

Extra-peritoneal hysteroannessiectomy with eventual concomitant *en bloc* rectal resection and cytoreductive surgery in epithelial ovarian cancer (and other peritoneal surface malignancies): technical details

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Abstract

Surgery allows the correct evaluation of the peritoneal dissemination of the epithelial ovarian cancer (EOC) and the removal of as much tumor as possible to maximize adjuvant chemotherapy. Neoadjuvant chemotherapy (NACT) and interval debulking surgery have been proposed as a reasonable alternative to primary complete cytoreductive surgery (CRS) in patients not fit for an initial extensive debulking surgery. Intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC) has been offered as a promising therapeutic procedure to increase survival by treating the microscopic component of the neoplastic disease.

Material and Method. 419 eligible patients with stage III-IV EOC were subjected to CRS, previous NACT in 343 patients, 20

of which with CRS combined with extraperitoneal hysterectomy (EH) + HIPEC. Purposes of our four years retrospective observational study are the revision of the surgical approaches to the EOC, a detailed report of the pelvic peritonectomy in association to hysteroannessiectomy (+/- consensual rectal resection) and the prospective review of the results.

Conclusions. This study shows that EH + HIPEC is feasible. The detailed description of the technique here depicted could help to standardize this type of peritonectomy.

Introduction

Epithelial ovarian cancer (EOC) is the leading cause of death from gynecological cancer in the Western world.¹ Although it was firstly supposed that EOC originates from the superficial lining of the ovaries or from the peritoneum,^{2,3} recent studies have revealed that most EOCs do not exhibit characteristics representative of mesodermal epithelium from which the ovaries develop and it has been theorized that EOCs, particularly those of the serous histotype, originate from the fallopian tubal fimbria.⁴ As the growth of EOC is most often relatively silent, at diagnosis it has usually already spread throughout the peritoneal cavity. The majority of women who contract this disease have a bad prognosis, commonly due to uncontrolled, large-volume disease within the peritoneal cavity. Unfortunately, more than 70% of women are initially diagnosed with disseminated intra-peritoneal disease.^{5,6} As EOC is generally diagnosed in advanced stage (Appendix Figure 1), the classical aims of the surgical procedure are the appropriate determination of extension of the disease and the removal of as much tumor as possible to maximize adjuvant chemotherapy (ACT). For these reasons, surgical treatment, mainly in advanced stages, remains a challenge for surgeons and gynecologic oncologists. The actual accepted standard is to perform maximal cytoreductive surgery in order to accomplish complete resection of the disease, and 6 cycles of carboplatin and paclitaxel, as systemic ACT.⁷⁻⁹ Nevertheless, in some patients, it is difficult to reach complete debulking surgery, even in experienced centers due to the peritoneal extension of the disease. Also there is a subgroup of patients in whom the maximum effort of primary extensive cytoreductive surgery (CRS) was not reflected in improved survival outcomes, but only in higher morbidity.¹⁰ In these patients in whom it is not possible or advisable an initial extensive debulking surgery, due to poor general condition, advanced age, or disease extension, has been proposed as a reasonable alternative to primary complete CRS, administra-

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See online Appendix for Figures.

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tion of 3-4 cycles of neoadjuvant chemotherapy (NACT) and interval debulking surgery. More recently, in an effort to increase survival by treating the microscopic component of the neoplastic disease, administration of intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC) after complete macroscopic CRS in advanced EOC, has been offered as a promising therapeutic procedure.

Purposes of this study are the revision of the surgical approaches to the EOC (also in relation to the different chemotherapy treatments), a detailed report of the pelvic peritonectomy in association to hysteroneomyectomy (and eventually to a consensual rectal resection) and the prospective review of the results of this surgical approach in our patients.

Materials and Methods

A narrative literature revision of the surgical approaches to primary EOC (also in relation to the different chemotherapy treatments) and the eventual use of HIPEC has been performed through a PUBMED and EMBASE research up to 2015.

A detailed description of the pelvic peritonectomy in association to hysteroneomyectomy with a consensual rectal resection, where indicated, and HIPEC has been obtained by reviewing the images, movies and diagrams made during surgery.

The present study is a retrospective observational study conducted in a four-year period (from December 2010 through December 2014) among hospitalized patients operated for EOC. Data on the observational study were recorded on a standardized case report form during review of medical charts and included demographic, tumor and treatment characteristics.

Results

Surgical approaches to the EOC in relation to the different chemotherapy treatments: narrative literature review

Primary cytoreductive surgery

Retrospective evidence studies support the value of optimal CRS in the initial treatment of patients with advanced EOC.¹¹

Specialized procedures, including radical pelvic surgery, bowel surgery, diaphragm and multi-visceral resections are sometimes necessary to accomplish CRS. EOC metastasizes by breaking through the ovarian capsule and spreading non-contiguously along parietal and visceral peritoneal surfaces. Normally, it does not invade deeply or into hollow organs and, in most patients, the disease remains confined to the peritoneal cavity until death. The disease may become focally confluent and can form large-volume masses anywhere in the peritoneal cavity but, since ovarian cancer metastases are usually relatively superficial, CRS can often be performed without major organ resection. Typical localizations include: omentum, sigmoid colon serosa, lesser omentum area and pericolonic gutters. Patients, usually, become symptomatic as a result of intra-peritoneal pressure increasing due to solid masses or fluid, even if some patients are asymptomatic in spite of surprisingly large volume intra-peritoneal lesions.

The regional lymph nodes, pelvic and periaortic ones are often involved. This is particularly frequent in stage III and IV disease in which Burghardt *et al.*¹² reported involvement in 74% of patients.

Interval cytoreductive surgery

To help achieving complete resection rate, the concept of NACT followed by interval CRS has been developed for patients with unresectable disease (stage IIIC/IV). Primary CRS followed by ACT was compared with NACT followed by interval CRS in women with advanced EOC. Vergote *et al.*¹³ found that survival after NACT followed by interval CRS was similar to survival with the standard approach of primary surgery followed by chemotherapy among patients with advanced EOC (stage IIIC or IV), or peritoneal ovarian carcinoma. Survival after NACT followed by interval CRS is similar to survival after primary CRS followed by chemotherapy. This result is consistent with the conclusion of a large meta-analysis of 21 non-randomized trials.¹⁴

More recently, a phase 3, controlled trial (CHORUS) undertaken in 87 hospitals in the UK and New Zealand, enrolled 550 eligible women with stage III or IV ovarian cancer: 276 were assigned to primary CRS and 274 to primary chemotherapy. In this study, survival with primary chemotherapy was non-inferior to primary CRS.¹⁵

HIPEC after cytoreductive surgery

Three randomized trials show that intra-peritoneal chemotherapy has a clinical advantage in the treatment of EOC. Although this advantage comes at the expense of increased toxicity and reduced quality of life during treatment, these results should encourage the use of intra-peritoneal chemotherapy in patients with advanced EOC.¹⁶ Intra-peritoneal chemotherapy can be even administered under hyperthermic conditions, which are poorly tolerated by a patient who is awake. Hyperthermia is directly cytotoxic and enhances the efficacy and penetration depth of many drugs, while the mild locoregional hyperthermia that is used has no significant adverse effects. The feasibility of hyperthermic intra-peritoneal chemotherapy (HIPEC), as a treatment for peritoneal carcinomatosis, was first demonstrated by Spratt *et al.*¹⁷ in the early 1980s. Its development continued under Dr. Sugarbaker in the mid-1990s, who advocated a combined procedure of CRS with peritonectomy procedures (aimed at resecting peritoneal surfaces with tumor implants) and visceral dissections, with maximal surgical effort to remove as much tumor as macroscopically possible, followed by direct instillation of heated chemotherapy to address microscopic residual disease.¹⁸ In practice, HIPEC has been used in locally advanced EOC as an adjuvant treatment after CRS with promising results.^{19,20}

Bergamo experience

From December 2010 through December 2014, 419 eligible patients with stage III-IV EOC were subjected to CRS: 343 patients were assigned to primary CRS and 76 to NACT followed by CRS.

In the NACT group, 20 women were treated with CRS combined with EH+HIPEC. Platinum-based NACT is the mainstay of treatment for advanced disease: the most common protocol adopted was CBDCA-TX (20/20, 100%). Drugs used for HIPEC were a combination of CDDP (100 mg/m²) and PTX (175 mg/m²) because of their favorable IP pharmacokinetics and their high local efficacy.²¹ Drugs have been instilled in the peritoneal cavity using the heart-lung pump at a mean flow of 600-1000 ml/min for 90 minutes with an intra-abdominal temperature of 42.5°C.

Population and tumor characteristics were: mean age 57.8 years, mean body mass index 23.7 kg/m², mean CA-125 at diagnosis 1341.3 U/ml, prevalent histologic serous type (20/20) G2-G3 with massive ascites and high anesthetic risk (95% ASA grade 2-3). Completeness of CRS were assessed by measuring the size of the residual peritoneal implants following surgery and assigning a

complete cytoreduction TR0 (CC0), no residual disease; TR<2.5 mm residual nodules measuring less than 2.5 mm (CC1); TR>1 residual nodules greater than 2.5 mm (CC2-CC3). At laparotomy the mean PCI was 15.75 (range 3 to 27). Complete cytoreduction was achieved for 19/20 (95%) adopting the EH technique in NACT+CRS+HIPEC group. In order to achieve CRS, EH combined with a complex multi-visceral surgery was necessary in all the patients. In NACT+EH+HIPEC group the mean operation time was 8.6 hours, and mean hospital stay was 27 days. The mean bleeding was 1.184 ml (range 300-2300 ml). Our patients were followed for a median of 29.83 months (range 6.50 to 52.63 months). No patients were lost at follow-up. Twelve patients (60%) treated with EH and HIPEC are still alive. Eight patients had disease relapse and are death of disease.

Technical details

Pelvic peritonectomy in association to hysteroneussiectomy and eventual concomitant en bloc rectal resection

Thromboembolic prophylaxis and bowel preparation are particularly important for patients undergoing CRS. The patient is positioned in the dorsal perineo-lithotomy position using Allen Stirrups Systems™ (Allen Medical System, Cleveland, OH).

The dissecting tool for peritoneal CRS is the so-called laser-mode electro-surgery using a ball tip that is very useful to isolate the peritoneal layer.²² The electrosurgical generator is positioned on pure cut and at high voltage. The ball tip results in a lens shaped (lenticular) defect. This greatly facilitates exposure of structure being dissected free. In contrast, a linear defect is created by the traditional spatula electrosurgical tip (Appendix Figure 2).

In our setting, as dissecting tool, we employ the ForceTriad™ Energy Platform (Covidien Medtronic). The ForceTriad™ energy platform is an electrosurgical system, providing not only electrosurgical cutting and coagulation with bipolar functionality, but even a vessel sealing (LigaSure™ fusion technology). In particular, the electrosurgical device has not only the usual cutting and coagulation modes, but even the Valleylab™ mode for a distinctive combination of monopolar hemostasis and dissection while using a lower power setting, resulting in less char, less thermal effect and less arching than traditional coagulation mode. In our experience we use the following power levels: cutting 250 Watts, coagulation 120 Watts and Valleylab™ 200 Watts. With this mode of electro-surgery, parietal and visceral peritoneum can be separate from the underlying layers, producing accurate hemostasis simultaneously. In areas where there is massive carcinomatosis high power levels allow to overcome the surface vaporizing the tumor disease and thus reaching the deeper layers apparently healthy. To avoid possible damage to the operating room staff, the use of these technologies must be provided with adequate means of smoke suction²³ (Appendix Figure 3).

Abdominal exposure is best achieved through a midline xyphopubic incision with placement of a self-retaining retractor. Bookwalter Retractor System (BRS) represents one of the most widely accepted *table fixed* retractor with a versatile system for multi-directional exposure of the surgical field. From eight to sixteen monofilament sutures can be placed in the skin edges and connected to the two arms of the BRS. These allow the elevation of the edges of the abdominal incision (called *coliseum technique*), for the time being converting the abdomen and pelvis into a reservoir for the eventual administration of hyperthermic chemotherapy solution (Appendix Figure 4).

Beginning the laparotomy, only the fascia in the linea alba is divided, maintaining intact the underlying peritoneal layer. During this phase the omphalectomy is performed and only a single, small

hole into the peritoneal cavity in the superior portion of the incision (peritoneal window) is made allowing the surgeon to evaluate the need for a broad parietal peritonectomy: the preliminary assessment is very important, with particular attention to the feasibility of resecting all abdominal disease. Taking care that the peritoneum is maintained intact, its dissection from the overlying fascia is accomplished laterally in both sides, down and possibly upwards (Appendix Figure 5).

By entering the abdomen, aspiration of ascites or peritoneal lavage should be performed for peritoneal cytological analyses. Intraoperative pathologic evaluation with frozen sections may help in management.

Extra-peritoneal hysterectomy (EH) with extended pelvic surgery

Standard surgery of EOC includes: hysterectomy, bilateral salpingo-oophorectomy with excision of the whole pelvic peritoneum, omentectomy, appendectomy, removal of bulky pelvic and peri-aortic nodes, and simple peritonectomies. When CRS is performed pelvic peritoneal surface and uterus sometimes are removed en bloc with the recto-sigmoid colon using typical surgical technique.

Total removal of the pelvic peritoneum is the most beneficial procedure in case of disease extended to the pelvis. With total removal of the pelvic peritoneum, we can even perform the EH. The goal for this procedure is the complete eradication of neoplastic cells in case of massive pelvic disease or residual pelvic tumor after NACT.

The EH begins by resecting the peritoneum from the anterior pelvis wall circumferentially to include all visible disease and moving in a centripetal mode from the Retzius retro pubic space and paravesical spaces toward the central pelvis. To achieve complete or optimal debulking with peritonectomy procedure (especially in case that HIPEC will follow in the same surgical session), extensive ureteric dissection may be required. Ureteric stents can be inserted before removing pelvic wall tissue involved with infiltrative tumor, which will enhance the identification of the ureter(s), aiding in ureteric dissection and avoiding operative injury.²⁴ An indwelling urethral three-way Foley catheter is inserted at the end of the preoperative cystoscopic procedure and left in place for 7 to 10 days. It allows the bladder to remain empty, thereby reducing any back pressure on possible ureteric anastomosis. The instillation of 200 ml of saline with blue dye into the bladder through the transurethral catheter can also be used to assist in delineating the dissection plane between the bladder base and anterior vaginal wall. Broad-spectrum antibiotics are in this case given to reduce the risk of infection in the immediate postoperative period.

The right and left ureters are identified and suspended with a silastic strip (Appendix Figure 6) and the ovarian veins and arteries are divided likewise with the use of a bipolar vessel sealing system.

Both round ligaments are then divided as they enter the internal inguinal ring with a bipolar tissue sealing system that can facilitate this procedure (Appendix Figure 7).

The urachus must be divided and it often represents the point of traction for the bladder (Appendix Figure 8).

The next step is the dissection of the peritoneum from the bladder wall. The bladder peritoneum is dissected until the uterine cervix and vaginal fascia appear. The bladder is then dissected off from the cervix. After mobilization of the bladder's peritoneum and pelvic sidewall, the ureter is dissected down until the entrance of the *ureteral tunnel*. In this manner the ureters are separated from uterine vascular tunnels on either side and widely mobilized laterally away from the central tumor mass (Appendix Figure 9). Then the uterine vessels and the cardinal ligament are secured and transected using a

bipolar vessel sealing system (Appendix Figures 10 and 11). The peritoneal dissection can continue circumferentially behind the rectum in both side reaching the space between the inferior mesenteric artery and the retroperitoneal space (Appendix Figure 12). Proximal vaginal resection (2-3 cm) allows precise entry into the recto-vaginal space and completion of the pelvic peritoneal dissection with en bloc removal of the internal genital tract (Appendix Figure 13). The vagina is incised circumferentially and the recto-vaginal space is developed first caudally then cranially to facilitate this procedure. In case that the rectum has to be resected consensually, the posterior and lateral dissection is further developed inferiorly, and the mesorectum divided with a vessel-sealing device, or suture ligatures. The proximal rectum is cleared of remaining fat and prepared for division using a thoraco-abdominal (TA) stapling device or a Contour™ Curved Cutter Stapler (Appendix Figure 14).

If necessary, the uterus is removed in block with peritoneal cul de sac (pouch of Douglas) and proximal rectum (Appendix Figures 15 and 16). Re-establishment of intestinal continuity is achieved via a stapled circular end-to-end anastomosis (29 mm to 31 mm) (Appendix Figure 17A and B); a protective colostomy/ileostomy is constructed in different cases.

Reasons mentioned for performing a protective colostomy/ileostomy include tension at the anastomotic staple line, concerns over adequate vascularization of the anastomosis, local contamination from spillage of bowel contents and HIPEC procedure.

Supra-radical surgery of EOC includes at least one of the following: extensive peritonectomies, including partial resection of the right and/or left diaphragm, resection of sub-capsular liver metastases, cholecystectomy, splenectomy, resection of pancreas tail, other bowel resection, partial gastrectomy, etc. In patients with extensive omental involvement extending into the splenic hilum, complete removal of the omentum can be safer, with less blood loss, if the spleen is removed en bloc with the omentum.

Pelvic and periaortic lymphadenectomy

Pelvic and periaortic lymph nodes are frequently involved in patients with advanced ovarian cancer. In advanced EOC, lymphadenectomy can be considered when intraperitoneal cytoreduction has been completed or when there are bulky nodes (Appendix Figure 18).

Aortic lymph node dissection should be performed by removing the nodal tissue from the vena cava and the aorta bilaterally, until at least the level of the inferior mesenteric artery and rather to the level of the renal vessels. Pelvic lymph nodes should be dissected. Removal of lymph nodes overlying and medial to the external iliac and hypogastric vessels, from the anterior obturator fossa to the obturator nerve and overlying and anterolateral to the common iliac vessel is preferred.

Discussion

EOC spreads by four principle routes: direct extension, peritoneal dissemination, retroperitoneal lymphatics and hematogenous dissemination. CRS addresses particularly the first three ways of diffusion in order to achieve the complete clearance of peritoneal cavity. Since the nineties the peritonectomy procedures (in the gynecological literature better known as extensive surgical debulking or CRS) have been standardized by Dr. Sugarbaker.^{25,26}

Benefits for patients from a primary CRS could include symptomatic relief, extension of survival even without adjuvant therapy and enhancement of postoperative therapy, in terms of chance for cure: all of these apply to EOC's CRS.

The most favorable survival outcome is associated with complete cytoreduction to no visible residual disease and the effect of diameter of largest residual disease after primary CRS is an important prognostic factor, which plays a crucial role in OS.

EOC spreads inside intra-peritoneal surfaces and, by flowing of malignant cells in peritoneal fluid, spreads in a clock-wise circulation. A preliminary assessment of the extent of disease to the upper abdominal area should be performed with particular attention: the exploration of the entire abdominal cavity and retro-peritoneum will facilitate the plan of the procedure and ensure a reasonable likelihood of achieving a complete overall resection. If neoplastic peritoneal nodules are present on the parietal peritoneum, a complete parietal peritonectomy should be made,²² even if bulky upper abdominal disease is often mentioned as an obstacle to effective surgical cytoreduction of primary EOC.⁹ The retroperitoneal space as well as the intraperitoneal space, must be considered in any cytoreductive strategy and massive involved lymph nodes should be removed if feasible to achieve optimal cytoreduction.

Since CRS is the only principal goal of primary or interval EOC surgery, the respect of a specific surgical technique is necessary to achieve a successful cytoreduction of extensive disease.

Post-HIPEC ureteric stenting can also be carried out in an attempt to reduce the risk of ureteric complications in postoperative period, for example, fistula formation. Most stents remain in situ for approximately 6 weeks before they are removed or longer if there is concern over the vascularity of the ureter after extensive dissection. Removing the stent is easily done under a light anesthetic using a pair of graspers by operative cystoscopy.

Vergote *et al.*¹¹ showed in a prospective randomized study that the survival results were not lower in patients undergoing debulking after NACT compared to those who were exposed to an initial debulking. If the standard of care for women with stage IIIB or earlier-stage EOC - a group with a better prognosis than our current study population - remains primary CRS. Patients with proven stage IIIC or IV disease should be considered for NACT.

During its natural history, EOC tends to be chemo-sensitive and to confine itself to the surface of the peritoneal cavity for a long time. These features should make it a perfect target for intraperitoneal chemotherapy, which is given by infusion of the chemotherapeutic agent directly into the peritoneal cavity. This may increase the anticancer effect with fewer systemic adverse effects in comparison to intravenous therapy.

HIPEC has been demonstrated already beneficial in the treatment of other peritoneal surface malignancies such as malignant peritoneal mesothelioma,²⁷ peritoneal pseudomyxoma,²⁸ colon²⁹ and gastric cancer.³⁰ Conversely, the use of HIPEC after maximal CRS is still at present debated in patients with EOC, having been heavily censured due to the lack of satisfactory levels of evidence to support its use.³¹ As a combination therapy, complete debulking surgery and administration of HIPEC in EOC can show a morbidity rate ranging between 15 and 45% and a mortality up to 10%.³²

Our retrospective experience shows that EH + HIPEC is feasible. These data have to be validated in the large multicentric randomized study *Chorine protocol* with a homogenous population, in order to demonstrate the DFS and OS with a longer follow-up time adopting this surgical procedure.³³

Conclusions

The pelvic peritonectomy in association to hysteroneomy and eventual concomitant en bloc rectal resection is probably among the peritonectomy procedures the most frequently per-

formed.²⁸ For sure it is the widest used in the treatment of primary EOC with peritoneal spread. But even the other tumors with peritoneal seeding in the pelvis frequently need this pelvic peritonectomy. The detailed description of the technique here depicted could help to standardize this type of peritonectomy.

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