning from diagnosis. Without trials in the U.S., non-randomized studies are an important source of evidence for the ideal treatment for AOC. However, several methodological challenges exist when assessing the comparative effectiveness of NACT versus PDS in a non-randomized setting. Future observational studies must ensure that treatment is consistent throughout the study period and that treatment groups are comparable. Rapidly-evolving oncology data networks may allow for identification of treatment intent and other important confounders.

1. Introduction

Ovarian cancer is the leading cause of death among gynecologic malignancies, chiefly due to the large proportion of cases diagnosed at advanced stage [1–3]. Optimal debulking (< 1 cm residual disease) is an important predictor of survival for patients with advanced ovarian cancer, and an additional survival benefit is conferred for those with resection to no gross residual disease [4–14].

The standard treatment for advanced ovarian cancer in the U.S. has traditionally been primary debulking surgery (PDS) – which aims to remove the majority of disease upfront – followed by adjuvant chemotherapy. However, optimal debulking often requires aggressive surgery that is associated with substantial morbidity, including complications that can delay chemotherapy [11,15–17].

Neoadjuvant chemotherapy (NACT) followed by interval debulking surgery and adjuvant chemotherapy has become an increasingly accepted alternative to PDS for advanced ovarian cancer [18–20]. NACT aims to reduce tumor burden and improve performance status preoperatively. This decreases the need for aggressive procedures, reduces post-operative complications, and increases the probability of optimal debulking [17,21,22]. However, it is unclear whether NACT provides a survival benefit.

In the U.S., the role of NACT in advanced ovarian cancer remains controversial [23–29]. Although two randomized controlled trials (RCTs) outside the U.S. observed non-inferior survival with NACT versus PDS [10,30], the generalizability of these trials to U.S. practice

Abbreviations: NACT, neoadjuvant chemotherapy; PDS, primary debulking surgery; RCT, randomized controlled trial

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has been questioned due to lower median overall survival and lower rates of optimal debulking compared to U.S. populations [28,29]. A less aggressive surgical effort compared to that commonly performed in the U.S. has been postulated as the cause of the observed non-inferiority results [27,24–29]. Among U.S. gynecologic oncologists surveyed in 2010, 82% did not believe there was sufficient evidence to justify NACT [31]; conversely, a European survey found that 70% of gynecologic oncologists believed there was sufficient evidence for use of NACT in advanced ovarian cancer [32].

In the absence of U.S. randomized studies on the effectiveness of NACT for advanced ovarian cancer, observational studies represent an important source of evidence. However, non-randomized treatment allocation presents challenges in obtaining unbiased estimates of effectiveness. In this article, we review studies comparing the effectiveness of NACT versus PDS in advanced ovarian cancer, emphasizing epidemiologic methods used, and discuss the strength of the U.S. evidence in the context of existing RCTs, with suggestions for future research.

2. Materials and methods

We conducted a PubMed search on February 5th, 2017 using keywords selected based on prior knowledge and examination of previously-identified studies (Fig. 1). Eligible studies met the following criteria: (1) compared the effectiveness of NACT and PDS on overall survival for advanced ovarian, fallopian, or primary peritoneal cancer; (2) conducted in the U.S.; (3) published in English, and (4) published 2010 or later (reviews published in 2007 and 2011 outline evidence before 2010) [33,34]. We screened titles and abstracts identified through the electronic search for eligibility. The full text of potentially-eligible articles was then reviewed to confirm eligibility.

Each eligible article was reviewed by two independent reviewers. The primary reviewer performed an in-depth review, abstracting information regarding study aims, design, setting, population, methods, overall survival results, and methodological strengths and limitations into an abstraction form designed for the purposes of the study. A second reviewer performed an independent in-depth review, and recorded additional information and/or disagreements into separate fields within the abstraction form. Disagreements between primary and secondary reviewers were discussed and resolved by all reviewers (ALC, AEA, RPH, MSD). References from eligible articles were hand-searched to identify additional studies.

3. Results

Nine observational studies met eligibility criteria for review (Table 1) [19,20,35–41]. Data from 1991 [20] through 2013 [41] were used to conduct these studies. Most studies included women with stage IIIC-IV ovarian cancer [19,36,37,39,41], one included only stage IV [35], and others included earlier stage disease [20,38,40]. Four studies included only NACT patients who received interval debulking surgery [35,37,39,41]. Three studies [20,36,40] used nationally-representative registry data, while the remaining studies used institutional medical record data.

All studies compared overall survival between patients treated with NACT versus PDS using hazard ratios and/or Kaplan-Meier survival estimates, except one study [40] that used incidence rate ratios (Table 1). Studies used various methods to control for confounding, including multivariable adjustment [20,35,39–41], propensity score methods [19,20,36], instrumental variable analysis [20], stratification [19,36,37,40], and restriction [36]. Two studies did not report any confounder control when comparing overall survival [37,38]. Though measured confounders were listed for most studies, covariates used for confounder control were unclear for some studies [20,35,39,41]. Four studies conditioned on residual disease, a variable on the causal pathway and one that is not known preoperatively when treatment decisions are being made [19,35,39,41].

Some studies attempted to address unmeasured confounding (Table 2). Wright used hospital referral region as an instrumental variable [20]. Two studies performed sensitivity analyses to assess the impact of unmeasured confounders, including preoperative disease burden [19,36], performance status [36], and breast cancer susceptibility gene (BRCA) status [36]. One study restricted to patients < 70 years old with Klabunde-Charlson comorbidity index of 0 to mitigate confounding by health status [36].

Four studies [19,36,37,40] attempted to assess heterogeneous treatment effects (Tables 1–2). Six studies restricted their study populations based on age [20,36,38–40], body mass index [37], or comorbidity index [36]. One study [40] stratified survival by a risk score based on age, comorbidity index, and stage. Three studies stratified survival estimates by stage [19,36,40].

Five studies had evidence of immortal time bias (Table 2). Of those, three [20,35,36] introduced immortal time by including person-time from diagnosis to first treatment in the survival calculation, and two [37,39] introduced immortal time by conditioning survival on events occurring after treatment began (i.e., interval debulking surgery). One study did not provide enough details on survival measurement to make a determination [38]. Another study measured survival from interval debulking surgery [41]. No studies reported the length of time between diagnosis and treatment, making the direction and magnitude of immortal time bias difficult to quantify.

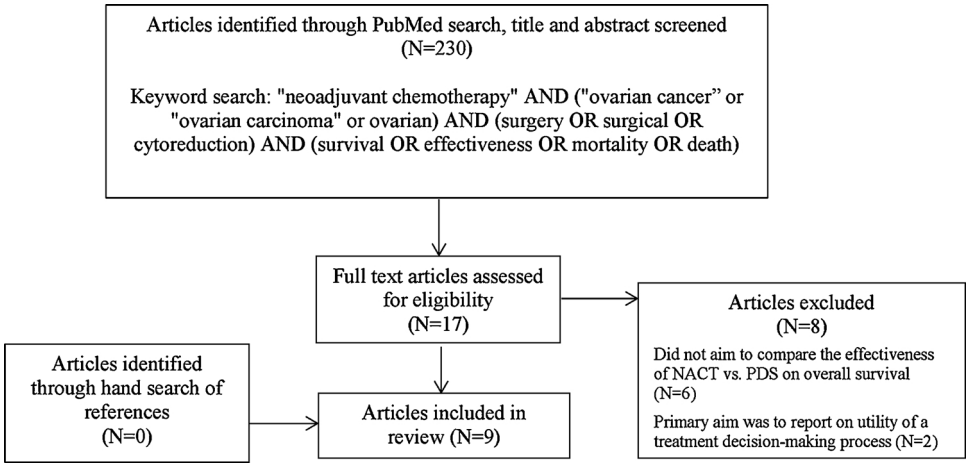

Fig. 1. Selection process for articles comparing the effectiveness of neoadjuvant chemotherapy versus primary debulking surgery for advanced ovarian cancer.