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Cost-effectiveness of hyperthermic intraperitoneal chemotherapy (HIPEC) at interval debulking of epithelial ovarian cancer following neoadjuvant chemotherapy

Stephanie L. Lim [a], Laura J. Havrilesky [b,c], Ashraf S. Habib [d], Angeles Alvarez Secord [b,c,*]

[a] Duke University School of Medicine, United States of America
[b] Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Duke University Medical Center, United States of America
[c] Duke Cancer Institute, United States of America
[d] Department of Anesthesiology, Duke University Medical Center, United States of America

HIGHLIGHTS

- HIPEC in addition to interval cytoreduction increases cost of care for stage III epithelial ovarian cancer.
- The addition of HIPEC at interval cytoreduction for stage III epithelial ovarian cancer is cost-effective.
- The ICER for HIPEC at ICS is $2436/QALY compared to ICS alone, which is far below the accepted threshold.

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ABSTRACT

Objectives. A recent randomized controlled trial demonstrated an overall survival benefit to the addition of hyperthermic intraperitoneal chemotherapy (HIPEC) to neoadjuvant chemotherapy (NACT) for stage III epithelial ovarian cancer (EOC). The objective of the current study was to quantify the cost-effectiveness of HIPEC in this setting.

Methods. A decision analytic cost-effectiveness model was designed from a payer perspective to compare 2 surgical management strategies for EOC: (1) interval cytoreductive surgery (ICS); (2) ICS + HIPEC. Overall survival and ostomy rates with HIPEC were modeled from published studies. We assumed that 25% of each arm would later undergo secondary cytoreductive surgery, with the ICS arm eligible for HIPEC at that time. Costs were obtained from Medicare data, published studies, and the financial department of an academic hospital. Quality of life was not different between the arms; we assigned utilities based on a prior time-trade off study of ovarian cancer treatment. A Monte Carlo probabilistic sensitivity analysis was performed in the base case; primary outcome was the incremental cost-effectiveness ratio (ICER), expressed in 2017 US Dollars/quality-adjusted life years (QALYs).

Results. ICS was the least costly strategy at $78,849, compared to ICS + HIPEC at $79,954. ICS + HIPEC was more effective than ICS (2.9 QALYs versus 2.45 QALYs for ICS). ICS + HIPEC was highly cost-effective, with an ICER of $2436/QALY compared to ICS. In one-way sensitivity analyses, probability of ostomy reversal and use of HIPEC at secondary cytoreduction did not substantially impact the cost-effectiveness of ICS + HIPEC.

Conclusion. ICS + HIPEC constitutes cost-effective management of stage III EOC when NACT is performed.

1. Introduction

Ovarian cancer is the highest cause of mortality among gynecologic cancers and is the fifth leading cause of cancer-related deaths among women in the United States, as it is often diagnosed at advanced stage. Once advanced, the 5-year survival is estimated to be 19–28% for epithelial ovarian cancer [1]. Current standard treatment for stage III ovarian cancer involves maximum effort cytoreductive surgery followed by 6 cycles of carboplatin-paclitaxel chemotherapy or neoadjuvant chemotherapy (NACT) with interval cytoreduction after 3 cycles. Randomized controlled trials (RCTs) have demonstrated conflicting results regarding the efficacy of HIPEC in colorectal cancer with some studies suggesting a significant increase in overall survival but more recent phase III trials

* Corresponding author at: Box 3079, DUMC, Durham, NC 27710, United States of America.
E-mail address: angeles.secord@duke.edu (A.A. Secord).

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suggesting no impact on overall survival [2–6]. Its efficacy in newly diagnosed ovarian cancer had previously been reported as encouraging in retrospective trials [7,8].

The trial by van Driel et al. is the first RCT to evaluate the impact of using HIPEC during interval cytoreductive surgery (ICS) following primary NACT in ovarian cancer [9]. After three cycles of carboplatin and paclitaxel, subjects were randomly assigned to undergo either ICS or ICS with administration of HIPEC with cisplatin. The median overall survival for the ICS group was 33.9 months, versus 45.7 months for the ICS + HIPEC group. Additionally, the median recurrence free survival for the ICS cohort was 10.7 months, versus 14.2 months for the ICS + HIPEC group [9]. The authors hypothesized that the success of this method lies in the ability of hyperthermic chemotherapy to more effectively eliminate residual microscopic peritoneal disease than intravenous chemotherapy alone [9].

Despite the clear clinical significance, the addition of HIPEC requires additional resources, personnel, and time; critics argue that it may substantially increase costs. With continuous health reform focused on providing value-based healthcare, addressing the cost-effectiveness of this intervention is critical if it is to become a standard of care option. In this analysis, we developed a decision model to quantify the cost and cost-effectiveness of different surgical strategies for treatment of stage III epithelial ovarian cancer following initiation of NACT.

2. Methods

2.1. Decision model

A decision analytic cost-effectiveness model was designed from a third party payer perspective to compare 2 surgical management strategies for EOC: (1) interval cytoreductive surgery (ICS); (2) ICS + HIPEC (Fig. 1). A modified Markov state transition design was employed using 6 month Markov stages and the following exhaustive and mutually exclusive Markov states: Alive, on active treatment; Alive, post-treatment; Alive, post-treatment with ostomy; Dead. The model's time horizon was 5 years, similar to the follow up time in the RCT of van Driel et al. [9]. Discounting was performed at 3% annually.

A Monte Carlo probabilistic sensitivity analysis was performed in the base case; the primary outcome was the incremental cost-effectiveness ratio, expressed in 2017 US dollars/quality-adjusted life years (QALYs).

2.2. Clinical estimates and key assumptions

Because adverse event rates were not significantly different between groups in the RCT (27% versus 25%, p = 0.76), we did not incorporate the incidence and costs of all severe adverse events into the model. Because ostomy creation is an impactful clinical event, we incorporated

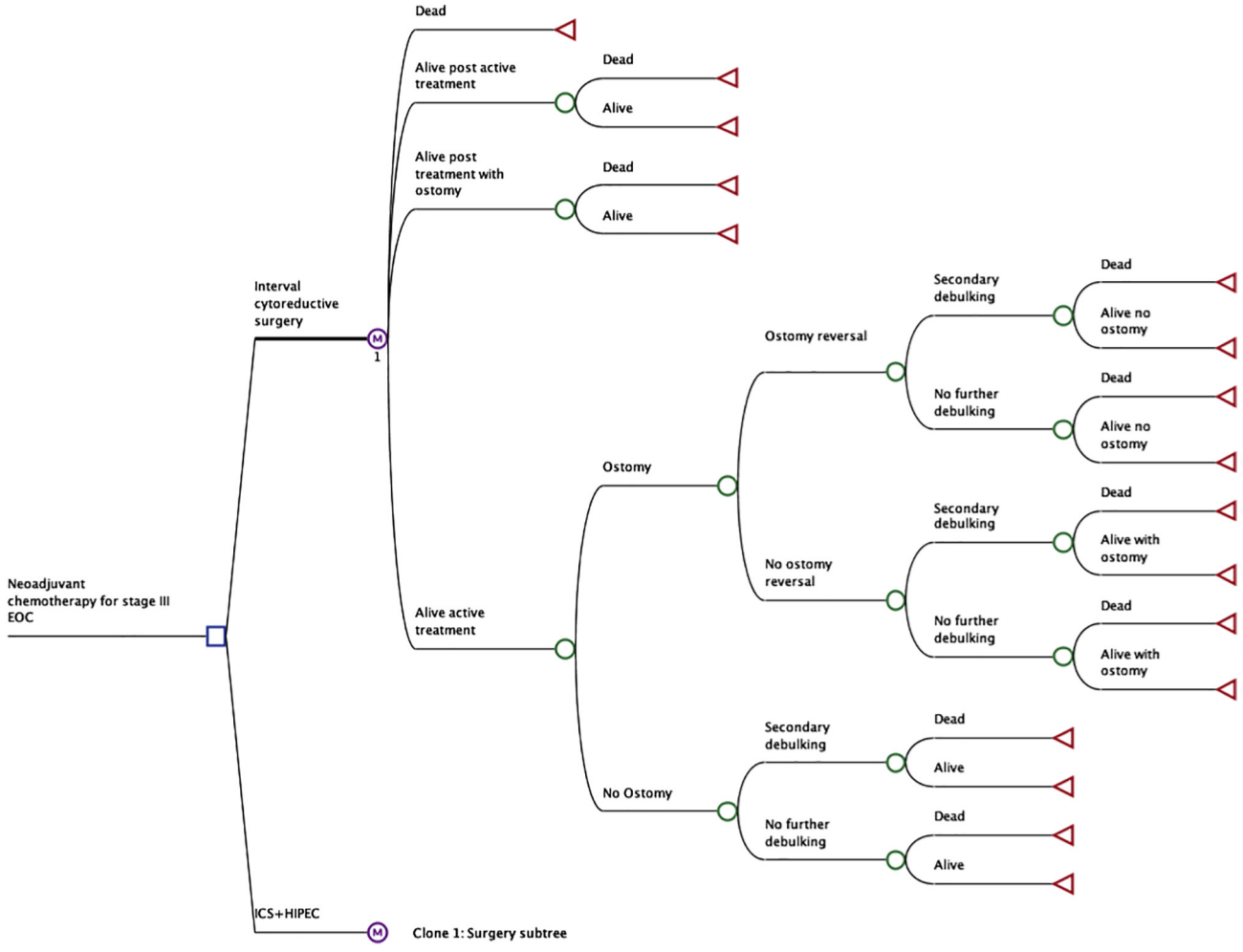

Fig. 1. Decision model. A decision model was constructed to evaluate two strategies (square-decision node) for management of stage III EOC: (1) interval cytoreductive surgery (ICS); (2) ICS + HIPEC. A modified Markov state transition design was employed using 6 month Markov stages and the following exhaustive and mutually exclusive Markov states: Alive, on active treatment; Alive, post-treatment; Alive, post-treatment with ostomy; Dead. Discounting was performed at 3% annually. The square represents a decision node; circle represent possible pathways (chance nodes); triangle represent possible outcomes (terminal nodes). Duplicate nodes are collapsed.

ostomy rates (17% ICS + HIPEC versus 11% ICS) using published trial data. We accounted for ostomy care and/or reversal (in 50%). We assumed based on the model design team's clinical estimates of the rate of platinum-sensitivity (approximately 50%) and future resectability of recurrent disease (approximately 50%) that 25% of patients in each arm would undergo future secondary cytoreductive surgery, with only the ICS arm eligible for HIPEC at the later surgery. We further assumed that 50% of those eligible for future HIPEC, or 12.5% of the entire ICS cohort, would receive HIPEC at secondary cytoreduction and incur additional costs as such.

2.3. Survival

Overall survival was modeled from the published trial data of van Driel et al. as follows: published overall survival (OS) data in the ICS arm was used to estimate raw survival data using the method of Hoyle and Hensley [10] and OS data was modeled as beta distributions at 6 month intervals as described previously [11]. The HR associated with HIPEC (0.67; 95% CI 0.48–0.94) was applied to survival in the ICS arm as a lognormal distribution to model OS in the HIPEC arm and simultaneously account for uncertainty.

2.4. Quality of life

In the base case, we assumed no quality of life (QOL) difference between arms based on results of the RCT. The QOL-associated utility during chemotherapy treatment was estimated at 0.80, improving to 0.85 after 6 months and remaining at 0.85 indefinitely, based on prior prospectively measured QOL-based utility calculations obtained in the setting of primary chemotherapy for advanced ovarian cancer [12]. In an alternative analysis, we applied a utility of 0.78 during time spent with an ostomy [13–15].

2.5. Costs

Costs were obtained from Medicare data, prior published studies, and the financial department of a private academic hospital, including NACT, operating room (OR) expenses, perfusionist labor, drug costs, hospital stay, ostomy supplies and reversal costs (Table 1). The annual cost of ongoing care for ovarian cancer and the cost of care in the last year of life were applied using data from Yabroff et al. [16]. For patients with an ostomy, we incorporated the annual cost of ostomy care as well as the cost of reversal based on data from published literature [13,17,18]. All costs were inflated to 2017 USD [19].

2.6. Sensitivity analyses

We performed multiple sensitivity analyses on key variables: probability of ostomy reversal, use of HIPEC at secondary cytoreduction in the ICS arm, and probability of future secondary cytoreduction (Table 2).

3. Results

3.1. Base case

ICS was the least costly strategy, at a mean cost of $78,849 (95% CI $71,977–$85,546), compared to ICS + HIPEC at $79,954 (95% CI 72,551-$87,610). ICS + HIPEC was more effective than ICS (2.90 QALYs (95% CI 2.46–3.29) versus 2.45 QALYs (95% CI 2.20–2.70) for ICS). ICS + HIPEC was highly cost-effective, with an ICER of $2436/QALY compared to ICS.

In an acceptability curve analysis using willingness to pay (WTP) thresholds of $50,000/QALY and $100,000/QALY, ICS + HIPEC was the strategy of choice in 91.5% and 94.1% of simulations, respectively (Fig. 2).

Table 1
Cost estimates.

Items	ICS costs	ICS + HIPEC costs	References
Pre-surgical and post-surgical adjuvant treatment			
1 cycle of carboplatin and paclitaxel	$79		[28]
Physician evaluation	$138		[29, 30]
Chemotherapy administration	$240		[29, 30]
Lab work	$114		[29, 30]
Total costs for 6 treatments	$3,423	$3,423	
Surgical costs			
Operating room costs*	$2,630	$4,243	
Surgical debulking	$2,120		[26]
Hyperthermia treatment		$500	[26]
Perfusionist labor cost		$346	[31]
Cisplatin		$377	[28]
Anesthesiology*	$1,370	$2,411	
Total surgical costs	$6,120	$9,997	
Post-operative course costs			
ICU hospital day 1 cost*	-	$1,767	
Hospitalization (excluding ICU)*	$4,737	$5,329	
Total post-operative costs	$4,737	$7,096	
Ostomy Reversal			
Operating room costs*	$2,154		
Surgical reversal of colostomy	$909		[26]
Anesthesiology*	$1,063		
Hospitalization*	$2,960		
Total Ostomy Reversal	$7,087	$7,087	
Surveillance/follow up care			
CA-125		$29	[28]
CT scan		$380	[26]
Cost for interval year of care		$5,963	[16]
Cost for last year of care		$76,841	[16]

3.2. One-way sensitivity analyses

In one-way sensitivity analyses, the following factors did not substantially impact the cost-effectiveness of ICS + HIPEC: probability of ostomy reversal (varied from 0 to 100%) and use of HIPEC at secondary cytoreduction in the ICS arm (varied from 0 to 100%). When the probability of future secondary cytoreduction was assumed to exceed 75%, ICS was dominated (both more costly and less effective that ICS + HIPEC).

3.3. Alternative analysis

When the utility associated with living with an ostomy was modeled at 0.78 (base case 0.85), ICS + HIPEC remained cost-effective with an ICER of $2689/QALY compared to ICS.

Table 2
Clinical estimates.

Items	ICS	ICS + HIPEC	95% CI	Reference
Overall survival hazard ratio	Reference	0.67	[0.48–0.94]	[9]
Duration of surgery (minutes)	192	338		[9]
Length of hospital stay (days)	8	10		[9]
Length of ICU stay (days)	0	1		[9]
Rate of bowel resection with ostomy creation	0.11	0.17		[9]

Items	Estimate	Range	Reference
Quality of life during treatment	0.80		[12]
Quality of life after treatment	0.85		[12]
Rate of platinum-sensitivity[a]	0.50		
Rate of future resectability of recurrent disease[a]	0.50		
Rate of secondary cytoreductive surgery[a]	0.25	0–1	
Rate of ICS arm that receives HIPEC at secondary reduction[a]	0.12	0–1	
Probability of ostomy reversal[a]	0.50	0–1	

[a] Clinical estimates; ICS – interval cytoreductive surgery; HIPEC – hyperthermic intraperitoneal chemotherapy; CI – confidence interval; ICU – intensive care unit.

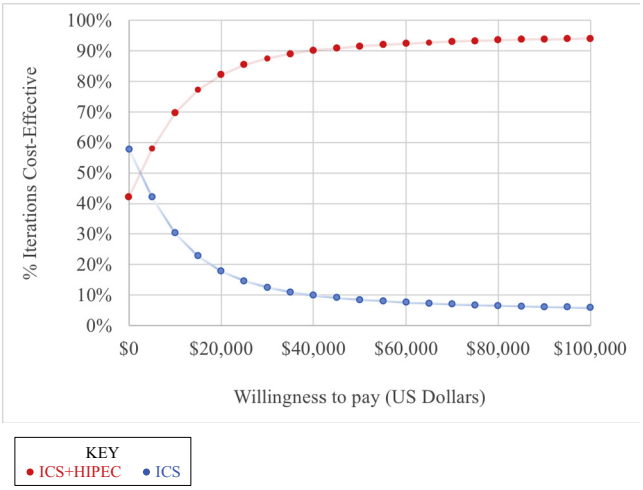

Fig. 2. Acceptability curve. In acceptability curve analysis using willingness to pay thresholds of $50,000/QALY and $100,000/QALY, ICS + HIPEC was the strategy of choice in 91.5% and 94.1% of simulations, respectively.

4. Discussion

Ovarian cancer is often diagnosed at an advanced stage and this portends a poor prognosis with a five-year survival rate of 28% for patients with Stage III invasive epithelial ovarian cancer [1]. The recent RCT by van Driel et al. demonstrated an overall survival benefit for ICS + HIPEC compared to ICS alone, with a difference of 33.9 months compared to 45.7 months, respectively [9]. The current model demonstrates that ICS + HIPEC is more costly but also more effective than ICS alone (2.90 QALYs (95% CI 2.46–3.29) versus 2.45 QALYs (95% CI 2.20–2.70) for ICS). ICS + HIPEC appears to be highly cost-effective, with an ICER of $2436/QALY compared to ICS. Furthermore, in an acceptability curve analysis (WTP = $50,000/QALY), ICS + HIPEC was the strategy of choice in 91.5% of the simulations.

The primary reason for the cost-effectiveness of ICS + HIPEC is that, while requiring more resources, this strategy incurs only a one-time additional cost related to surgical resources and hospital stay. Given the observed life expectancy benefit of approximately one year and the associated improvement in QALYs, this appears to be a highly cost-effective procedure. The observed outcomes persisted over a range of sensitivity analyses on key clinical parameters, specifically the probability of ostomy reversal and use of HIPEC at secondary cytoreduction. In a previously published brief commentary by Behbakht et al, ICS + HIPEC was noted to be cost-effective with an ICER of $25,492 per life year saved compared to neoadjuvant chemotherapy alone in patients with stage III EOC [20]. This commentary additionally noted that ICS + HIPEC is cost-effective when compared to the addition of bevacizumab to neoadjuvant chemotherapy. Other cost-effectiveness studies based on the ICON7 and GOG 218 trials have similarly indicated that the addition of bevacizumab is not a cost-effective addition to the primary treatment of ovarian cancer, with incremental cost-effectiveness ratios of greater than $600,000/QALY and $479,712 per progression-free life-years saved, respectively, compared with patients receiving chemotherapy alone [21,22]. The high third party payer costs of many novel maintenance therapies of between $6000–$12,000/month necessarily also raises the effectiveness level necessary to achieve value-based care. HIPEC has been reported to be cost-effective in other peritoneal surface malignancies and colorectal peritoneal carcinomatosis [23,24].

Our model adds to the literature by examining the cost-effectiveness of HIPEC for ovarian cancer in detail. The prior analysis of Behbakht et al did not account for a number of costs, including cost of colostomy care and/or reversal, costs of ovarian cancer care during treatment, surveillance, end of life costs, or possibility of HIPEC in future treatment; our current analysis accounts for all of these. Additionally, the previous analysis used life years saved (LYS), while the current analysis utilized quality-adjusted life years saved (QALYs), accounting for both morbidity and mortality [20]. At the commonly accepted willingness to pay thresholds of $50,000/QALY and $100,000/QALY, we found that ICS + HIPEC was the strategy of choice in 91.5% and 94.1% of simulations, respectively. In more recent years, health economists have stated that the willingness to pay in the United States should be as high as $160,000/QALY [25]. Therefore, with an ICER of $2436/QALY compared to ICS alone, ICS + HIPEC is shown to be highly cost-effective in this model.

There are several limitations to this study. First, while a prospective randomized trial was used to estimate most of the clinical parameters, expert opinion was used for a number of key parameters, including quality of life during treatment, probability of ostomy reversal, probability of platinum sensitivity, and if platinum sensitive, percent of patients that would be a candidate for HIPEC if they had not received it before. These were agreed upon by several gynecologic oncologists at the authors' institution. While these parameters may vary based on populations, regional variations, and institutional preferences, we performed multiple sensitivity analyses with robust results. Second, while published literature was used for costs when possible, several costs were derived from Medicare reimbursements, CMS physician Fee Services, and the financial department of an academic hospital [9,19,26,27]. We additionally did not include indefinite costs, such as the reduction in efficiency to the hospital system a longer procedure might add; we did, however, account for the additional OR time the longer procedure would cost. Third, we did not include the costs of all adverse events in the study, as many were not statistically different between the two groups in the RCT. Fourth, it remains to be seen if the findings reported by van Driel et al. are generalizable. Whether or not the positive findings from this study are ultimately confirmed in a pragmatic setting for ovarian cancer remains to be determined. Finally, patient preferences are an integral part of the treatment decisions not accounted for in the current study; our group is conducting ongoing preferences research to better understand patients' willingness to undergo more extensive surgery with higher rates of ostomy and surgical complications in exchange for improved survival time.

The importance of exploring HIPEC in additional RCTs in ovarian cancer is highlighted by the recent negative findings in prospective phase III trials of HIPEC in colorectal cancer. HIPEC combined with cytoreductive surgery has been used for more than a decade as a standard therapy in colorectal cancer patients with isolated peritoneal carcinomatosis based on a small single-center RCT [6]. However, the negative results from the PRODIGE 7 and PROPHYLOCHIP phase III trials question the generalizability of HIPEC. The PRODIGE 7 compared surgery with or without HIPEC (intraperitoneal oxaliplatin heated to 43 °C) in patients with stage IV colorectal cancer with peritoneal carcinomatosis. The recurrence-free and overall survival were similar in both groups. However, the rate of complications in the HIPEC group was 1.8-fold higher than in the non-HIPEC group (24.1% vs 13.6%) [4]. The PROPHYLOCHIP randomized phase III trial compared surveillance to second-look surgery plus HIPEC (intraperitoneal oxaliplatin) in patients at high risk of developing colorectal peritoneal metastases [3]. Three-year disease-free survival, peritoneal relapse, and 3-year overall survival were not significantly different between groups. These trials have led to controversy regarding whether there are subgroups of patients who may still benefit from HIPEC and the optimal intraperitoneal chemotherapy choice, as other agents may be more effective than oxaliplatin.

The benefit of HIPEC combined with cytoreductive surgery in ovarian cancer awaits confirmation, and several HIPEC RCTs in front-line and recurrent ovarian cancer are ongoing. In the interim, our modeling of the currently available data indicates that while interval cytoreductive surgery with HIPEC is a more costly strategy, it appears to be highly cost-effective, with an ICER of $2436/QALY compared to ICS alone. This demonstrates that the addition of HIPEC favorably

impacts clinical outcome and is not cost-prohibitive. Neoadjuvant chemotherapy plus HIPEC constitutes cost-effective management of stage III EOC and may be considered a reasonable standard of care choice for patients with stage III epithelial ovarian cancer.

Conflicts of interest

The SL, LH, AH, and AS declare no relevant conflict of interest with regard to this study.

Authors contribution

Stephanie Lim made a substantial contribution to the conception and hypothesis generation, and was responsible for data acquisition, table and figure preparation, and manuscript writing. Dr. Laura Havrilesky contributed to the conception, hypothesis generation, study design, data analysis, and critical evaluation of tables, figures, and manuscript writing. Dr. Ashraf Habib contributed to study design, data acquisition, and critical evaluation of the manuscript. Dr. Angeles Alvarez Secord was responsible for the conception of the project, study design, and critical evaluation of the manuscript.

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