Review Article

Impact of surgical volume of centers on post-operative outcomes from cytoreductive surgery and hyperthermic intra-peritoneal chemoperfusion

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Abstract: Complex surgical operations performed at centers of high volume have improved outcomes due to improved surgical proficiency, and betters systems of care including avoidance of errors. Cytoreductive surgery (CRS) and hyperthermic intra-peritoneal chemoperfusion (HIPEC), which has been shown to be an oncologically effective strategy for peritoneal carcinomatosis (PC), is one such procedure with significant morbidity and mortality. The learning curve to reach technical proficiency in CRS + HIPEC is about 140-220 cases for a center. Focus on improving surgical proficiency through training, improving systems of care through partnerships and reporting mechanisms for quality could reduce the time to proficiency.

Keywords: Learning curve; cytoreductive surgical procedures; induced hyperthermia; peritoneal neoplasms; high-volume hospitals

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Introduction

Cytoreductive surgery (CRS) and hyperthermic intra-peritoneal chemoperfusion (HIPEC) has evolved into an oncologically effective technique for patients with peritoneal metastases from a variety of malignancies. Akin to other complex surgical oncology operations, performance of such a procedure requires considerable expertise in the peri-operative management of the patient for both the surgeon and the peri-operative team. In this article, we explore the premise of higher surgical volume improving peri-operative outcomes for patients undergoing CRS + HIPEC as well as its ramifications.

Problem statement

CRS and HIPEC is currently applied to patients with peritoneal dissemination from appendiceal cancer, mesothelioma, colorectal cancer, gastric cancer and ovarian cancer commonly and to desmoplastic small round cell tumors and sarcomas infrequently. Given the diverse histology groups included in the target population, it is difficult to estimate the true burden of patients who might benefit from this therapy. However, conservative estimates based on published data suggest that the annual burden of patients in the United States eligible for consideration of CRS + HIPEC is 29,260-40,890 (*Table S1*).

Estimating the true incidence of patients undergoing CRS and HIPEC in the United States is difficult. There is no current procedural terminology (CPT) code that encompasses the cytoreduction, the instillation of intra-peritoneal chemotherapy and the generation of hyperthermia. Additionally, varied ICD-10 procedure and diagnosis codes utilized in the practice make it difficult to ascertain such information from administrative/claims databases. Furthermore, registries such as the Surveillance End Results and Epidemiology Registry (SEER) or

National Cancer Data Base (NCDB) do not capture this information separately.

The National Surgical Quality Improvement Project collects data on 653 hospitals of the 5,686 (11%) hospitals in the United States (1,2). CPT code combinations have been used to ascertain the number of patients that underwent intra-peritoneal chemotherapy concurrent with cytoreduction in these hospitals and includes 795 patients from 2005-2011 (6 years; estimated 132 patients/year) and 694 patients from a separate report in the same time period (3,4). Assuming uniform population distribution in the hospitals is fallacious but would yield an estimate of 1,521 patients per year.

Upon examining the volumes of centers reporting outcomes on more than 500 patients, it is apparent that the number of HIPEC procedures performed over a long time period yields a simple rate of 50 cases/year assuming no growth and 55 per year assuming annual growth rate of 3% (*Table 1*). While such estimates are likely inaccurate, it is important to understand the scale of the problem before understanding the impact of surgical volume on outcomes.

Center volume and outcomes in oncological surgery

It has been suggested that hospital volume is a proxy measure of superior outcomes in numerous oncological operations (17,18). The association between increasing hospital volume and better peri-operative outcomes appears to be more clearly seen with increasing complexity of the operations. Large differences in mortality and morbidity have been seen with oncological operations such as pancreatectomies, esophagectomies, colectomies, pancreatoduodenectomies and gastrectomies which are commonly performed during CRS (19). The volume of a center may have a causal effect on the improved outcomes, although likely the volume is an indicator of other processes that improve outcomes. While the volume-outcome relationship has not been studied in centers performing CRS + HIPEC, factors associated with alteration of outcome in higher volume centers are shown in *Table 2*. The majority of the studies examining volume-outcome data use administrative/claims data to support their hypothesis (20). Specific registry data such as the VA-NSQIP, which includes detailed peri-operative data collection in a standardized fashion, has, however, not shown the same strength of association between volume of a center and outcome (21,22).

While it is assumed that higher hospital volume leads to higher per surgeon cases, this inference is not always true. Some studies have suggested that regardless of surgeon volume, increased hospital volume can reduce complications (23). Yet the most appealing and clinically intuitive argument asserts that gaining proficiency in both operating and systems of care has the most significant impact on the outcomes for patients. A systematic review in 2007 examined over 127 studies for hospital volume and 58 studies which included surgeon volume and concluded that high volume surgeons and specialists had significantly reduced complications, although the hospital volume did not play as important a role in the outcomes (19). Such a systematic review has not been repeated in the past 5 years.

Learning curve for CRS + HIPEC

Numerous studies over the years have examined the effect of the learning curve. It is clear that technical proficiency and improvement of systems of care occur over time and with repetition. In addition, patient selection and prediction of morbidity also improves over time. While the former is represented in being more selective and conservative in operating on patients, gain of technical proficiency and prediction of morbidity is represented by occasionally operating on more challenging, complex cases. For purposes of examining this, we have divided the studies into two groups—those that include cohorts separated by temporality in the performance of the procedures and those that have used risk adjusted probability models to detect the "inflection point" of the curve.

Consecutive cohort studies

Scientific groups from UK, Netherlands and Australia examined their cumulative experience to discern the effect of learning on performance of CRS. Moran divided their cohort into three consecutive groups of 33 patients each (one group had 34) and found that over time, there was improved patient selection (fewer patients underwent surgery 61% reduced to 37%) and reduced morbidity and mortality (18% mortality reduced to 3%, 27% morbidity reduced to 0%) (13). The Dutch group similarly examined 323 procedures performed over 10 years. The cohorts were divided by time periods and separated by histology. The simplified PCI score reduced over time for both peritoneal carcinomatosis (PC) and appendiceal histologies, while the R1 cytoreduction rate increased over time (47% to 74% PC, 15% to 49% appendiceal) (24). The Australian

Table 1 Selected peritoneal surface malignancy centers and their patient volume

Peritoneal surface malignancy center	Total number of cases	Years	No. of cases/year	Current No. of cases per year assuming a 3% annual growth rate
MD Anderson Cancer Center (5)	221	6 [2006-2012]	36.8	40
University of Pittsburgh Medical Center (6)	1,432	12 [2002-2014]	119.3	123
Wake Forest University School of Medicine (7)	1,000	22 [1991-2013]	45.5	48
Washington Cancer Institute (8)	183	3.5 [1994-1998]	52.3	86
Centre Hospitalier Lyon-Sud, France (9)	207	12 [1989-2001]	17.3	26
Kusatsu General Hospital, Japan (10)	250	4 [2007-2011]	62.5	70
National Cancer Institute, Milan, Italy (11)	414	15.5 [1995-2011]	26.7	30
Netherlands Cancer Institute, Amsterdam (12)	554	17 [1995-2012]	32.6	36
North Hampshire Hospital, Basingstoke, UK (13)	100	6.5 [1994-2000]	15.4	24
University Medical Center, Regensburg, Germany (14)	307	6.5 [2004-2010]	47.2	55
University of New South-Wales, Australia (15)	562	7.5 [2006-2013]	74.9	79
Uppsala University Hospital, Sweden (16)	103	3 [2003-2006]	34.3	45
Mean				55

Table 2 Association of center volume with improved surgical outcomes

Favoring association
Practice makes perfect: increased volumes can lead to more proficient surgeons
Better ability to rescue patients from complications
Better implementation of process measures known to improve outcomes (e.g., administration of antibiotics before an operation)
Better teams leads to better systems of care
Fewer errors
Better technology, ICUs, support staff
Fallacies in association
Confounding by unmeasured patient characteristics-only patients with better performance status will travel to high volume centers
Selective referral bias: better outcomes in a center attract more patients leading to higher volumes
Higher hospital volume does not accurately reflect higher surgeon volume, better process measure implementation, or better ability to rescue

group similarly examined their first 70 patients with the subsequent 70 patients and found that while they operated on patients with more disease (PCI ≥20 in 37.1% compared to 18.6% previously), the completeness of cytoreduction score remained the same. In addition, the severe morbidity rates decreased from 30% to 10% in this time period (25).

Adjusted models

Three adjusted models have examined the learning curve for CRS + HIPEC. Andreasson *et al.* used the partial least squares (PLS) method and the cumulative sum control chart (CUSUM) to examine the learning curve. In the cohort of 128 patients, stabilization of the curve was seen after 220 procedures, and comparing the first 73 patients to the subsequent 55 patients revealed better patient selection (65% low grade histology *vs.* 34% previously) with similar burden of disease reflected by PCI scores (26). The completeness of cytoreduction (48% *vs.* 80% R1) and the overall survival were significantly improved in the latter cohort. Kusamura *et al.* and Polanco *et al.* used their prospective cohorts from large institutions to create a risk adjusted sequential probability ratio test (11,27). This plot compared the composite outcome of suboptimal

Table 3 Learning curve in cytoreductive surgery and HIPEC assessed by consecutive and risk-adjusted cohorts

Author	No. of cases for operative IP	No. of cases for oncologic IP	Statistical technique	Initial/pre inflection-point cohort					Experienced/post inflection-point cohort				
				n	Mean PCI	CC 0/1 (%)	Severe morbidity (%)	Mortality (%)	n	Mean PCI	CC 0/1 (%)	Severe morbidity (%)	Mortality (%)
Consecutive cohorts													
Yan *et al.* (25)	–	–	Longitudinal cohort study	70	–	87	30.0	7.1	70	–	90	10	1.4
Moran *et al.* [a] (13)	–	–	Longitudinal cohort study	33	–	66.6	27	18	34	–	55.9	0	3
Smeenk *et al.* (24)	130	–	Longitudinal cohort study	194	9.5	–	59.8	6.7	129	7	–	34.1	3.9
Risk-adjusted cohorts													
Polanco *et al.* [b] (27)	180	90	RA-SPRT	200	14.2	83.5	25.5	–	170	12.2	86	35.2	–
Andreasson *et al.* [c] (26)	73 (220 procedures)	–	PLS & CUSUM	73	26	–	47	1.4	55	26	–	58	1.8
Kusamura *et al.* (11)	140	–	RA-SPRT	150	18.1	82	26	–	270	18.8	93.6	29.6	–

[a], initial and experienced cohorts are first 33 and last 34 cases of a consecutive 100 case series; [b], reported simplified PCI score. Instances of mortality were not included in the learning curve analysis; [c], median PCI score reported. Morbidity not classified into severe. Cases consisted of pseudomyxoma peritonei and experienced cohort had less cases of higher grade disease. HIPEC, hyperthermic intraperitoneal chemoperfusion; IP, inflection point; PCI, peritoneal cancer index; CC, completion of cytoreduction scoring system; RA-SPRT, risk adjusted sequential probability ratio test; PLS, partial least square; CUSUM, cumulative sum control chart.

cytoreduction and grade 3-5 morbidity to a pre-specified odds ratio and error rate. Consecutive hypothesis testing occurred and risk was predicted by using logistic regression models which allowed for risk adjusted cohorts. This method is superior in discerning the surgical aggressiveness that occurs with technical proficiency with the superior selection and improvement of systems of care. Both studies found an inflection point of 140 and 180 patients respectively before technical proficiency occurred (11). Oncological proficiency was calculated in the study by Polanco and was achieved at 90 patients (*Table 3*) (27).

Implications of learning curve for regionalization of care

Most studies that have examined an inflection point in technical expertise found that around 140-220 cases need to be performed before such expertise is reached. If a new center were to aim to achieve expertise within 5 years, this would require the center to perform 28-44 HIPEC procedures per year. Considering data for individual surgeons such as reports from UK or Australia, it appears that the learning curve can be achieved with 33-70 cases for an individual surgeon. Currently in the United States, such annual volumes are encountered only at a few major regional centers. The argument for regionalization of care is robust; it leads to more proficient teams, surgeons and better systems of care. However, regionalization of care comes with difficulties in travel especially for elderly patients and disenfranchises providers in non-referral hospitals. Further, it mitigates the ability to truly study a system of care and attempt to improve it. In addition, transition of population to urban referral facilities might overload them and thus compromise care. Conversely, performing infrequent procedures with an ill-equipped team and without studying outcomes is certainly a disservice to our patients.

Upon examining the initial learning curve of centers that embraced this procedure early, it is apparent that this procedure occurred with significant morbidity and mortality. We compared this, however, to reports from recently initiated centers in different parts of the world, specifically with expertise help from established centers (28). It is apparent from these early reports from the newly established centers in the United States, Italy, Germany,

Table 4 Morbidity and mortality rates of cytoreductive surgery and HIPEC in selected new centers and early reports of established centers

Authors	Center	Morbidity (%)	Mortality (%)
Selected new peritoneal surface malignancy centers (after 2005)			
Tabrizian *et al.* (29)	Mount Sinai Medical Center, NY, USA	52.4[a]	2.4
Kerscher *et al.* (30)	University Hospital of Wurzburg, Germany	30.2[b]	0
Konstantinidis *et al.* (31)	University of Arizona, USA	36.0[a]	0
Arias *et al.* (32)	Fundación Santa Fe de Bogotá, Colombia	37.5[c]	2.8
Garcia-Matus *et al.* (33)	HRAEO, Mexico	19.5[a]	3.8
Turrini *et al.* (34)	Institut Paoli-Calmettes, France	33.0[a]	0
Mizumoto *et al.* (10)	Kusatsu General Hospital, Japan	45.0[a]	3.5
Selected established peritoneal surface malignancy centers (before 2005)			
Gusani *et al.* (35)	University of Pittsburgh Medical Center, USA	56.5[a]	1.6
Kuijpers *et al.* (36)	Netherlands Cancer Institute, Amsterdam	64.0[b,d]	13.0[d]
Levine *et al.* (37)	Wake Forest University, USA	43.1[a]	4.3
Stephens *et al.* (8)	Washington Cancer Institute, USA	27.0[b]	1.5
Piso *et al.* (38)	University of Regensburg, Germany	34.0[a]	4.5
Glehen *et al.* (9)	Centre Hospitalo-Universitaire Lyon Sud, France	24.5[b]	3.2
Van Leeuwen *et al.* (16)	Uppsala University Hospital, Sweden	56.3[a]	0.9

[a], Overall morbidity rate; [b], grade III/IV morbidity rate; [c], major safety events rate; [d], rates from pre-2005 pioneer phase of study. HIPEC, hyperthermic intra-peritoneal chemoperfusion; HRAEO, Hospital Regional de Alta Especialidad de Oaxaca.

Table 5 Strategies to reduce the time to achieving the inflection point on the learning curve for performing CRS + HIPEC

Improve surgical proficiency
Establish training programs at high volume centers
Improve patient selection via dissemination of knowledge
Improve current levels of evidence of studies that guide patient care
Surgical workshops and mentorship
Consider a volume cut off for basic proficiency skills to be maintained every year
Improve systems of care
Create systems of care including checklists for peri-operative services (anesthesia, nursing, critical care, pathology, integrative medicine, cancer supportive services, palliative care)
Create continuum of learning for peri-operative services
Mentorship amongst peri-operative service between established centers and newly developing centers
Reporting of data
Continuous reporting of data via registry mechanisms to facilitate quality improvement

CRS, cytoreductive surgery; HIPEC, hyperthermic intra-peritoneal chemoperfusion.

Colombia and Mexico that the learning curve can clearly be shortened with training, expertise, and mentorship (*Table 4*) (29,30,32,33). Yet, it is distinctly possible that this could be a reflection of publication bias, where by only centers with positive outcomes report them in the literature. Uniform reporting mechanisms are essential to ensure that all centers, whether high or low volume, are measured for their risk adjusted performance against their peers to improve performance. Some of the suggested strategies in reducing time to proficiency are outlined in *Table 5*.

Conclusions

In summary, development of surgical, technical and oncological proficiency occurs with accruing experience that requires center volume. Efforts to improve delivery of care in the United States must focus on improving surgical proficiency, improving systems of care and create a reporting mechanism to study outcomes.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Supplementary

Table S1 Annual burden of patients in the United States eligible for consideration of CRS + HIPEC

Primary tumor	Estimated new cases per year	% of peritoneal metastases	Estimated new cases of peritoneal metastases per year
Colorectal carcinoma	132,700 (39)	8-17% (40,41)	10,620-22,550
Appendiceal carcinoma	1,500	40%	600
Gastric carcinoma	24,590 (39)	20%	4,920
Ovarian carcinoma	21,290 (39)	60% (42)	12,770
Peritoneal mesothelioma	350 (43)	100%	350

CRS, cytoreductive surgery; HIPEC, hyperthermic intra-peritoneal chemoperfusion.

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