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Short communication

Cost-effectiveness of hyperthermic intraperitoneal chemotherapy at primary cytoreduction of epithelial ovarian cancer based on residual disease status

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A B S T R A C T

Hyperthermic intraperitoneal chemotherapy (HIPEC) with cisplatin when used at the time of interval cytoreductive surgery (ICS) after neoadjuvant chemotherapy (NACT) has been shown to provide a survival advantage compared to interval cytoreduction alone for patients with advanced epithelial ovarian cancer in a cost-effective manner. A recent large multi-center retrospective cohort study showed a survival advantage with HIPEC given during primary debulking surgery compared to surgery alone. While there is an ongoing randomized controlled trial examining HIPEC at the time of primary cytoreductive surgery (PCS) before chemotherapy (OVHIPEC-2), there is currently no study of this practice in the United States or cost data to inform incorporation of this practice. To help guide the use of HIPEC in the upfront setting until the results of the OVHIPEC-2 are available in 2026, a decision-analytic cost-effectiveness model of the US healthcare sector was developed for patients undergoing PCS with or without HIPEC. Effectiveness inputs were extracted from a Chinese retrospective cohort study of 425 patients who underwent PCS with HIPEC and 159 patients who underwent PCS alone. We found incremental cost effectiveness ratios (ICER) of $9,789 per life year saved (LYS) for optimal PCS, $18,164/LYS for suboptimal PCS, and $7,854/LYS for all patients. Our findings provide preliminary data to support that HIPEC at the time of primary cytoreductive surgery can be considered cost-effective regardless of residual disease status when using a standard willingness to pay threshold.

1. Introduction

A 2018 Dutch multi-center, phase 3 clinical trial demonstrated an overall survival (OS) benefit of hyperthermic intraperitoneal chemotherapy (HIPEC) with cisplatin when used at interval cytoreductive surgery (ICS) after neoadjuvant chemotherapy (NACT) for advanced epithelial ovarian cancer (van Driel et al., 2018). Subsequent analysis revealed HIPEC in this setting was cost-effective (Lim et al., 2019; Koole et al., 2019). Since then, HIPEC with cisplatin has been one accepted standard of care in patients with advanced epithelial ovarian cancer after NACT. Regarding HIPEC with primary cytoreductive surgery (PCS) prior to chemotherapy, a large multi-center retrospective cohort study of 584 patients conducted in China demonstrated an OS advantage compared to PCS alone in women with FIGO stage III EOC (Lei et al., 2020). The results from that study combined with the evidence regarding HIPEC with ICS suggest that HIPEC in the upfront setting may be appropriate in select candidates. However, there has not yet been a published randomized controlled trial with regards to HIPEC at the time of primary cytoreduction. OVHIPEC-2 is currently underway, although preliminary results are not anticipated until 2026 (Koole et al., 2020). As a result, HIPEC is not generally offered to patients receiving PCS in the United States (US). To help inform the potential use of HIPEC in the upfront setting until the results of the OVHIPEC-2 are available, the objective of this study is to evaluate the cost-effectiveness of HIPEC at primary cytoreduction using existing data.

2. Methods

This study was conducted in accordance with Consolidated Health Economic Evaluation Reporting Standards (CHEERS) (Husereau et al.,

Abbreviations: HIPEC, Hyperthermic Intraperitoneal Chemotherapy; PCS, Primary Cytoreductive Surgery; CEA, Cost-Effectiveness Analysis.

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2013) and is exempt from institutional review board review given use of publicly available data.

A decision-analytic cost-effectiveness model of the US health care sector using simulated patients with FIGO stage III primary epithelial ovarian cancer was developed for three base cases: 1) optimal cytoreduction, 2) suboptimal cytoreduction, and 3) all patients regardless of residual disease status. The base case for each model compared two surgical strategies: 1) PCS versus 2) PCS with HIPEC (Fig. 1). Effectiveness inputs (median OS and Kaplan-Meier time-to-event estimates) were obtained from the retrospective cohort study on PCS with HIPEC by Lei et al., and costs in US dollars from a payer perspective were obtained from published studies (Lim et al., 2019; Lei et al., 2020).

The Lei et al. cohort was comprised of 584 patients with stage III primary epithelial ovarian cancer treated with either PCS alone (n = 159) or PCS with HIPEC (n = 425) between January 2010 to May 2017 at five high-volume institutions in China. The average age was 55, most patients (98.5%) had an ECOG performance status of 0–1, and optimal debulking (defined here as < 1 cm residual disease) was achieved in 72% of patients with no difference between groups. The HIPEC protocol used described circulating heated saline with cisplatin at a dose of 50 mg/m^2 performed on days 1, 3, and 5. The mean number of HIPEC treatments was 2.8 (Lei et al., 2020).

Our cost-effectiveness model assumed a one-time dose of intraperitoneal cisplatin 100 mg/m^2 at the time of surgery since this is the regimen commonly used in the US. The time horizon employed was 36 months. No discounting was performed given the limited time horizon. Utilities were measured in life-years saved (LYS). The primary outcome was incremental cost-effectiveness ratio (ICER) in US dollars per LYS. A standard willingness-to-pay (WTP) threshold of $100,000/LYS was used to guide the interpretation of the model.

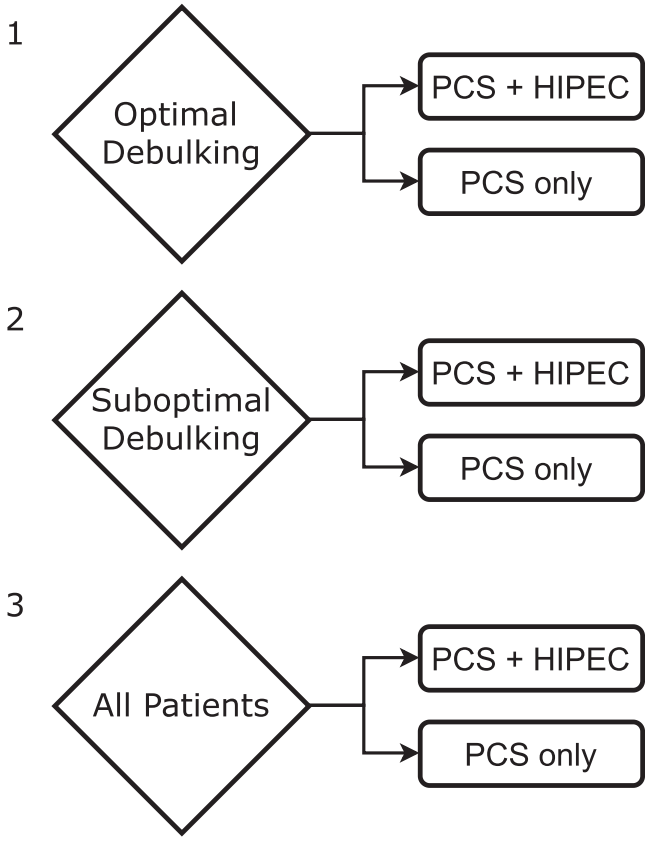

Fig. 1. Summary Schematic of Treatment Strategies for base cases with 1) optimal cytoreduction, 2) suboptimal cytoreduction, and 3) both optimal and suboptimal cytoreduction. **Abbreviations:** PCS, primary cytoreductive surgery. HIPEC, hyperthermic intraperitoneal chemotherapy.

3. Results

Total costs for PCS were $32,169 compared to $38,405 for PCS plus HIPEC, considering the costs of surgery, adverse events, post-operative hospital stay (including ICU), adjuvant chemotherapy, and cost of care per year thereafter. The total cost difference (incremental cost) between PCS plus HIPEC and PCS alone was $6,236. With regards to specific costs, surgery was $6,120 in the PCS alone group versus $9,997 in the PCS plus HIPEC group and general care hospitalization was $4,737 in the PCS alone group versus $5,329 in the PCS plus HIPEC group. It was also assumed that HIPEC patients required an ICU stay, which added an additional $1,767 for the HIPEC group. Given the only significant adverse event in the study by Lei et al. was electrolyte disturbances, it was assumed that there was no difference in cost for management of adverse events (Lei et al., 2020). It was also assumed that there were no differences in cost for adjuvant chemotherapy ($3,423) and cost of care per year ($5,963). The median LYS was 1.0 for optimal PCS, 0.8 for suboptimal PCS, and 1.3 for all patients. The 36-month overall survival probabilities for the PCS alone group compared to the PCS plus HIPEC group were 49.5% versus 60.3% overall, 55.4% versus 65.9% in patients with optimal PCS, and 36.7% versus 44.3% in patients with suboptimal PCS. Using the above data, the ICERs amounted to $9,789/LYS for optimal PCS, $18,164/LYS for suboptimal PCS, and $7,854/LYS for all patients (Table 1).

4. Discussion

The addition of HIPEC to PCS appears to be cost-effective compared to PCS alone, with ICERs well below the assumed WTP threshold of $100,000 per LYS in patients with both optimal and suboptimal cytoreduction. As we await results from an ongoing randomized control trial, our current study provides a perspective from which to interpret the potential value of adding HIPEC to PCS.

A notable limitation of this analysis is that our effectiveness inputs were derived from a study based in China, which may be less valid in the US given differences in HIPEC protocols typically used and differences in patient population. However, HIPEC with PCS in the US is rarely employed, so the data from the Lei et al. study was necessary for our analysis. With regards to the treatment protocol, there is no research directly comparing 50 mg/m^2 on days 1, 3 and 5 to a one-time treatment with 100 mg/m^2 on day 1. That said, studies in both China and Europe examining HIPEC at the time of ICS for ovarian cancer show significant survival benefit with both regimens. The European study by Van Driel et. al. used a one-time treatment with cisplatin 100 mg/m^2 at the time of ICS. (van Driel et al., 2018) Overall survival was reported as 45.7

Table 1
Summary base case results.

Optimal		
Outcome	PCS	PCS + HIPEC
Cost, $US	$32,169	$38,405
Incremental cost	(referent)	$6,236
Incremental LYS	(referent)	1.0
Incremental cost-effectiveness ratio per LYS	–	9,789
Suboptimal		
Outcome	PCS	PCS + HIPEC
Cost, $US	$32,169	$38,405
Incremental cost	(referent)	$6,236
Incremental LYS	(referent)	0.8
Incremental cost-effectiveness ratio per LYS	–	18,164
All Patients		
Outcome	PCS	PCS + HIPEC
Cost, $US	$32,169	$38,405
Incremental cost	(referent)	$6,236
Incremental LYS	(referent)	1.3
Incremental cost-effectiveness ratio per LYS	–	7,854

months in the ICS with HIPEC arm compared to 33.9 months ICS alone arm (HR = 0.67, p = 0.02). Similarly, a Chinese retrospective study examining cisplatin 50 mg/m^2 in three doses at ICS, showed an overall survival of 51 months, compared to 40 months with ICS alone (HR 0.52, p = 0.001)[7]. Even with some variation in efficacy between regimens, it is unlikely this difference will cause the WTP threshold to exceed $100,000/LYS. With regards to the patient population, this analysis assumes that PCS plus HIPEC will have a similar prognostic benefit in the contemporary treatment setting in the US as it did in China from 2010 to 2017. This may not be the case given demographic differences between countries and the increased use of maintenance therapies such as bevacizumab and PARP inhibitors in recent years. Such variables are being investigated in the ongoing OVHIPEC-2 trial.

Despite the above limitations, our analysis of the current data demonstrates the potential benefits relative to costs may justify HIPEC with PCS in select candidates anticipated to have a response to chemotherapy while we await the results of OVHIPEC-2 trial.

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CRediT authorship contribution statement

Courtney A. Penn: Conceptualization, Data curation, Writing – review & editing. **Erica V. Carballo:** Writing – original draft. **Christine S. Walsh:** Writing – review & editing. **Oliver Zivanovic:** Writing – review & editing. **Kenneth H. Kim:** Supervision, Conceptualization, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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