Multidimensional Analysis of the Learning Curve for Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy in Peritoneal Surface Malignancies

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Objective: To evaluate the learning curve of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) in treating peritoneal surface malignancies (PSM).

Summary and Background: CRS and HIPEC to treat PSM is a complex procedure with a significant morbidity. A long-lasting training program is required to acquire expertise in this type of operation.

Methods: We performed CRS using peritonectomy procedures. HIPEC through the closed abdomen technique employed cisplatin and mitomycin-C or cisplatin and doxorubicin. Risk-adjusted sequential probability ratio test was used to assess the learning curve on a series of 420 cases of PSM on the basis of rates of incomplete cytoreduction and G3-5 morbidity (NCI-CTCAE v3). We determined control limits setting the type I/II error rates and unacceptable odds ratios (ORs) for the outcomes being studied. We performed the risk adjustment using logistic regression model.

Results: Rates of incomplete cytoreduction, G3-5 morbidity, and postoperative mortality rates were 10.2%, 28.5%, and 2.1%, respectively. The risk-adjusted sequential probability ratio test curve crossed the lower control limit at the 137th and 149th case, respectively, for incomplete cytoreduction and G3-5 morbidity. At those points, the actual ORs are lower than the prespecified ORs for outcomes being studied. Therefore, we estimated that approximately 140 cases are necessary to ensure surgical proficiency in CRS and HIPEC.

Conclusions: CRS and HIPEC to treat PSM has a steep learning curve requiring 140 procedures to acquire expertise.

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In the past, peritoneal surface malignancies (PSM) were considered a terminal disease, amenable only to palliation. However, recent reports describe curative treatment options for selected patients with PSM. Over the past 2 decades, a novel therapeutic approach to this clinical entity has emerged that combines cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC). Theoretically, CRS is performed to treat macroscopic disease, and HIPEC is used to treat microscopic residual disease (RD). The combined treatment has been suggested as the standard of care for pseudomyxoma peritonei (PMP) and peritoneal mesothelioma (PM).[1–4] Promising results have been reported in a subset of peritoneal carcinomatosis from colorectal cancers, gastric cancers, and advanced epithelial ovarian cancers.[5–8]

The achievement of proficiency in the performance of surgical procedures requires a proper, long-lasting, and well-structured training program not only of the surgical staff but also of the multidisciplinary team that cares for the perioperative aspects of the patient. The combined procedure is technically demanding and carries a significant morbidity, even in referral centers.[9,10] Few studies addressing the learning curve of CRS and HIPEC have been conducted thus far.[11–14]

Sequential probability ratio test (SPRT) is a method originally conceived for quality control of military supplies during World War II. The SPRT represents one of the statistical process control tests that has been largely employed in medicine to monitor the safety of medical interventions.[15] It offers an advantage over other statistical process control methods by allowing formal hypothesis testing. This method incorporates selection of type I and II error rates and a threshold of an unacceptable odds ratio (OR) for an outcome. The SPRT is then able to determine whether the hypothesis has been accepted or rejected, or whether further information is required to determine the answer. Moreover, by providing a graphic summary of changes in performance with time, SPRT can alert a surgeon to suboptimal performance. SPRT is also well suited to monitoring surgical learning curves.[16]

The aim of this study was to evaluate the learning curve of a single surgeon undertaking CRS and HIPEC by analyzing, in a multidimensional perspective, the changes in surgical outcomes according to case sequence in a series of patients affected by PSM. Particular emphasis was given to the adjustment of potential confounders that may affect surgical outcomes, and the risk-adjusted (RA) SPRT model was used to assess the extent of surgical experience required to overcome the learning curve.

PATIENTS AND METHODS

All patients were treated under an institutionally approved protocol and provided written informed consent. The eligibility requirements for treatment were as follows: histologically confirmed diagnosis of PSM judged resectable on the basis of clinical and radiological data; age younger than 75 years; no distant metastasis; adequate renal, hematopoietic, and liver functions; and performance status (Eastern Cooperative Oncology Group = 0, 1, or 2).

We obtained data from the prospectively collected institutional database on PSM program of the National Cancer Institute of Milan. In total, 414 cases of PSM treated by 420 CRS and HIPEC procedures represented the study group. Six cases underwent the procedure twice for disease recurrence. The study period lasted from August 1995 to January 2011.

CRS and HIPEC

The technique of CRS has been described elsewhere.[17,18] Briefly, the surgical procedure was conducted with 1 or more of the following steps, depending on disease extension: (1) greater omentectomy, right parietal peritonectomy ± right colon resection; (2) pelvic peritonectomy ± sigmoid colon resection ± hystero-adnexectomy; (3) lesser omentectomy and dissection of the duodenal-hepatic ligament ± antrectomy ± cholecystectomy; (4) right upper quadrant peritonectomy ± Glisson capsule resection; (5) left upper quadrant

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