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TITLE

Learning curve, training program, and monitorization of surgical performance of PSM centers

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KEY POINTS

- Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) is a complex procedure with a very steep learning curve (LC).

- Using specific statistics with risk adjustment it was observed that approximately 137 to 180 cases are necessary for the achievement of proficiency considering radicality and safety. Eighty-six to 100 cases were necessary to assure short-term prognostic gains in rare Peritoneal Surface Malignancies (PSM).

- Centralization of PSM centers is advisable for rare diseases such as PMP and Peritoneal Mesothelioma.

- Mentoring is a key-factor to shorten the LC and assure quality of the training in CRS and HIPEC.

- A well-structured training program was implemented in European context to standardize the treatment, ease the setting up of new centers, and improve the quality of the services

SYNOPSIS

Cytoreductive surgery (CRS) and HIPEC is a complex procedure with high cost and significant morbidity and mortality. The associated learning curve (LC) is steep and could reliably be evaluated using specific statistics. The Risk adjusted sequential probability ratio test is an effective and robust method to monitor surgical performance both in the learning and audit phase of a PSM center development. Several factors are associated with surgical performance and the most critical is mentoring of the trainee by an expert. Rare PSM like PMP and peritoneal mesothelioma are specific clinical circumstances that require further effort in the training process. Their extremely low incidences make reasonable regional centralization to ease centers' quality control and improve cost effectiveness. A well-structured tutor based training program has been implemented in Europe. This initiative is expected to improve the standardization of the combined procedure and improve the quality of the services across the continent.

Introduction

The advent of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) changed dramatically the approach to peritoneal surface malignancies (PSM). The combined treatment allowed the achievement of durable oncological results in clinical conditions that were formerly considered amenable only to palliative therapies. This combined treatment is currently accepted as the standard of care for pseudomyxoma peritonei (PMP) and peritoneal mesothelioma (PM).[1,2,3,4] and is also applicable in selected cases of Peritoneal Metastasis (PM) from colorectal and advanced epithelial ovarian cancers.[5,6,7,8]

This new therapeutic modality has spread widely around the world and new PSM centers are continuously emerging. However, the annual overall (i.e. from main etiologies) estimated incidence of PSM, is about 709,941 cases.[9] The following clinical entities were considered in this evaluation: peritoneal mesothelioma, primary peritoneal carcinoma, desmoplastic small round cell tumor, PM from colorectal cancer, PM from gastric cancer, ovarian cancer, and pancreatic cancer. Considering the estimated number of main active PSM centers in the world of 150,[10] and even if liberally assuming a 10 times larger actual number of institutions, each center would need to treat more than 400 cases per year to provide an acceptable response to the global population demand. Therefore, more PSM units are required.

On the other hand, CRS and HIPEC is a resource consuming operation with an estimated cost of up to €39,000 per procedure.[11,12] Moreover, it is a high risk intervention with perioperative morbidity and mortality rates of about 28.8% and 2.9%, respectively.[13] Consequently, the associated learning curve (LC) is intuitively expected to be steep. Furthermore, the availability of methods for quality control of established centers is of best interest of regional health care systems for the optimization of resources allocation. In the following paragraphs we will discuss: 1) the available methods to monitor surgical performance both in the learning and audit phase of a center development; 2) the factors associated with the surgical performance; 3) what type of training program to shorten the learning process of the surgeon; and 4) what aspects related to logistics and infrastructure of the center could be modulated to optimize the achievement of its proficiency.

The LC process

The process of setting up a new PSM is a complex issue whose main limiting factor is that of the LC. The LC could be conceived as the achievement of proficiency in the performance of surgical procedures. This encompasses not only the technical dexterity, but also the ability to select the right case for the surgery and the excellence in the management of the patient in the postoperative period in a multidisciplinary environment.[14] Several outcomes could be used for LC evaluation: completeness of cytoreduction rates, morbidity-mortality, prognosis, and quality of life. The LC could be applicable not only for individual surgeons but also for PSM institutions.

Different approaches have been used in the literature to assess LC and surveillance of surgical performance. The traditional method is represented by classic frequentist statistics without adjustments. The second approach is represented by statistical process control tests.

Assesment of LC using traditional frequentist statistics

Traditional frequentist statistics assess the LC by arbitrarily splitting the cases into different groups. Moran et al. reported his single-surgeon LC in 100 consecutive cases of CRS and HIPEC for PSM dividing his series into 3 equal groups of consecutive cases and comparing outcomes across groups.[15] He reported a drop in major morbidity and mortality rates from 27 to 0 % and 18 to 3 %, respectively from the first to the last group of cases. Similarly, Smeenk et al. reported on 323 procedures for PSMs in Netherland Cancer Institute.[16] The rate of complete cytoreductions increased from 35.6 to 65.1 per cent ($P = 0.012$). The postoperative morbidity rate decreased from 71.2 to 34.1 per cent ($P < 0.001$). The median duration of hospital stay decreased from 24 to 17 days. The mean simplified PCI score decreased significantly over the study period ($P < 0.001$). Yan et al. reported outcomes of one surgical team performing 140 cases of CRS/HIPEC, divided into two sequential time periods of 70 cases each. They demonstrated a reduction in severe morbidity (30 - 10 %), transfusion requirement, operative time, and ICU - length of stay.[17]

Overall, these studies suggest improved proficiency as case numbers increased; however, they failed to control for covariates known to affect surgical outcomes (confounders). Eventual improvement in surgical outcomes should not be attributed entirely to an actual improvement of the surgical proficiency as less complex cases could have been selected across the timeline of the center’s experience. Thus, this arbitrarily splitting method, associated with classic frequentist statistics, is not appropriate in the assessment of surgical performance and LC of complex surgical procedures.

Statistical process control tests

Although originally developed for quality control of military supplies during World War II, statistical process control tests have been largely used in medicine to monitor the safety of medical interventions such as interventional cardiology, cardiac surgery, emergency medical services, and other procedures . Two tests are most frequently employed: the Cumulative Sum (CUSUM) and sequential probability ratio test (SPRT). [18],[19],[20],[21],[22]

The SPRT 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. The SPRT allows for adjustment of confounders by multivariate analysis. Moreover, by providing a graphic summary of changes in performance over time, SPRT can alert a surgeon to suboptimal performance. SPRT is also well suited to monitor surgical LCs.

The risk-adjusted SPRT could be plotted to chart, across the case sequence, changes in the outcomes of interest. The latter should be variable of binary nature such as rates of incomplete cytoreduction, rates of G3-5 morbidity, and short-term oncologic failure. To elaborate the SPRT, four parameters are defined: estimated probabilities of outcomes of interest for each case, a prespecified odds ratio (OR) for the outcomes of interest, and type I and II error rates. Probability of type I and type II (a and b) error usually are set at 0.05. From these, two control limits (h0 and h1) and the cumulative sum of log-likelihood ratio with risk-adjustment are calculated according to equations outlined by Rogers and colleagues.[23] The estimated risk of an adverse outcome is expected to suffer a wide variation from case to case and does not depend exclusively on the expertise of the surgical team. Factors related to the characteristics of patients and tumours do exert an impact on the outcome of interest. Therefore, an adjustment for pre-operative (baseline) risk is critical to ensure that unfavourable event rates that appear unusual are not erroneously attributed to insufficient proficiency. Accordingly, the probability of event is calculated using the logistic regression model, which is adjusted with independent risk factors of incomplete cytoreduction, G3-5 morbidity, or short-term oncologic. Then, the multivariate model's performance is evaluated by means of two parameters: discrimination and fitness. Discrimination is measured by the area under the receiver-operating characteristic curve (AUC),[24] with values of 0.5 representing no discrimination and 1.0 representing perfect discrimination. Model fitness is assessed by the Hosmer-Lemeshow goodness-of-fit test,[25] with P values of greater than .05 indicating acceptable fit.

When creating the RA-SPRT curve, each case is plotted in sequence along the x-axis. When a success occurs a risk adjusted log-likelihood ratio is subtracted from the cumulative score. When a failure occurs, the constant 1-s is added to the cumulative score. In practice there are four possible situations:

1. If a low-risk case happens to present an adverse outcome (G3-5 morbidity, incomplete cytoreduction, or early oncologic failure) the surgeon is penalized with a high positive score.

2. If a low-risk case presents a favourable outcome (uneventful postoperative period, complete cytoreduction, or absence of early oncologic failure) the surgeon is granted a low negative score.

3. If a high-risk case presents an adverse event the surgeon is penalized with a low positive score.

4. If a high-risk case presents a favourable outcome the surgeon is granted a high negative score.

The scores are plotted consecutively and cumulatively according to the case-sequence and this originates the RA-SPRT curve. An ascending slope in the RA-SPRT line indicates deterioration of performance, whereas a descending slope indicates improvement of performance. Unacceptable ORs for the outcomes of interest are set considering the highest and lowest rates of these outcomes available in the literature. The upper and lower control limits are respectively defined as h1 (reject line) and h0 (accept line). If the RA-SPRT curve crosses the upper decision limit (h1) from below, this means that the actual OR for outcome is equal to or higher than the prespecified OR with the probability of type I error of 0.05. If the line crosses the lower decision limit (h0 or accept line) from above, this indicates that the actual OR for the outcome being studied is less than the unacceptable OR with the probability of type II error of 0.05. When the line is between h0 and h1, no statistical inference could be made. Expertise is estimated to be achieved at point in which the curve of RA-SPRT crosses the accept line (h0) for outcomes of interest. At the time of crossing to the lower boundary, the graph is reset to 0 to start the surveillance of surgical performance with audit intent.[26] Once the expertise is acquired, the surveillance continues to monitor any eventual deterioration of the performance. The RA-SPRT curve could assume a positive slope in the case of enrolment of new surgeons to the surgical team, introduction of new protocols, and the adoption of innovations or changes in surgical strategy based on new data obtained from other centers.

The LC of CRS and HIPEC for PSMs

Kusamura et al. assessed the LC using Risk-adjusted SPRT on 420 cases of PSM on the basis of rates of incomplete cytoreduction and G3-5 morbidity (NCI-CTCAE.v3). They estimated the control limits setting the type I/II error rates at 0.05 and unacceptable odds ratios (ORs) at 1.8 for incomplete cytoreduction and 1.4 for severe morbidity, based on the literature data. The RA-SPRT 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.

Subsequently Polanco et al. reported similar results using the same methodology. The breaking point of the proficiency was located at the 180th case for severe morbidity.[27]

How to shorten the LC: the role of tutor

The results of Kusamura et al. and Polanco et al. confirm that a lengthy LC is required for the acquisition of proficiency in performing CRS and HIPEC. Considering the high morbidity rate and the high cost of the treatment,**¡Error! Marcador no definido.** developing strategies to shorten the LC is critically important. Shortening the LC would imply a substantial reduction in the number of adverse events resulting from inexperience, as well as a reduction in costs associated with procedures performed by non-experts.

The NCI of Milan, after having overcome its own LC, has provided technical and scientific assistance to a community-based hospital, located 250 km from Milan. The first step of the tutorial consisted of visits to the NCI of Milan by members of the emerging center. The second step was the development of study protocols, the definition of a multidisciplinary team, and logistic troubleshooting. The third step was the selection of initial cases and performance of CRS and HIPEC at the emerging center with the assistance of the tutor. The expert (DM) supervised Bentivoglio's operations participating in the surgeries during the first two years. The visits of the tutor to the Bentivoglio center were maintained on a regular basis every two months thereafter. The RA-SPRT curves were plotted for the two centers considering the following outcomes: incomplete cytoreduction rates, G3-5 morbidity, and Procedure Related Mortality (PRM).[28] The Bentivoglio's center successfully managed to overcome the LC much earlier as compared to NCI of Milan regarding all three outcomes: 126 vs. 141 for incomplete cytoreduction, 134 vs. 158 for G3-5 morbidity, and 60 vs. 144 for PRM. The authors concluded that surgical tutoring could substantially shorten the steep LC associated with CRS and HIPEC.

Which parameter should we use to evaluate LC and to monitor surgical performance?

Up to date four outcomes have been used to evaluate LC and surgical performance: incomplete cytoreduction rate, severe morbidity, PRM, and early oncological failure. Each one has its own pros and cons.

Recently Voron T et al.[29] have evaluated the LC of a high-volume center in Paris. The analysis was conducted on a case mix of 290 PSM cases operated with CRS and HIPEC, prevalently composed by PM from colorectal cancer. The outcomes of interest were rates of incomplete cytoreduction and severe morbidity. The principal surgeon has set up the PSM unit after having attended a long lasting training program, with more than 200 procedures performed in another referral center. Therefore it was assumed that he was already proficient in performing the combined procedure in the early beginning of the new center's activity. The RA-SPRT curves breach the lower boundary at 40th case to lower the risk of incomplete cytoreduction and 140 cases to lower the risk of severe morbidity. The authors highlighted the substantial difference in the number of cases that were necessary for the achievement of expertise between the two outcomes of interest. These results are in perfect line with the concept that the ability to cytoreduce a PSM is much more related to surgeons' technical dexterity while severe morbidity is related to the expertise of the entire multidisciplinary team. Professionals from different disciplines like anesthesiologists required their own time to acquire proficiency in managing the patient in the perioperative setting, and this learning process developed separately from the excellence of the principal surgeon. Thus, incomplete cytoreduction is a parameter to appraise the surgeons' LC while severe morbidity, the institutions' LC.

Another outcome for the evaluation of LC is the PRM. Kevin et al. have recently discussed the interesting notion of failure to rescue (FTR) in patients suffering a complication following CRS and HIPEC.[30] A total of 915 eligible CRS and HIPEC cases were identified from American College of Surgeons National Surgical Quality Improvement Program data set. FTR was defined as 30-d mortality in the setting of a complication. Overall, 382 patients (42%) developed more than one postoperative complication, and 88 patients (10%) suffered more than one major complication. The FTR rate was 4% and was independently associated with ASA class 4 (adjusted odds ratio [OR]: 13.4, 95% confidence interval [CI], 1.2-146.8) and major complications (adjusted OR: 66.0, 95% CI, 8.4-516.6). This means that PRM is connected to the selection process performed in the preoperative period, or the ability of the surgeon to choose cases with a general clinical condition compatible with the extent of surgical trauma associated with this major operation.

Finally the prognostic outcome is the best parameter to evaluate LC and surgical performance. Survival has been deemed the ultimate testament to a learning process as it represents a single parameter that encompasses other aspects included in the concept of expertise such as capacity to choose the right candidate for the combined treatment by means of a judicious preoperative evaluation, to cytoreduce PSM completely in a safe way, and to conduct postoperative care.[31] However SPRT requires the outcome of interest being binary so that a surrogate marker of prognosis with a yes/no format would be necessary. Such strategy has recently been employed in a study that evaluated the quality of US transplant units.[32] More recently a multicentric study on LC of CRS and HPEC was conducted in a cohort of PMP cases. The target outcome was early oncological failure defined as progression of the disease or death within two years from the procedure.31

Institutional factors affecting LC

In the above-mentioned multicentric study, 2,451 cases of PMP treated by 47 surgeons in 33 PSM centres from around the world were considered for the LC analysis.[31] In the elaboration of multivariate model the authors included not only factors related to biology of the tumor, but also characteristics related to the surgeon's background and institutions' organization. The following factors resulted to be independents variables related to early oncological failure: center volume, proportion of PMP, number of principal surgeons on the team, type of fellowship, previous systemic chemotherapy, histological subtype, Peritoneal Cancer Index, completeness of cytoreduction, HIPEC and early postoperative intraperitoneal chemotherapy.

The center volume resulted to be independently correlated with early oncological failure in a non-linear manner. Centers with annual caseload of more than 60 cases of PSM were associated with lower risk of early oncological failure. Likewise, the higher the proportion of PMP in the center's experience in treating PSM the better was the outcome. And finally the increased number of principal surgeons on the team was correlated with higher risk of early oncological failure.

This study confirmed that the learning process and surgical performance are influenced by aspects related not only to team's abilities and the complexity of the case, but also to characteristics of center's organization. Only eight of the 33 centres overcame the LC, and after a median of 100 (range: 78–284) procedures (Figure-1a/b).

Centralization for rare diseases

Kusamura et al. have conducted the LC analysis on their center's experience on peritoneal mesothelioma. They adopted the early oncological failure as target outcome and the breaking point of LC was 86 cases.[33] Given the extremely low incidence of these conditions, it is virtually impossible for a center to gather experience on 100 cases of PMP or 86 of peritoneal mesothelioma, to be considered proficient in the treatment of such rare diseases, unless health care authorities set up mechanisms of regional centralization. Centralization could also be utilized for cost containment, as institutions, which completed the LC, are expected to be more economically efficient. Finally, centralization will ease regulation and quality control for the insurers. Considering that the approximate annual incidence of PMP is 1–2 million, it can be estimated reasonably that one centre for every 10–15 million inhabitants would be ideal.

One could raise a criticism to this thesis arguing that cytoreduction and HIPEC could be applied uniformly to treat different diseases and that surgeons would not need specific training for rare diseases. This counter argument apparently makes sense but is unsustainable due to several weaknesses. Most of PSM centers' experiences in the world are characterized by a predominance of peritoneal metastases from colorectal cancer, a clinical circumstance where the combined procedure is indicated in patients with less extensive and consequently less complex disease. PMP and peritoneal mesothelioma, in contrast to PM from colorectal cancer, are clinical circumstances where the extension of the disease is not a criterion to indicate CRS and HIPEC. A surgeon to become proficient in treating cases with PCI>17 [34] would need to gather experience in rare diseases. Moreover, the extension of the surgery should be modulated according not only to the PCI but also to the biological characteristics of the disease. The surgeon should know how much he could push the maximal surgical effort according to his knowledge regarding the biological aggressiveness of the tumor. Furthermore, good prognostic outcome does not depend exclusively on excellent surgical performance but also on the work of the multidisciplinary team in the context of a multimodal treatment strategy where perioperative treatments could further improve survival results.[35] In summary, technical proficiency in CRS and HIPEC and acquaintance with the biology of the diseases are different qualities that are developed separately during the learning process in Peritoneal Surface Oncology.

Training program

The ever growing increase in the number of services offering the combined treatment has occurred along the last decades with neither a well-coded training program and nor regional government regulations. Therefore, it is likely that a significant number of recently emerged low-volume institutions claiming to have the knowhow to manage PSM might not be properly capacitated for this task, as their learning processes are still ongoing. Consequently, the current number of proficient centers in the world is unlikely able to response adequately to the demand of the population affected by PSM.

The European Society of Surgical Oncology (ESSO) in a joint venture initiative with Peritoneal Surface Oncology Group (PSOG) developed a well-structured training program in Peritoneal Surface Oncology in 2014.[36] The program is named European School of Peritoneal Surface Oncology (ESPSO) and has the objective to offer a tutor-based fellowship to surgeons with strong interest in this field. During the training the fellow should accomplish a series of theoretical and practical activities in a proficient center accreditated by PSOGI. With duration of two years, this non-profit initiative has no pretension to follow the trainee along the entire duration of his LC. However it intends to provide essentials that will help the surgeon to set up a new center in his institution of origin and complete his training until the achievement of proficiency (Figure-2).

Conclusions

The RA-STPRT is an effective and robust method to monitor surgical performance both in the learning and audit phase of a center development. Several factors are associated with surgical performance and the most critical is mentoring of the trainee by an expert in CRS and HIPEC. Parameters related not only to patient and disease but also to logistics and infrastructure of the center could influence prognosis. The latter should be carefully adjusted to further optimize the achievement of center's proficiency. Rare PSM like PMP and peritoneal mesothelioma require further effort in the training process and their extremely low incidences make reasonable regional centralization. A well-structured tutor based training program has been implemented in Europe. This initiative is expected to improve the standardization of the combined procedure and improve the quality of the services across the continent.

Figures

Figure-1

Legend: RA SPRT: risk adjusted sequential probability ratio test. EOF: early oncological failure. PMP: pseudomyxoma peritonei. Red area: learning phase. Blue are: audit phase. The breaking point of the learning curve is the moment in which the curve surpasses the lower boundary. Before this point: learning phase. After this point, the curve is reset to zero to start the audit phase.

Figure-2

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