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Current status of hyperthermic intraperitoneal chemotherapy (HIPEC) for ovarian cancer in the United States

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HIGHLIGHTS

- HIPEC for ovarian cancer increased in US after phase III trial publication, though absolute number of cases remains modest.
- HIPEC was associated with increased cost, hospital length of stay, ICU admission, and hospital-acquired complication rates.
- Additional studies are warranted to further evaluate long-term HIPEC outcomes, including morbidity and survival.

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ABSTRACT

Objectives. 1.) To compare frequency of HIPEC use in ovarian cancer treatment before and after publication of the phase III study by van Driel et al. in January 2018. 2.) To compare associated rates of hospital-based outcomes, including length of stay, intensive care unit (ICU) admission, complications, and costs in ovarian cancer surgery with or without HIPEC.

Methods. We queried Vizient's administrative claims database of 550 US hospitals for ovarian cancer surgeries from January 2016–January 2020 using ICD-10 diagnosis and procedure codes. Sodium thiosulfate administration was used to identify HIPEC cases according to the published protocol. Student *t*-tests and relative risk (RR) were used to compare continuous variables and contingency tables, respectively.

Results. 152 ovarian cancer patients had HIPEC at 39 hospitals, and 20,014 ovarian cancer patients had surgery without HIPEC at 256 hospitals. Following the trial publication, 97% of HIPEC cases occurred. During the index admission, HIPEC patients had longer median length of stay (8.4 vs. 5.7 days, $p < 0.001$) and higher percentage of ICU admissions (63.1% vs. 11.0%, $p < 0.001$) and complication rates (RR = 1.87, $p = 0.002$). Index admission direct costs ($21,825 vs. $12,038, $p < 0.001$) and direct cost index (observed/expected costs) (1.87 vs. 1.11, $p < 0.001$) were also greater in the HIPEC patients. No inpatient deaths or 30-day readmissions were identified after HIPEC.

Conclusions. Use of HIPEC for ovarian cancer increased in the US after publication of a phase III clinical trial in a high-impact journal, though the absolute number of cases remains modest. Incorporation of HIPEC was associated with increased cost, hospital length of stay, ICU admission, and hospital-acquired complication rates. Further studies are needed in order to evaluate long-term outcomes, including morbidity and survival.

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1. Introduction

Few studies have examined change in clinical practice after seminal article publications to examine the impact of these publications on real-world clinical practice [1–4]. Phase III clinical trials are considered by many to be the "gold standard" for the evaluation of new treatments, and it is anticipated that their findings are widely, and eagerly adopted by practitioners. It is hoped that results and conclusions of well-conducted, prospective randomized studies are sufficiently free of bias and confounding so as to be regarded as one of the most important contributors to improved patient outcomes and advancement of the standard of care. How the magnitude and pace of practice change occur after publication of phase III clinical trials has been reported infrequently. The pattern and rate of practice changes in response to publication of a significant research study is of interest to practitioners, sponsors, patients, and the medical community at large. Observations

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regarding these changes have implications for outcomes, costs, workforce planning, capital expenditures, and healthcare disparities, among others.

In the past 25 years, four influential phase III trials have examined the role of intraperitoneal (IP) chemotherapy in epithelial ovarian cancer [5–8]. The first three trials showed 20–40% reduction in death compared to intravenous (IV) chemotherapy alone in advanced stage ovarian cancer; the results of GOG 172 led to a 2006 National Cancer Institute alert supporting IP chemotherapy in this patient population. Despite this, IP chemotherapy was not widely adopted, likely due at least in part to concern for toxicity, catheter complications, and inconvenience [9]. Subsequently, GOG 252 did not show an improvement with IP compared to IV chemotherapy, though this study included maintenance therapy and was conducted in the modern era of newer therapeutics and improved overall survival (OS) (median OS in GOG 252 ranged from 73 months to over 105 months). Although these trials have been criticized for the chemotherapy regimens used, the peritoneal distribution and chemosensitivity of ovarian cancer make intraperitoneal delivery appealing. Additionally, HIPEC has the advantage of being given one time intraoperatively without the inconvenience of catheter complications and multiple outpatient administrations. Intraperitoneal chemotherapy improves drug delivery to the peritoneal surface, while hyperthermia activates heat-shock proteins, induces apoptosis, inhibits angiogenesis, promotes protein denaturation, and, when given with cisplatin, increases DNA crosslinking and adduct formation and deepens penetration into peritoneal tumor implants [10–15]. Prior to 2018, HIPEC was shown to have excellent efficacy in non-gynecologic peritoneal carcinomatosis [16–18], however the literature in ovarian cancer was limited mostly to small case series and phase II trials demonstrating feasibility without significant data for impact on efficacy or survival [19–23].

"Hyperthermic Intraperitoneal Chemotherapy in Ovarian Cancer" was published in the New England Journal of Medicine (NEJM) in January 2018. In this European multicenter, randomized controlled phase III trial, the addition of HIPEC to interval cytoreductive surgery after three cycles of paclitaxel and carboplatin led to a statistically significant 11.8-month improvement in overall survival (HR for death, 0.67; 95% CI 0.48–0.94; $P = 0.02$) [24]. The authors reported similar grade 3 or 4 adverse events, 25% in the control arm vs. 27% in the HIPEC group, $p = 0.76$. The goal of our study was to characterize trends in use of HIPEC for ovarian cancer patients in the United States following the NEJM publication. We hypothesized that the publication was associated with increased HIPEC use and sought to describe factors that may be associated with the adoption of this therapeutic modality. We also compare associated rates of hospital-based outcomes, including length of stay, ICU admission, complications, and costs, in ovarian cancer patients who underwent surgery with or without HIPEC.

2. Methods

We queried the Vizient (formerly University HealthSystem Consortium), a member-driven, health care performance improvement company that captures detailed billing data and administrative claims from approximately 550 hospitals throughout the United States, clinical database/resource manager (CDB/RM™). The CDB/RM™ includes health care data from 50% of the nation's acute care providers, 95% of academic medical centers, and over 300 community hospitals from 45 states and the District of Columbia. All data are de-identified and comply with Health Insurance Portability and Accountability Act (HIPAA).

2.1. Setting and participants

Using ICD-10 codes for diagnosis of ovarian cancer and procedure codes for a variety of procedures used for cytoreductive surgery, we captured monthly discharge data for all ovarian cancer patients who had surgery from January 1, 2016-January 31, 2020. Currently available ICD-10 procedure codes do not permit discrete identification of, or selection for, patients having primary, interval or salvage cytoreductive surgery, nor was there a unique identifying code assigned to the HIPEC procedure until late 2019. Administration of sodium thiosulfate is an integral component of the HIPEC regimen published by van Driel et al. Therefore, in our study, receipt of sodium thiosulfate during a hospitalization for an ovarian cancer operation was used as a surrogate marker for HIPEC according to the published protocol. Ovarian cancer patients who had surgery and were not coded as receiving sodium thiosulfate comprised the non-HIPEC group. We then calculated monthly fraction of admissions that included both ovarian cancer surgery and sodium thiosulfate administration. The total number of ovarian cancer surgeries served as the denominator. We examined trends in monthly rates of HIPEC, before and after the van Driel et al. publication in January 2018. Data regarding age, race, and insurance type were abstracted from Vizient's CDB/RM™.

2.2. Hospital-based outcomes and descriptive statistics

We evaluated median hospital-reported mean length of stay, percentage of ICU admissions, 30-day readmissions, inpatient deaths, individual complications, and direct costs. Direct costs are the costs to produce care. We also evaluated length of stay index and direct cost index, which divide the observed by expected length of stay and direct costs, respectively. Vizient employs a proprietary multivariable risk-adjustment methodology, specific to each Medicare Severity-Diagnosis Related Group (MS-DRG). Case mix index (CMI) is the average relative DRG weight of a hospital's inpatient discharges, calculated by summing the MS-DRG weight for each discharge and dividing the total by the number of discharges. CMI was used as an indicator of clinical complexity. Complications were examined individually and collectively. Monthly rates of HIPEC were plotted over time. Student *t*-test was used to compare continuous variables and relative risk (RR) was calculated to compare contingency tables. Statistical analyses were performed in SPSS version 24.

3. Results

3.1. Use of HIPEC for ovarian cancer increased immediately after the "Hyperthermic Intraperitoneal Chemotherapy in Ovarian Cancer" publication, though number of cases remains modest

From January 2016 to January 2020, 152 ovarian cancer patients had surgery with HIPEC at 39 hospitals, and 20,014 ovarian cancer patients had surgery without HIPEC at 256 hospitals in the United States. Sixty four percent of HIPEC cases were performed at ten hospitals (five academic and five non-academic), with the remainder of hospitals performing fewer than five HIPEC cases over the four-year study period. During the 24 months prior to the NEJM publication, a total of five ovarian cancer patients had HIPEC when using sodium thiosulfate as a selection factor. After the January 2018 publication, monthly rates of sodium thiosulfate use in ovarian cancer surgery steadily increased (Fig. 1). After the publication, the percentage of ovarian cancer surgeries performed with HIPEC rose by 0.08% per month to a maximum of 3% in November 2019 ($R^2 = 0.48$; standard deviation = 0.8% per month), with 97% of all HIPEC cases ($N = 147$) occurring after the publication. Relative risk of an ovarian cancer patient having HIPEC with their surgery was 26.9 (95% CI 11.0 to 65.6, $p < 0.0001$) in the two years following the publication compared to the two years prior to the publication.

3.2. Insurance status and race did not correlate with receipt of HIPEC

Table 1 shows patient demographics. Patients aged ≥65 were not significantly less likely to receive HIPEC compared to women <65 (HR = 1.12, 95% CI 0.8, 1.5; $p = 0.491$). However, the subset of women age ≥ 75 (RR = 0.40, 95% CI 0.19, 0.83, $p = 0.013$) were significantly

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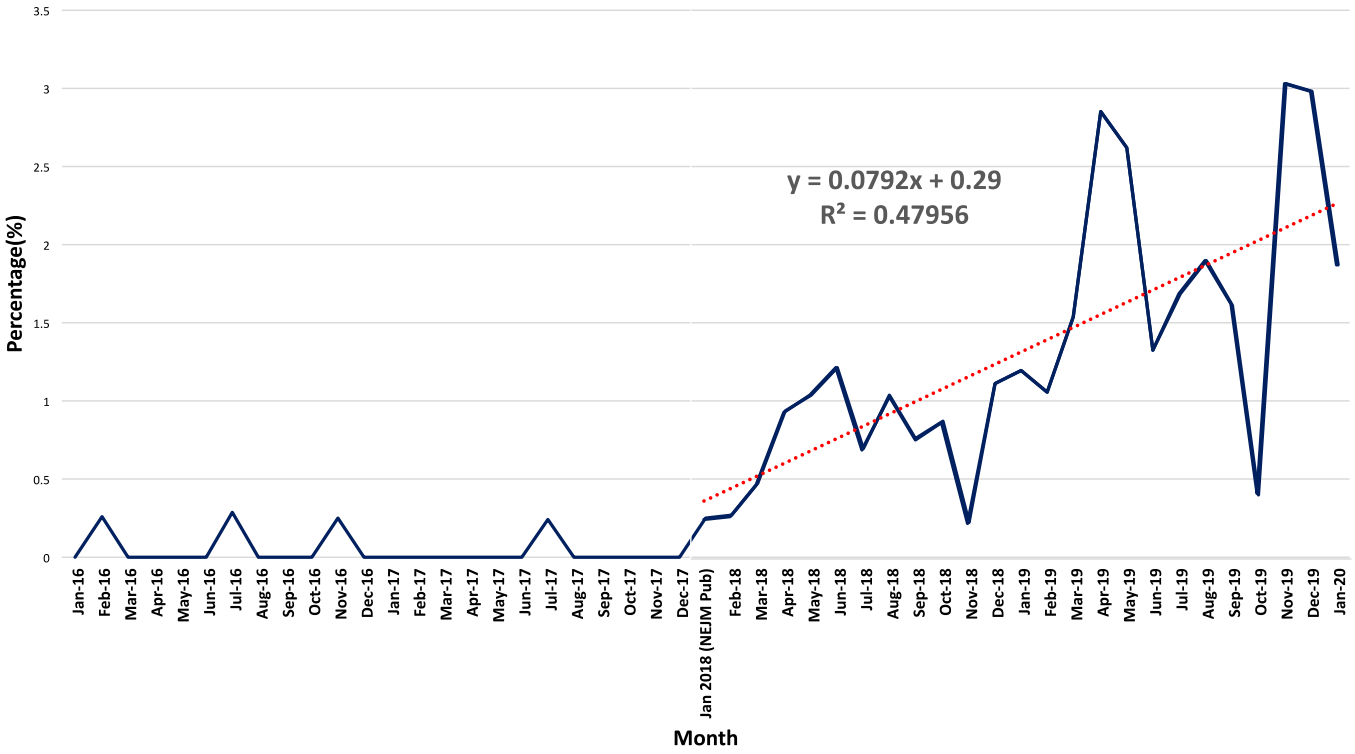

Fig. 1. Monthly percentage of ovarian cancer surgeries performed with heated intraperitoneal chemotherapy (HIPEC) from January 2016–January 2020. Rates of HIPEC use in ovarian cancer surgery increased after January 2018, the month that van Driel et al.'s "Hyperthermic Intraperitoneal Chemotherapy in Ovarian Cancer" was published in the New England Journal publication (NEJM Pub). Trendline added to post-publication period, from January 2018–January 2020, showing increase in rate of HIPEC of 0.08% per month (standard deviation = 0.8%).

less likely to receive HIPEC during their ovarian cancer surgery than younger women. Van Driel et al.'s population had a median age of 63 (interquartile range 56–66) in the surgery alone group and 61 (interquartile range 55–66) in the surgery plus HIPEC group. In comparison, median age was 60 (interquartile range 50–69) in the surgery alone group and 63 (interquartile range 52–68) in the HIPEC group in our study. Non-white women were not significantly less likely to receive HIPEC than White women (RR = 0.847, 95% CI 0.56, 1.28, $p = 0.433$). The number of Black women receiving HIPEC was too small to report given Vizient's privacy policy.

3.3. Incorporation of HIPEC was associated with increased cost, ICU admissions, hospital length of stay, and perioperative complications

Table 2 compares hospital-based outcomes in ovarian cancer patients who had surgery with and without HIPEC. During the index admission, HIPEC patients had longer median length of stay (8.4 vs. 5.7 days, $p < 0.001$) and higher percentage of ICU admissions (63.1% vs. 11.0%, $p < 0.001$) (Table 2). HIPEC patients, however, did not have significantly longer ICU length of stay (2.8 vs. 3.6 days, $p = 0.168$). Direct costs for the index admission ($22,257 vs. $12,032, $p < 0.001$) and direct cost index (observed/expected costs) (1.9 vs. 1.1, $p < 0.001$) were also greater in the HIPEC patients.

Complication rates were higher in ovarian cancer patients who received HIPEC at the time of surgery (RR = 1.9, 95% CI 1.3, 2.9; $p = 0.002$) (Table 3). Specifically, the risk of infection was over twice as high in HIPEC patients compared to patients who did not receive HIPEC (RR = 2.1, 95% CI 1.2, 3.6; $p = 0.014$). No inpatient deaths or 30-day readmissions were identified after HIPEC in this cohort, and 102 (0.5%) deaths and 600 (3%) 30-day readmissions were reported in the non-HIPEC group.

4. Discussion

We have demonstrated a real world change in practice patterns after the publication of a randomized controlled phase III trial that showed improvement in overall survival in newly diagnosed ovarian cancer patients with the incorporation of HIPEC at the time of interval surgical cytoreduction. After the publication, monthly rates of sodium thiosulfate use at the time of ovarian cancer surgery increased steadily in the US, which we hypothesize correlates with increased incorporation of HIPEC. We did not find that practice changes were associated with insurance status. Unfortunately, given small numbers of Black women in the HIPEC group, we are not able to report rates of HIPEC use by

Table 1
Demographics.

$N = 20,166$	HIPEC (%) ($N = 152$)	No HIPEC (%) ($N = 20,014$)
Age group (years)		
≤50	26 (17.1)	5089 (25.4)
51–64	66 (43.4)	7566 (37.8)
65–74	53 (34.9)	5055 (25.3)
75–84	7 (4.6)	2026 (10.1)
≥85	0 (0.0)	278 (1.4)
Race		
White	123 (80.9)	15,511 (77.5)
Non-White	27 (17.8)	4025 (20.1)
Unavailable	2 (1.4)	478 (2.4)
Insurance		
Public	77 (50.7)	9813 (49.0)
Private	75 (49.3)	9562 (47.6)
Other	0 (0.0)	675 (3.4)

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Table 2
Comparison of hospital-based outcomes in ovarian cancer patients who had surgery with and without HIPEC.

Hospital-based outcomes[a]	HIPEC ($N = 152$)	No HIPEC ($N = 20{,}014$)	Mean difference (95% CI)	*P* Value
Median length of stay (days)	8.4	5.7	2.8 (2.6, 3)	**<0.001**
Length of stay index (Observed/Expected length of stay)	1.4	1.1	0.3 (0.3, 0.4)	**<0.001**
Percentage of ICU admissions	63.1%	11.0%	52.1% (50.5%, 53.7%)	**<0.001**
Length of ICU stay (days)	2.8	3.6	−0.7 (−1, 0.3)	0.168
Case Mix Index	2.6	2.2	0.4 (0.4, 0.4)	**<0.001**
Total direct costs	$21,824.53	$12,037.50	$9787.02 ($9171.01, $10,430.04)	**<0.001**
Direct cost index (Observed/Expected direct costs)	1.9	1.1	0.8 (0.7, 0.8)	**<0.001**

Bold *P* values are significant (<0.05)
Abbreviations: CI, confidence interval; HIPEC, heated intraperitoneal chemotherapy; ICU, Intensive care unit.
[a] Medians are calculated of hospital-reported means.

individual race due to Vizient's privacy policy. When grouping non-white racial groups together, there was not a difference in rates of HIPEC between non-White and White ovarian cancer patients. Prior studies have shown that Black women are less likely to receive surgery and chemotherapy and more often treated with chemotherapy alone, with one study showing that Black ovarian cancer patients had 40% higher odds of not having an operative procedure compared to White patients [25–28]. Racial disparities in adoption of novel treatment strategies are improtant to track and will need to be reported once numbers reach a threshold that protect patient privacy.

We did not find that women greater than or equal to 65 years of age were significnatly less likely to receive HIPEC, however the subset of women 75 and older were less likely to receive HIPEC at time of ovarian cancer surgery. Studies have shown that older ovarian cancer patients are less likely to receive surgery and combination chemotherapy, even after controlling for comorbidities [29,30]. To help put these findings in perspective, we note that the power of our subset analyses was limited by the relatively small number of patients receiving HIPEC in our study; therefore, it is possible that there are some additional factors, including comorbidities and disease stage, associated with use of HIPEC, that were not identified in this investigation.

In our study, patients treated with HIPEC stayed in the hospital 2.8 (95% CI 2.6 to 3) days longer than those who were not treated with HIPEC; however, the median lengths of stay were shorter in our study than in van Driel's trial (5.7 versus 8 days for surgery alone and 8.4 versus 10 days for HIPEC). In the van Driel trial, patients who received HIPEC were admitted to the ICU for at least one night per study protocol. This protocol criteria may account for the higher proportion of ICU admissions found in comparison to the Vizient HIPEC cohort, especially since the total number of days in the ICU did not differ significantly between the two groups in our study. Of note, only 63% of patients who received HIPEC in our population were admitted to the ICU, suggesting that over 1/3 of surgeons who adopted sodium thiosulfate use in HIPEC did not incorporate the entire study protocol into clinical practice.

Table 3
Number of ovarian cancer patients with perioperative complications in the HIPEC vs. No HIPEC groups.

Complication	HIPEC (%) ($N = 152$)	No HIPEC (%) ($N = 20{,}014$)	Relative Risk in HIPEC vs. No HIPEC (95% CI)
Stroke/MI/DVT/PE	[a]	268 (1.3%)	
Infection	11 (7.2%)	707 (3.5%)	
Respiratory failure	[a]	92 (0.5%)	
Adverse events due to anesthesia	[a]	114 (0.6%)	
Post-op shock	[a]	156 (0.8%)	
Wound complications	[a]	19 (0.1%)	
Hemorrhage/hematoma	[a]	45 (0.2%)	
AKI requiring dialysis	[a]	14 (0.1%)	
Other (including stage III/IV pressure ulcer, pneumothorax, unrecognized abdominopelvic puncture, fall/trauma, retained foreign object, poor glycemic control)	[a]	63 (0.3%)	
Total	21 (13.8%)	1478 (7.4%)	1.87 (1.25, 2.79) $p = 0.002$

Abbreviations: AKI, acute kidney injury; CI, confidence interval; DVT, deep vein thrombosis; HIPEC, heated intraperitoneal chemotherapy; MI, myocardial infaction; PE, pulmonary embolus.
[a] Due to HIPAA, we are not able to report any number or patients less than 10 to protect their identities. The total number of complications, excluding infection, in the non-HIPEC group was 10, distributed over 4 categories (stroke/MI/DVT/PE, respiratory failure, adverse events to anesthesia, and post-operative shock).

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With regard to cost, van Driel et al. cited an unspecified additional standard cost due to two additional hours of surgical time, disposable products required for HIPEC adminstration, HIPEC machine use, and the additional 1-day stay in the ICU. We calculated that HIPEC cases incurred approximately $10,000 additional direct costs. A cost-effectiveness ratio of $50,000 per quality-adjusted life-year (QALY) has been used historically to justify cost of an intervention; however, more recent opinion supports increasing the value of one QALY to $150,000 [31]. Regardless, the additional $10,000 cost would seem well justified if the the additon of HIPEC is confirmed to improve overall survival by one year. It is important to keep in mind that the cost of care may differ subtantially between healthcare delivery systems rendering it challenging to make cross system and international comparisons. Therefore, if cost effectiveness is to be used as an input to decision making regarding HIPEC use in ovarian cancer patients in the US, either a study performed in the US, or modeling done with domestic inputs may provide a meaningful perspective.

Although van Driel et al. did not find a significant difference in grade 3 or 4 adverse events (25 vs. 27%, $p = 0.76$), we found more frequent perioperative complications in the HIPEC group; although we did examine somewhat different complications. When we looked at the complications available in the CDB/RM™ 2018 risk adjustment model, including thromboembolism, infection, repsiratory failure, adverse anesthesia evnents, and hemorrhage (Table 3), we found that HIPEC cases had 1.9 times the risk of major complications compared to non-HIPEC ovarian cancer surgeries. In van Driel et al.'s study, there were no deaths in the HIPEC group ($N = 0/118$) and one in the non-HIPEC group ($N = 1/122$,0.8%); we similarly did not find any deaths in the HIPEC group ($N = 0/155$) and total inpatient deaths were 102/20,014 (0.5%) in the non-HIPEC group. Our 30-day readmission rates (0% in HIPEC and 3% in non-HIPEC group) were lower than expected; for example, one study found 19.5% of advanced ovarian cancer Medicare patients were readmitted within 30 days [32]. This may be due to readmissions to other than the index hospital not being captured on our dataset, or reflective of an overall healthier, younger patient population in our study cohort. Although they are different populations, the two arms in our study are comprable to each other, supporting the internal consistency of our findings.

Adverse events in our HIPEC group (13.8% adverse events, 0% mortality) are similar to those reported in an earlier, retrospective study of 246 patients with recurrent or persistent ovarian cancer treated with HIPEC (11.5% adverse events, 0.4% mortality) [20]. The authors of that study acknowledge their rate is lower than that of other HIPEC studies, which have reported 30–40% rates of grade 3 and 4 morbidity [17,18,23,33–37]. The authors suggest that this may be due to less frequent peritoneal carcinomatosis and less extensive involvement of abdominal organs in epithelial ovarian cancer compared with other, non-gynecologic malignancies, and also to the extensive experience of the surgeons and centers involved in their report [20]. Overall, in contrast with the van Driel study, the literature suggests somewhat higher morbidity in HIPEC patients, when compared to a surgery alone group. Even considering that van Driel has reported results of the sole prospective, phase III HIPEC study, it is worth being cognizant of the findings in other series when considereing HIPEC. It may be that HIPEC treatments, given outside the highly controlled context of a clinical trial, have a somewhat different profile; this merits further study.

We have previously shown rapid and widespread practice changes after presentation of the LACC trial, a provocative, international, randomized phase III trial, which showed inferior outcomes with minimally invasive surgery for early stage cervical cancer treatment [4]. In our current study, we again demonstrate real world practice changes; however, the adoption of HIPEC in the initial two years after van Driel et al.'s publication was compartively desultory, slower and more modest. Both the LACC trial and van Driel's HIPEC study were the first phase III trials to address their respective questions. A distinction between the two is that the LACC trial showed compromised outcomes with a modification to the previous standard intervention; this, in itself, may have led to a relatively rapid reversion to the prior standard of open radical hysterectomy. In the case of radical hysterectomy, abandoning the minimally invasive technique brought senior surgeons back to a technique with which they were comfortable. This may be different than adopting a technique for which there is no prior experience. In contrast, the psychology of incorporating a new change may be associated with slower modification of surgical practice. If so, this would be contrary to the limited literature regarding the psychology of medical practice changes; two studies have shown that it is more difficult to "unlearn" or "de-implement" old, outmoded knowledge than it is to acquire new medical practices [38,39]. These studies, however, admit that they are unable to account for physician bias, including perceived strength and quality of a randomzied control trial in their model.

Promising improvements in survival in the upfront treatment of ovarian cancer have been shown with intraperitoneal therapy (without HIPEC) and dose dense therapy [5,40]. However, these improvements were not replicated in a subsequent trial [6,41,42]. This history may have tempered enthusiasm for wider and more rapid adoption of HIPEC after publication of the van Driel study; gynecologic oncologists may be waiting for confirmatory studies, specifically in the US, prior to making substantial changes to current practice. Also, although this study was multiinstitutional, it was conducted only in Europe. This may inhibit acceptance among US oncologists. Even among the coauthors of our study, there are diverse opinions as to whether or not HIPEC will be broadly applicable. Other barriers to faster adoption may be relatively small numbers of medical personnel and hospital staff with HIPEC experience, as well as a lack of equipment, supplies, and other resources required for HIPEC; unfortunately, we were not able to assess some of these technical or instituional barriers through the database. Additionally, as publications lag trial design by years, newer interval discoveries may cloud the applicability of findings; for example, patients were not stratified by genetic or molecular characteristics, nor were they prescribed maintenance therapies, which have been widely adopted espcially for patinets *BRCA*/homologous recombination deficiency. Further study into the psychology, biases, and other factors that affect a surgeon's decision to adapt a new practice or stop an old practice would be of great interest.

Eligible patients for van Driel's trial included those in whom neoadjuvant chemotherapy was recommended because their disease was thought to be too extensive for primary cytoreductive surgery or because thay had a suboptimal primary cytoreductive surgery. Unfortunately, we were not able to capture from the CDB/RM™ whether patients had received neoadjuvant chemotherpay or had a prior suboptimal cytoreductive surgery. In this retrospective, observational study, there is likely a selection bias, as HIPEC patients may be a healthier cohort with a more favorable response to neoadjuvant chemotherapy. Due to limitations in the current coding system (ICD-10), we were also not able to capture patient comorbidites, performance status, stage, or tumor factors. The ICD-10 procedure code for HIPEC, 3E0M30Y, only became available at the end of 2019, so we used sodium thiosulfate at time of surgery, a key component of van Driel's protocol, to capture HIPEC cases. We are likely underestimating the number of cases, especially those in the period prior to the publication, with this method, as evidenced by higher HIPEC rates in a recent Society of Gynecologic Oncology survey. The ICD-10 code will hopefully provide insight into numbers of patients who receive HIPEC on a modified protocol. Also, hospitals who do not report pharmacy data were included in the total number of non-HIPEC cases, and this may also underestimate the rates of HIPEC. Regardless, this study demonstrates an association with a rise in HIPEC, or at the very least adoption of van Driel's protocol, for ovarian cancer treatment in the US with the publication.

Strengths of our study include a relatively large number of HIPEC cases, evaluation of hospital-based outcomes, and comparisons of complications between ovarian cancer patients who received HIPEC versus those who did not. Additionally, it provides contemporaneous, real-world data that reflect practice changes after publication of an important clinical trial for the management of ovarian cancer. We believe

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that it is extremely important to study how practice changes, including the psychology, biases, technical and/or institutional barriers and socio-economic factors that may motivate a surgeon's practice changes, in response to clinical trials in order to try to appreciate the magnitude of their real-world impact.

There are currently approximately 50 clinical trials listed on clinicaltrials.gov examining HIPEC in the treatment of upfront and recurrent ovarian cancer. These trials are exploring HIPEC at primary, interval, and secondary cytoreduction; different agents, such as cisplatin, carboplatin, paclitaxel, cisplatin with doxorubicin, and cisplatin with docetaxel during HIPEC; combination with other IP therapies, such as Nivolumab, after HIPEC; second HIPEC; patient and tumor genomics and molecular characteristics; and maintenance therapy after HIPEC. We eagerly await the results of these trials, as well as the impact they will have on practice patterns, to define the magnitude of associated morbidity and costs and whether they are justified by improved oncologic outcomes.

Author contributions

Drs. Plaxe and Charo designed the study and analyzed the data. Dr. Charo wrote the manuscript, and Drs. Plaxe, McHale, Saenz, Binder, Eskander, Hohmann, and Jou substantively revised it. All authors read and approved the final manuscript.

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