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Modeling treatment outcomes for patients with advanced ovarian cancer: Projected benefits of a test to optimize treatment selection☆,☆☆

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HIGHLIGHTS

- Even a "perfect" test only minimally outperforms clinically-based treatment selection in stage IIIC ovarian cancer.
- Correct a priori identification of resectable disease is more important than correct identification of unresectable disease.
- Current, clinically-based treatment selection for women with stage IIIC ovarian cancer has limited room for improvement.

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ABSTRACT

Objective. For patients with advanced stage epithelial ovarian cancer (EOC), substantial emphasis has been placed on diagnostic tests that can discern which of two treatment options – primary cytoreductive surgery (PCS) or neoadjuvant chemotherapy followed by interval cytoreductive surgery (NACT + ICS) – optimizes patient-level outcomes. Our goal was to project potential life expectancy (LE) gains that could be achieved by use of such a test.

Methods. We developed a microsimulation model to project LE for patients with stage IIIC EOC. We compared: a "standard-of-care" strategy, in which patients were triaged to PCS vs. NACT + ICS based on current clinical practice; and a "test" strategy, in which patients were triaged based on results of a hypothetical test. We identified those test performance characteristics for which the test strategy outperformed the standard-of-care strategy, from a LE standpoint. Effects of parameter uncertainty were evaluated in sensitivity analysis.

Results. Even with a perfect test, the LE gain was modest (LE with test vs. standard-of-care strategy = 67.6 vs. 66.4 months; LE gain = 1.2 months). In order to outperform the standard-of-care, the test had to have a high probability of correctly identifying "resectable" patients at PCS (i.e. those for whom complete or optimal cytoreduction would be possible); this test property was more important than correct triage of unresectable patients to NACT + ICS. Results were sensitive to the proportion of patients whose underlying disease was resectable at PCS.

Conclusion. Diagnostic tests that are designed to triage patients with advanced stage EOC will likely have only a modest effect on LE.

1. Introduction

In 2017, 22,440 women in the United States will be diagnosed with epithelial ovarian cancer (EOC) [1]. EOC is associated with the highest case-fatality ratio of all gynecologic cancers, reflecting a propensity for early peritoneal dissemination and advanced-stage disease at clinical diagnosis. The five-year relative survival is 39% and 17% for patients with International Federation of Gynecology and Obstetrics stage IIIC and IV EOC, respectively [2–4]. National guidelines recommend primary cytoreductive surgery (PCS) followed by chemotherapy as the mainstay

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treatment option for patients with advanced stage EOC [5,6]. For patients who are not expected to achieve complete or optimal cytoreduction at PCS, neoadjuvant chemotherapy followed by interval cytoreductive surgery (NACT + ICS) is recommended [5,6].

Such guidelines – which favor PCS – exist despite results from two randomized controlled trials (RCTs) showing that PCS and NACT + ICS yield similar survival in advanced stage EOC [7,8]. A valid question may be raised as to the rationale for guidelines that seem inconsistent with the results of these trials [5,6]. In the United States, many gynecologic oncologists remain uncertain about whether these results are generalizable due to concerns about selection bias, study patients' disease burden, and differences in surgical practices [5,9–11]. Furthermore, results from observational studies suggest that PCS may be superior for patients in whom complete or optimal cytoreduction can be achieved (here classified as 'resectable') [12,13]. Because most patients with stage IIIC EOC present with a high tumor burden, but have a relatively high likelihood of resectable disease, the choice between PCS and NACT + ICS is especially unclear.

Development of a test that can identify which patients are likely to achieve an optimal resection at PCS is a principal focus of efforts to improve survival in patients with advanced stage EOC. Investigators have utilized computed tomography (CT), magnetic resonance imaging (MRI), CA-125 levels, and diagnostic laparoscopy to predict the likelihood of optimal cytoreduction [14–17]. However, none of the approaches studied to date have demonstrated survival benefits.

In this study, we sought to estimate the potential life expectancy (LE) gains that could be achieved by implementation of a test to guide treatment selection in women with stage IIIC EOC. To accomplish this, we developed a microsimulation model to estimate LE associated with two strategies for assigning treatment: a standard-of-care strategy in which patients are triaged to PCS vs. NACT + ICS based on current, observed practices [18], and a test strategy in which patients are triaged to PCS vs. NACT + ICS based on the results of a hypothetical test. Our purpose was to identify the performance characteristics that would be required for a test to outperform standard-of-care triage practices, and to quantify the LE gains that could be achieved with use of a "perfect" test.

2. Methods

2.1. Model overview

We developed a microsimulation model to project outcomes associated with the treatment of patients with newly diagnosed stage IIIC EOC. We analyzed the model to determine whether a hypothetical test developed to optimize triage of patients to PCS or NACT + ICS could outperform current standard-of-care triage practices, using life expectancy (LE) as the outcome measure (Fig. 1).

The goal of the hypothetical test was to increase the proportion of patients that achieved complete or optimal cytoreduction at either PCS or ICS. We defined a 'resectable' patient as one in whom cytoreduction would be achievable with either no visible disease in the abdomen (complete cytoreduction), or with the largest visible mass ≤ 1 cm in diameter (optimal cytoreduction) after PCS. An "unresectable" patient was one in whom PCS would result in visible disease with the largest mass > 1 cm in diameter (suboptimal cytoreduction). We defined the test by its ability to detect unresectable disease. Accordingly, test-positive patients were triaged to NACT + ICS and test-negative patients were triaged to PCS (Table 1).

In the model, patients transitioned through multiple health states – each defined by specific, common events or circumstances (e.g., "initial work-up," "PCS," "NACT + ICS," and "post-treatment") – over time. In each health state, they were assigned specific characteristics that influenced their risks of death. These included: surgical cytoreductive outcome (complete, optimal, or suboptimal); the nature and timing of chemotherapy received (standard intravenous (IV), intraperitoneal (IP), or dose-dense IV); and treatment failure (i.e., the inability to tolerate chemotherapy after PCS, or ICS after NACT). Each patient was also subjected to 90-day surgical mortality risks specific to PCS or ICS. Surgical morbidity was not incorporated in the model.

The primary benefits of superior triage were as follows. If, a priori, one knew that a patient's disease would be unresectable at PCS, then that patient would be triaged to NACT + ICS. By opting for NACT + ICS over PCS, this patient – on average – would live longer due to a higher likelihood of complete or optimal cytoreduction at ICS (relative

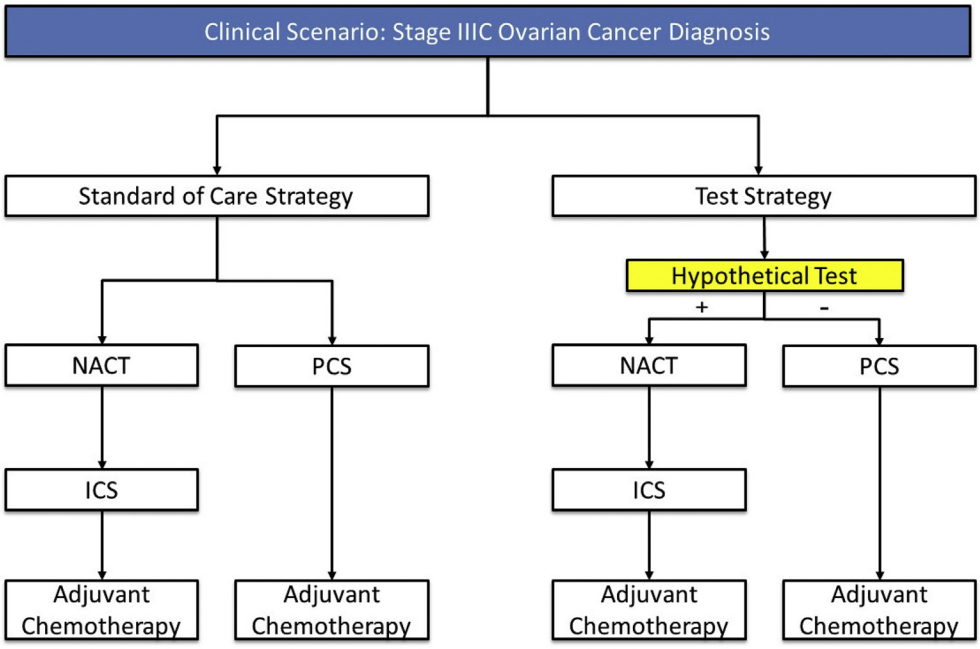

Fig. 1. Simplified Schematic of the Model. Using microsimulation methods, we modeled outcomes for patients with Stage IIIC ovarian cancer who underwent treatment selection (neoadjuvant chemotherapy (NACT) followed by interval cytoreductive surgery (ICS) vs. primary cytoreductive surgery (PCS)) using two different strategies: 1) "standard-of-care" in which patients were triaged based on observed clinical practice; or 2) "test" in which patients were triaged using a hypothetical test.

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