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4. Surgical and chemotherapeutic cytoreduction for advanced primary and recurrent ovarian cancer, the Washington Cancer Institute approach

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Abstract. Ovarian cancer remains the number one cause of death from gynecological malignancies. Currently, the conventional treatment approach for advanced (stage III and IV) ovarian malignancy is surgical debulking and systemic chemotherapy. Negative second-look laparotomy is attainable in only 20 to 40% of the cases. Up to 47% of these patients relapse within 5 years. In an effort to improve the results of treatment a *Comprehensive Approach* including cytoreductive surgery and perioperative intraperitoneal chemotherapy has been utilized. This approach is based on the success achieved with other peritoneal surface malignancies.

The goal of these treatments is to surgically eradicate all visible tumor and then to chemically eradicate microscopic residual disease. Cytoreductive surgery includes peritonectomy procedures and visceral resections. Cisplatin and doxorubicin are administered through the intraperitoneal route with heat during the surgical procedure. In the first five postoperative days patients receive normothermic intraperitoneal paclitaxel.

Results of a phase II trial with this *Comprehensive Approach* suggests improved survival as compared to historical controls with reasonable morbidity and mortality.

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Introduction

Ovarian cancer is the number one killer among gynecological malignancies. Information from the Surveillance, Epidemiology and End Results (SEER) program of the National Cancer Institute (NCI) shows that the incidence of ovarian cancer in the US for all races has been fluctuating between 14 and 16 per 100,000 persons during the 1991-2001 decade.[1] According to the same source, the US Estimated Complete Prevalence Counts on 1/1/2001 were 167,002.[2] Also, a woman age 45 living in the United States has a probability of developing ovarian cancer of 0.117%; and at age 75 a probability of 1%.[3] Ovarian cancer is the fifth more common cause of cancer death in Western countries.[4]

Unfortunately, symptoms are generally unspecific. A recent case-control study showed that when either increasing abdominal size, bloating, urinary urgency or pelvic pain occur more frequently, and with more intensity than expected or these symptoms are of recent onset, further investigation searching for an ovarian mass is warranted.[5] In the past, CA-125 tumor marker levels, transvaginal ultrasound, and pelvic examinations were thought to be potential effective screening tools. However, none of them have proved to decrease mortality from ovarian cancer and may lead to unnecessary emotional distress and invasive diagnostic procedures. As a consequence of its internal location and non-specific symptomatology most patients are diagnosed with ovarian cancer in late stages of the disease.

Most tumors are epithelial in origin (approximately 90%) and the minority is either germ cell or stromal tumors (roughly 10%). Once a tumor starts growing in the ovary, spread of cancer cells throughout the abdominopelvic cavity occurs very early in the natural history of the disease probably due to the anatomic structures of the ovary. This organ is covered by a thin layer of visceral peritoneum which is easily disrupted by the expansion and the invasive nature of the cancerous growth. This early intracoelomic dissemination causes ovarian cancer to spread beyond the internal female genitalia at the time of diagnosis in a great majority of patients.[6,7] However, peritoneal implantation is not the only route of dissemination. Depending on the stage, up to 74% of the women with ovarian cancer have pelvic and/or paraaortic lymph nodes involvement.[8] A smaller percentage of these women may develop hematogenous metastases in the liver, lungs, bone marrow, and brain.

In many patients the natural history of ovarian cancer is similar to other secondary peritoneal surface malignancies; for example, carcinomatosis from primary gastric cancer. Carcinomatosis results in debilitating ascites formation and intestinal obstruction in late stages. With knowledge of the

progression of this disease, the targets of the treatment should be the peritoneal surface spread as well as the systemic metastases. Eradication of the peritoneal surface component of this disease would be a major contribution to the overall management of this disease. Comprehensive management using surgical cytoreduction to decrease the tumor load to a minimum and perioperative intraperitoneal chemotherapy to eliminate macroscopic disease on peritoneal surfaces has the potential to greatly improve quality of life and have some impact on survival in ovarian cancer patients.

A comprehensive approach to ovarian cancer treatment

The Program in Peritoneal Surface Malignancy at the Washington Cancer Institute has initiated a treatment strategy that combines as a single event surgery and perioperative chemotherapy. Cytoreductive surgery, including peritonectomy procedures and visceral resections, has been used in a surgical effort to eradicate all visible disease from peritoneal surfaces and from the viscera. Peritonectomies are performed on demand; that is, only when there is visible disease on the peritoneal surface are these membranes stripped by electrosurgical dissection. Also, visceral resections are carried out as needed to clear the abdominal cavity from visible ovarian cancer. Retroperitoneal and pelvic lymphadenectomy are included to resect palpably involved lymph nodes. After all resections are completed and before any reconstructions, heat-augmented chemotherapy agents are administered in a large volume of chemotherapy solution. The heated intraoperative intraperitoneal chemotherapy (HIPEC) is administered with the goal of destroying microscopic residual disease and preventing cancer cell implantation. As a result of surgical trauma and visceral manipulation, extensive raw tissue surfaces are vulnerable to cancer cell adherence, implantation and progression. This chemotherapeutic cytoreduction is supplemented with the administration of early postoperative intraperitoneal chemotherapy (EPIC) using paclitaxel. EPIC is the use of an additional cell cycle-specific intraperitoneal chemotherapeutic agent during the first five days of the postoperative period.

The intraperitoneal route for administration of chemotherapy has been shown to improve progression-free survival and overall survival as compared to a systemic route in ovarian cancer patients.[9-11] However, a significant contrast exists between this experience and the comprehensive management discussed in this manuscript. As itemized in Table 1, the efficacy and the simplicity of intraperitoneal chemotherapy administration may be greatly augmented by a perioperative timing of the regional drug delivery. Nevertheless, these two intraperitoneal treatments are regarded as complimentary rather than competitive.

Table 1. Contrast of long-term intraperitoneal chemotherapy and perioperative intraperitoneal chemotherapy for ovarian cancer.

	Long-term intraperitoneal chemotherapy	Perioperative intraperitoneal chemotherapy
Multiple cycles possible	Yes	No
Limited distribution because of adhesions	Yes	No
Can be readily combined with hyperthermia	No	Yes
Uniform manual distribution of chemotherapy solution possible	No	Yes
Heat targeted systemic chemotherapy possible	No	Yes

Selection criteria and institutional requirements for a comprehensive treatment plan

Cytoreductive surgery and perioperative intraperitoneal chemotherapy represents an innovative strategy for treatment of ovarian malignancies, requiring a knowledgeable selection of patients, a strong commitment from the surgical team, and long-term institutional support.

Selection of patients is based on two well-defined criteria: ability of the patient to survive an extensive surgical procedure with acceptable morbidity and mortality and no evidence of clinical findings that would result in a futile surgical procedure with residual cancer present after a best surgical effort. Patients of advanced age, poor performance status, malnourished or with medical conditions that would decrease the likelihood of postoperative survival should not be selected for combined treatment. Also, patients with systemic metastases, two or more sites of bowel obstruction, common bile duct obstruction or bilateral ureteral obstruction should not be submitted to this comprehensive treatment.

This procedure requires dedication from an oncologic surgeon who must have broad surgical knowledge, a thorough understanding of intraperitoneal chemotherapy, unusual technical skills and the stamina to endure long procedures. Because these interventions are extensive and thereby costly, institutional backing is important. Early in the effort, Institutional Review Board approval is advised to protect the patients, the surgeons and the institution itself. An effort to educate other physicians involved in this treatment, as well as nurses and ancillary personnel, should occur. Standardized orders for chemotherapy

and a clear written clinical pathway will help to coordinate the actions of the clinical staff. The learning curve that accompanies a new program requires careful planning and frequent morbidity/mortality review on a regular basis.[12]

Quantitative prognostic indicators

The three assessments useful for patient selection in order to treat patients most likely to benefit are the prior surgical score (PSS), the peritoneal cancer index (PCI) and the completeness of cytoreduction score (CC).

The abdominopelvic regions are used to study in a quantitative manner factors that may control the outcome of peritoneal surface malignancy treatments (Figure 1). Two transverse planes and two sagittal planes are used to divide the abdomen into 9 abdomino-pelvic regions (AR 0-8). The upper transverse plane is located at the lowest aspect of the costal margin. The lower transverse plane is placed at the anterior superior iliac spine. The sagittal planes divide the abdomen into 3 equal sectors. These lines define nine regions, which are numbered in a clockwise direction with 0 at the umbilicus and 1 defining the space beneath the right hemidiaphragm. The anatomic structures that are associated with each of these 13 regions have been designated.

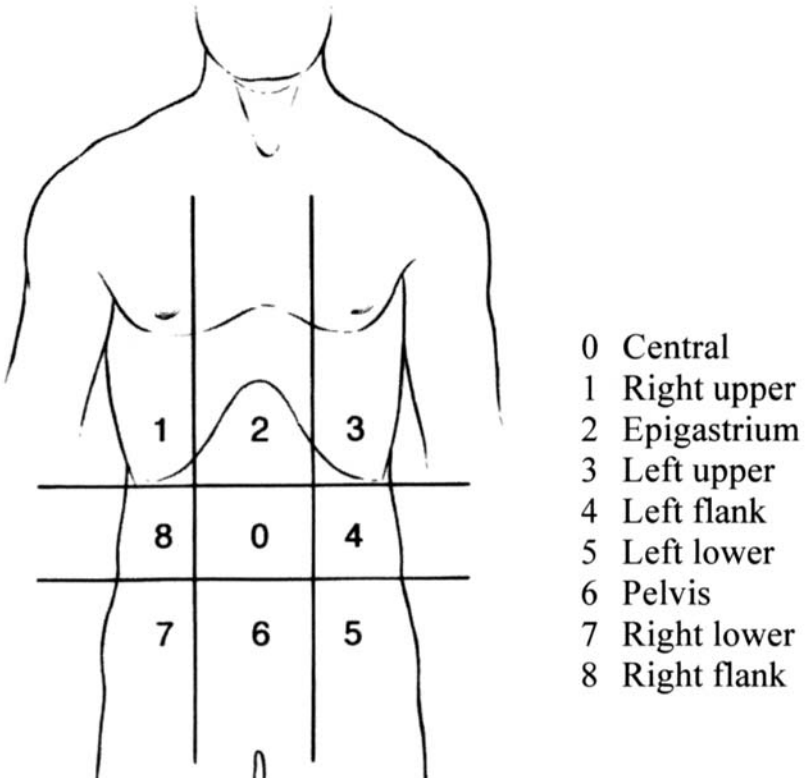

Figure 1. The abdomino-pelvic regions.

Prior surgical score

Surgical trauma promotes cancer cell implantation. Prior surgeries may modify the natural history of ovarian cancer by inducing cancer growth at crucial anatomic sites located beyond the peritoneal layer (e.g. ureters and pelvic sidewall). Complete cytoreduction may not be possible if tumor nodules are allowed to implant on vital structures. It is therefore very important to preoperatively assess the extent of prior surgeries before attempting a definitive cytoreductive surgery with perioperative intraperitoneal chemotherapy. The prior surgical score (PSS) uses abdominopelvic regions 0-8 to create an important quantitative prognostic indicator. Patients with no prior abdominopelvic surgery or biopsy only received a PSS of 0, those with up to one abdominopelvic region dissected received a PSS of 1, those with two to five abdominopelvic regions received a PSS of 2 and those with six or more regions dissected received a PSS of 3. Look and colleagues showed that patients who had a PSS of 3 or higher had a significantly reduced survival than those patients with a PSS of 0, 1 or 2.[13]

Peritoneal cancer index

The peritoneal cancer index (PCI) is a quantitative prognostic indicator that is useful for patient selection for the *Comprehensive Approach.* The PCI is determined after abdominal exploration and complete separation of intestinal adhesions. This index combines a size and a distribution parameter to achieve a numerical score. The lesion size score (LS) is used to quantitate the size of peritoneal nodules. LS-0 indicates no tumor seen, LS-1 indicates tumor implants up to 0.5 cm, LS-2 indicates tumor implants between 0.5 cm and 5 cm. LS-3 indicates tumor implants larger than 5 cm or a layering of cancer. The distribution of tumor is determined in the thirteen abdominopelvic regions. In contrast to the PSS, the small bowel is assessed as an additional four abdominopelvic regions, designated AR-9 to AR-12 and includes the upper jejunum, lower jejunum, upper ileum and lower ileum respectively. The summation of the lesion size score in each of the 13 abdominopelvic regions is the peritoneal cancer index (PCI), ranging from 0 to 39 (Figure 2). As discussed later in this manuscript the PCI provides a useful guideline that helps direct the surgeon toward comprehensive treatment when the score is low. A high score would suggest a minimal palliative intervention.

Completeness of cytoreduction score

Completeness of cytoreduction (CC) is a quantitative prognostic indicator determined after the surgical resection has been completed. A patient receives a CC-0 score when no visible peritoneal carcinomatosis remains

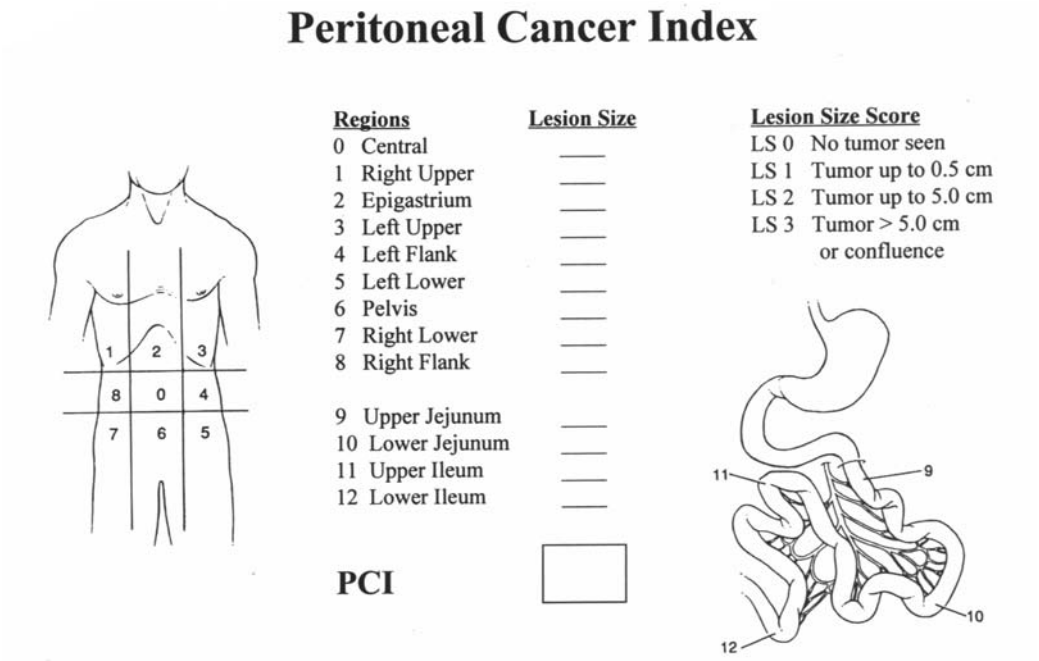

Figure 2. Peritoneal cancer index (PCI). The score is a summation of cancer implant lesion size (scored 0 to 3) present in 13 abdominopelvic regions. (From Esquivel J, Sugarbaker PH: Elective surgery in recurrent colon cancer with peritoneal seeding: When to and when not to proceed. Cancer Therapeutics 1998; 1:321-325).

after cytoreduction. CC-1 is recorded when tumor nodules persist after cytoreduction but they measure less than 0.25 cm. CC-2 indicates that residual tumor nodules measure between 0.25 to 2.5 cm. When tumor nodules are greater than 2.5 cm or there is confluence of unresectable tumor, a CC-3 score is given. Several prior studies in ovarian cancer have shown that the size of the cancer nodules remaining after cytoreduction is directly related to the survival. The smaller the residual nodules, the greater the likelihood of a long-term survival.[14,15] By a “log-kill” hypothesis one would predict this observation to be true.

Surgical techniques used for a complete cytoreduction in selected patients

Patient preparation for surgery

Once a decision to proceed with surgery is made, before the surgical intervention the patient follows an exercise program that would improve aerobic capabilities and increase muscular mass. A routine bowel preparation is prescribed for the day prior to the surgery. Under general endotracheal anesthesia with adequate monitoring, the surgical team introduces a double-lumen central venous line for the purpose of both central venous pressure

monitoring and fluids administration. For the first five postoperative days this line will be used for administration of total parenteral nutrition. Both arms are placed in abduction and the back in extension. Sequential compression boots (SBC Compression Boots, Kendall Co., Ma.) are placed surrounding the calves for deep venous thrombosis prevention. The patient is placed in the lithotomy position using St. Mark's leg holders (AMSCO, Erie, Pa.) so that weight of the leg is held by the heels and not by the calves.[16] Because the surgical intervention lasts for 8 to 12 hours, it is extremely important to verify that the patient's position on the table is proper. Decubitus ulcers, nerve damage and compartment syndromes are common and must be avoided. Egg-crate foam padding for arms and legs are used to decrease the risk of these complications. The body temperature must be carefully monitored for low temperature from extensive exposure of viscera during the cytoreductive surgery and for high temperature during heated intraoperative intraperitoneal chemotherapy.

Antibiotics are administered in a prophylactic fashion during the surgery. The extent of the raw surface after peritonectomies increases the risk of postoperative hemorrhage precluding the use of heparin for deep vein thrombosis prophylaxis for the first four days after surgery. This prevention is limited to the sequential compression boots as described above during this time; heparin is used after bleeding and clotting tests have returned to normal.

Other requirements for a successful cytoreductive surgery are two suction tubes in the operative field, an electrosurgical unit capable of high voltage pure cut and spray coagulation modes, a 3-mm electrosurgical ball-tip, an electrosurgery tip extender, and at least one smoke evacuator. The temperatures at the electrosurgical dissection plane can be very high and result in heat damage to tubular structures. The second assistant or the scrub nurse frequently irrigates with room temperature normal saline solution. Frequent large volume irrigation is necessary when dissecting around tubular structures. The irrigation also keeps tissues free of debris and blood, thereby preserving tissue transparency. Residual saline solution in small volume promotes an efficient electrosurgical dissection.

Once the surgical field is properly prepared and draped, the Thompson self-retaining retractor's frame is placed (Thompson Surgical Instruments, Inc., Traverse City, Mi.). The surgeon may fasten suction tubes, electrosurgery cable, and smoke evacuator hoses to the Thompson retractor's frame.

Anterior parietal peritonectomy and complete abdominal exploration

In order to perform a full abdominal exploration a vertical median xipho-pubic incision is performed. The incision should always include the

umbilicus since, in cases of peritoneal carcinomatosis, this anatomic site is at a very high risk of cancer involvement. When patients desire preservation of the umbilicus for aesthetic reasons a plastic reconstruction can be accomplished.

The incised skin edges are elevated in a symmetrical manner by cutaneous traction sutures (Figure 3). The fascia is incised directly through the linea alba.[17] The posterior rectus sheath is dissected away from the underlying anterior parietal peritoneum towards the left and the right of the midline, initially in a centrifugal fashion. Once the dissection has progressed approximately 10 cm from midline to lateral, the Thompson retractor blades are placed so that they pull back the abdominal wall creating an angle between the peritoneum and the posterior rectus abdominis sheath (Figure 4). The initial centrifugal dissection continues laterally to the paracolic sulci. In the cephalic direction the resection includes the round and falciform ligaments but not the undersurface of the hemidiaphragms. In the caudal direction the anterior parietal peritoneum specimen is separated from the pelvic peritoneum at the dome of the bladder. The urachus is identified and elevated on a clamp. This will be the lead point for pelvic peritonectomy at a later time.

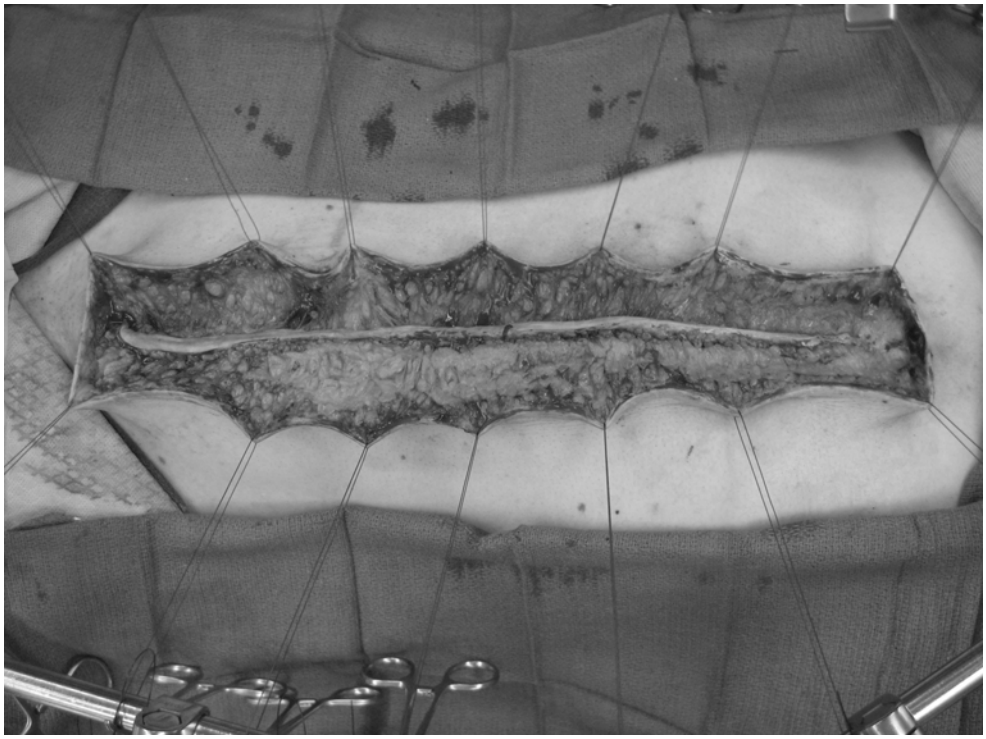

Figure 3. Cutaneous traction sutures are placed using a strong monofilament suture. The sutures are placed approximately every 8 cm along the skin edge. The traction sutures are secured to a self-retaining retractor using hemostats.

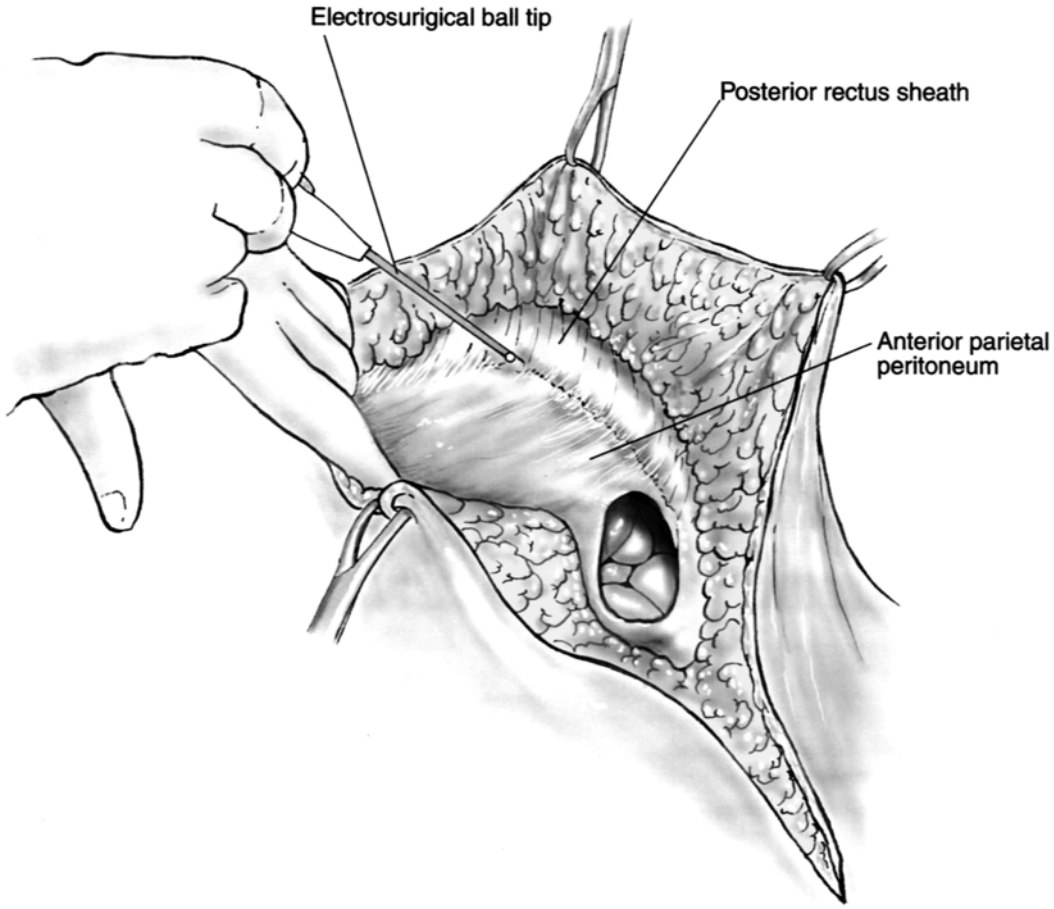

Figure 4. Anterior parietal peritonectomy.

Once the anterior parietal peritoneum specimen is removed, the surgeon can perform a complete abdominal exploration. This includes a lysis of all adhesions. At this time, the peritoneal cancer index (PCI) can be determined. The success of complete cytoreduction and long-term survival can be estimated by assessment of the distribution and the mass of peritoneal surface cancer.[18] The PCI has been established as a quantitative prognostic indicator for advanced ovarian cancer.[19]

Right and left subphrenic peritonectomies

The right subphrenic peritonectomy is a centripetal dissection that detaches the peritoneum with its layer of cancer from the undersurface of the right hemidiaphragm (Figure 5). It is also necessary to detach the peritoneum from the liver surface and to electroevaporate any disease from Glisson's capsule. In the retrohepatic space, the dissection extends centripetally to the inferior vena cava. The peritoneum covering the perirenal fat and the right adrenal gland is also detached from the postero-inferior edge of the liver.

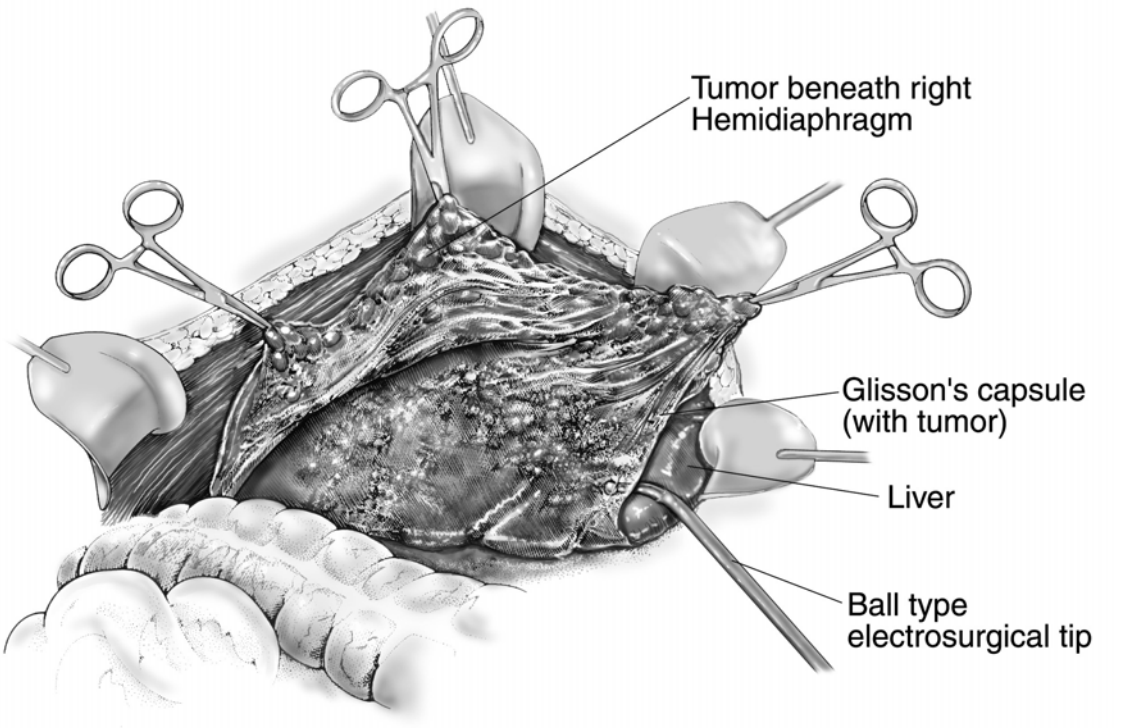

Figure 5. Right upper quadrant peritonectomy.

The duodenum and the porta hepatis constitute the medial border of the right subphrenic peritonectomy.

Also as a centripetal dissection, the left subphrenic peritonectomy includes the undersurface of the left hemidiaphragm. It requires separation of the left lobe of the liver from the triangular ligament that becomes a part of the peritonectomy specimen. Electroevaporation of tumor layering out on the left lobe Glissons's capsule is required. This dissection liberates the spleen, which at this point in time remains attached to its pedicle, to the greater omentum, and to the lienocolic ligament.

The surgeon must avoid penetrating the pleural cavity because that will allow cancer dissemination within the thoracic cavity. In case of chest penetration through the diaphragm, the heated intraoperative intraperitoneal chemotherapy should be allowed to enter the chest cavity by enlarging the diaphragmatic incision to prevent pleural implantation. The closure of the diaphragm should take place after the HIPEC is completed.

Greater omentectomy and splenectomy

The greater omentum is elevated under strong traction as it is detached from the transverse colon along with the visceral peritoneum that covers the anterior aspect of the transverse mesocolon mesentery. The right gastroepiploic

artery is ligated in continuity and all the small gastroepiploic branches on the greater curvature are also individually ligated as they reach the stomach. The short gastric vessels are also ligated and divided. At this point it is necessary to carefully evaluate the splenic hilum which is prominent site for cancer deposits. If the spleen or its hilum appear to be involved, the splenic artery and veins are individually ligated. In order to complete the greater omentectomy the left gastroepiploic vessels are ligated in continuity and divided.

In all of the left upper quadrant dissection the pancreas needs to be protected from trauma especially when dissecting the splenic vessels.

Cholecystectomy, lesser omentectomy and stripping of the omental bursa

The most dependent part of the omental bursa is the space behind the pylorus, called the “retropyloric space.” This is a common site in which tumor accumulation takes place. Since the vessels along the greater curvature of the stomach have been divided, the blood supply for the stomach is limited to the right and left gastric arteries. With these crucial concepts in mind the surgeon can continue with the next step. The lesser omentectomy is a circular dissection that starts with a cholecystectomy and dissection of the anterior and posterior aspect of the hepatoduodenal ligament. The gastrohepatic ligament is divided at the peritoneal reflection along the gastrohepatic fissure between the left lateral liver segment and the caudate lobe. An accessory left hepatic artery may occur in the mid-portion of this ligament. After confirmation that the main left hepatic artery is intact, the accessory left hepatic artery can be ligated. The surgical dissection continues at the crus of the diaphragms. In order to protect and preserve the vessels of the lesser curvature (only remaining blood supply to the stomach after the greater omentectomy), the lesser omental fat and adherent tumor is crushed between the thumb and index fingers. This digital dissection exposes the network of vessels between the right and left gastric arteries and therefore the surgeon can resect the lesser omental adipose tissue along with tumor without damage to the vascular arcade.

The last portion of the lesser omental dissection is the stripping of the floor of the omental bursa. The peritoneum is divided at the reflection between the caudate lobe and the left side of the inferior vena cava. Then dissecting in a cephalic direction, the peritoneum covering the right diaphragmatic crus is elevated. The peritoneum can then be bluntly stripped by pulling it in a caudal and external direction. Once it is stripped down to the superior edge of the pancreas, the peritoneum can be incised, keeping in mind the close proximity of the left gastric artery and lymph nodes of the common hepatic artery.

Pelvic peritonectomy

The stripping of the pelvic peritoneum includes the cul-de-sac. Before starting the dissection the surgeon must evaluate tumor involvement of the sigmoid colon and rectum. The epiploic appendages contain a large amount of lymphoid aggregates, which have great absorptive capabilities similar to those of the greater omentum, making it possible that these appendages may require resection. Also, tumor cells accumulate by gravity at dependent sites. This and the fact that the peritoneal cul-de-sac is intimately attached to the rectum frequently make it impossible for the surgeon to make the patient disease-free without a rectosigmoid resection along with the pelvic peritonectomy.

The centripetal dissection for the pelvic peritonectomy starts with the creation of an anterior flap of peritoneum by separating it from the bladder. The posterior peritoneal flap starts at the ligament of Treitz. There, the posterior parietal peritoneum is separated from the fourth portion of duodenum, the inferior mesenteric vein is ligated in continuity, and the dissection progresses medially separating the peritoneum from the third portion of the duodenum. The stripping proceeds caudally as the sigmoid colon is divided by a linear stapler and the inferior mesenteric artery is ligated and divided. Both ovarian veins are ligated and divided at the level of the inferior border of the perirenal fat. Left and right ureters are identified in the abdomen as peritoneal stripping continues towards the pelvis. The centripetal dissection joins the anterior and posterior flaps. The anterior pelvic peritonectomy proceeds to go across the vagina reaching the anterior aspect of the rectum by elevating the *cul-de-sac.* Laterally, the uterine arteries are ligated lateral to the ureters and the vagina is incised. The dissection meets the lateral aspect of the rectum below the peritoneal *cul-de-sac.* Once the circumferential electroevaporation has freed up the rectum, the organ is divided across the mid-rectum with a linear stapler. The specimen of pelvic peritonectomy contains the pelvic peritoneum, the sigmoid and the upper portion of the rectum, and if they had not been extirpated before, the uterus and both ovaries.

Heated intraperitoneal chemotherapy (HIPEC) and early postoperative intraperitoneal chemotherapy (EPIC)

After the cytoreductive surgeries with peritonectomies have been completed, the chemotherapy washing of the abdomen is performed. Even if a CC-0 score is determined, it is invariably true that invisible to the naked eye, cancer cells remain within the peritoneal cavity. Tumor manipulation,

transected lymphatic ducts leaking tumor cells throughout the procedure, and small tumor nodules remaining on the abdominal and pelvic surfaces of organs not amenable to peritonectomy procedures, namely small bowel, require the implementation of some method that will cytoreduce residual tumor cells. The technique uses mechanical removal, chemical (chemotherapeutic killing) and physical killing of cancer cells. A well known site for persistent disease are the suture lines; they represent an ideal site for cancer cell implants. Tumor cell entrapment occurs on these raw surfaces with fibrin accumulating and tissues compressed together by stitches or staples. Suture lines are at high risk of recurrence if constructed before the intraperitoneal chemotherapy and therefore not directly treated for residual cancer cells.

HIPEC using an open technique employs mechanical, physical and chemical effects to further cytoreduce cancer cells after surgery. A mechanical effect to eradicate cancer cells trapped in fibrin and tissue debris takes place during 90 minutes of continuous rubbing and washing of the intraabdominal surfaces. Heat, a physical effect, promotes cell death by various mechanisms affecting nucleic acids, cell membranes and the cytoskeleton.[20] The target temperature within the peritoneal cavity is approximately 42°. Some chemotherapeutic agents such as mitomycin C, doxorubicin, cisplatin and melphalan among others, have their cell killing effect enhanced by heat creating a synergistic result.[21] Also, penetration of chemotherapy into tissues is augmented by heat.[22]

The intraperitoneal route of chemotherapy administration for carcinomatosis has another advantage. The concentration times time (area under the curve or AUC) of the cytotoxic agent in the peritoneal cavity is many times higher than that in the plasma compartment. The AUC ratio of peritoneal to plasma varies for different drugs, but it can be as high as 1,000 for paclitaxel, for example.[23] This feature of intraperitoneal chemotherapy with selected drugs makes possible high concentration of the agent where the disease is localized, enhancing the cell killing effect and decreasing the systemic toxicity. Ideally, the drug to be used should be active against ovarian cancer, non-toxic for non-cancer cells, of high molecular weight to cause a slow peritoneal clearance, and have a high penetration into tumor tissues.

Several drugs have been used for intraperitoneal irrigation for patients with ovarian cancer: cisplatin alone, carboplatin alone, mitoxantrone alone and cisplatin plus doxorubicin.[24-27] Our group has used a combination of cisplatin (50 mg/m^2) and doxorubicin (15 mg/m^2). Sugarbaker, after a dose escalation study, determined that a low dose of doxorubicin (15 mg/m^2) would result in a thin layering of fibrous tissue on peritoneal surfaces that has not been reported to interfere in any way with subsequent gastrointestinal function.[28]

There are multiple reasons to recommend doxorubicin as an intraperitoneal chemotherapy agent.[29] Perhaps most important, due to the large molecular size of this drug its clearance from the peritoneal cavity is greatly delayed. It is also known that its penetration is at least five cell layers making it appropriate for the elimination of small volume residual disease postoperatively. It is also augmented in its anticancer effects by heat.[22]

Cisplatin has been shown to have improved penetration into cancerous tissue when administered with heat as compared to normothermic conditions. The increase in cytotoxicity is estimated at 1.8 times.[30] Also, the peritoneum/plasma area under the curve ratio is favorable. These factors plus the activity of this drug both for primary and recurrent ovarian cancer has led to its frequent use by intraperitoneal administration.[31]

Technique for heated intraoperative intraperitoneal chemotherapy

An abdominopelvic reservoir is constructed by tenting up the skin edges to a specially designed instrument that allows hand distribution of the chemotherapy agent and total containment.[32] The double-gloved hand guarantees that the perfusate reaches particularly difficult places within the peritoneal cavity, such as the space between the bowel loops, the space behind the liver, and the rectal stump deep within the pelvic cavity.

In order to keep the temperature at a constant 42ºC, a roller pump forces the solution through a heat exchanger. Then it proceeds to that abdominopelvic cavity through a catheter. The hyperthermic perfusate is drained from the abdomen through drains going back to the heat exchanger, and closing the circuit. The inflow catheter and the closed suction drains are secured watertight with purse-string sutures on the skin of the abdomen to avoid leaks and spillage. The chemotherapy solution circulates for 90 minutes at 42ºC.

After the 90 minutes of HIPEC with manual distribution, the surgeon may assume that fibrin and tissue debris and the microscopic residual disease they contain have been eradicated. At this time, all the anastomosis and any additional reconstruction can occur. Closed-suction drains and an inflow catheter are properly positioned for subsequent EPIC.

In the first five postoperative days ovarian cancer patients receive EPIC. This involves normothermic intraperitoneal paclitaxel (20-40 mg/m^2/day). Systemic paclitaxel has been used to treat advanced ovarian cancer alone and in combination with other drugs. In phase III clinical trials the combination resulted in improved response rates and also improved survival.[33] The extremely favorable area under the curve ratio (1000) and the remarkable drug penetration of up to 80 cell layers deserve mention.[34]

Mohamed and colleagues studied the use of paclitaxel in 6% hetastarch as a carrier solution. The retention of the high molecular weight carrier solution

as compared to the salt solution in the abdominopelvic space improved the drug exposure to peritoneal surface cancer nodules without any increase in systemic toxicity.[35]

A potential problem with intraperitoneal paclitaxel is the lipid solvent and the fact that carcinogens can be leached out of soft plastic used to administer the infusions. Stuart and colleagues discussed the technical precautions that will minimize this potential hazard.[36]

In summary, HIPEC and EPIC combine mechanical, physical and chemical effects for continued tumor cell cytoreduction. They are used as a planned part of the surgical procedure and the postoperative care in the highly controlled environments of the operating room, surgical intensive care unit, and a specialized nursing unit.[34]

Results of comprehensive treatment in advanced primary and recurrent ovarian cancer treated at the Washington Cancer Institute

In patients who have failed the standard treatments of primary ovarian cancer the survival is short with an estimated median survival of 8 months.

Figure 6 shows the survival curve of 28 patients with advanced primary and recurrent epithelial ovarian cancer or papillary serous cancer. These patients had exhausted all conventional treatments for ovarian cancer. Median survival was 45.8 months. Further analysis of the clinical features that affected survival determined that extent of prior surgery (PSS), the peritoneal cancer index (PCI) and completeness of cytoreduction (CC) were factors significantly affecting survival.

Those patients with extensive prior surgery, that is with three or more abdominopelvic regions subjected to surgical dissection were less likely to receive a complete cytoreduction and their survival was significantly shorter.[13] Patients with a low prior surgical score (PSS 0 or 1: less than three abdominopelvic regions previously dissected) had a median survival of 6.5 years, compared to 1.5 years for those patients with a higher PSS ($p=0.001$)(Figure 7). Patients who had extensive disruption of peritoneal surfaces are not expected to receive maximal benefit from peritonectomy. These observations reported by Look and colleagues have not been previously published. In the past and prior to the utilization of our comprehensive management strategy one assumed that the more aggressive the surgical extirpation of ovarian cancer the greater the likelihood of a prolonged systemic chemotherapy benefit. These new data regarding prior surgical score show that other critical factors concern the survival of ovarian cancer patients when cytoreductive surgery plus perioperative intraperitoneal chemotherapy are directed at patients after standard therapy has failed.

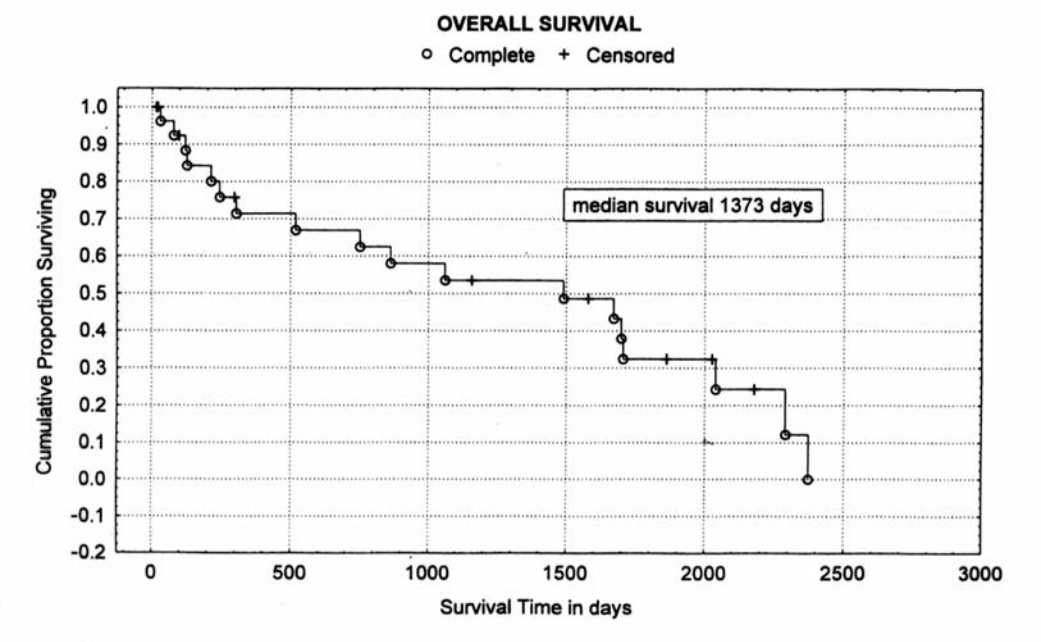

Figure 6. Overall survival of 28 patients with advanced primary or recurrent epithelial ovarian cancer or papillary serous cancer.

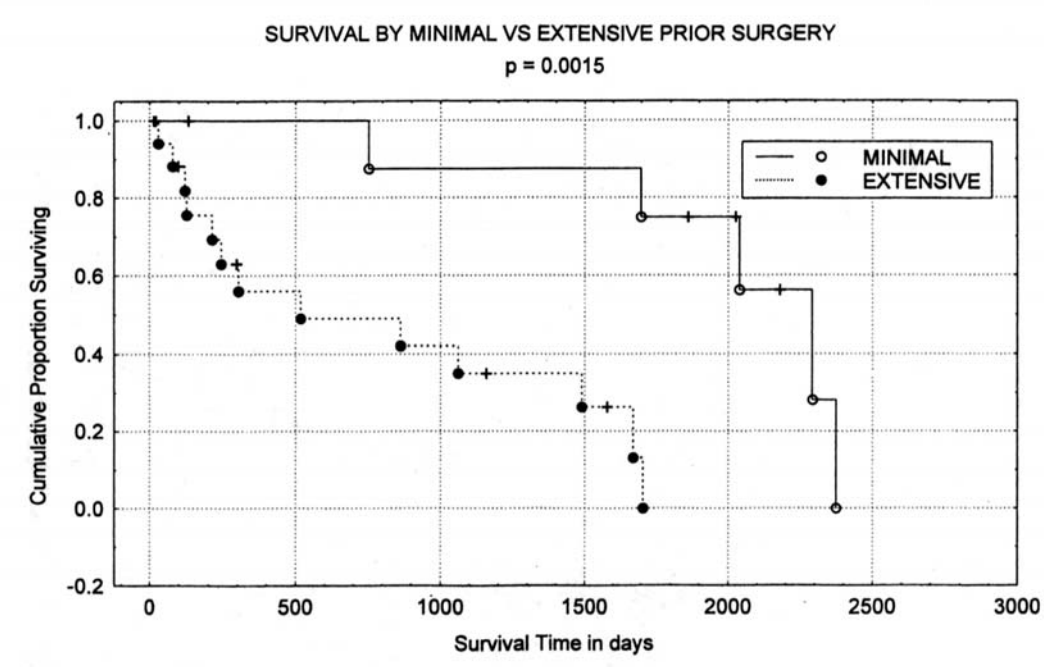

Figure 7. Survival of ovarian cancer by prior surgical score.

Tentes and colleagues reported on the PCI as a quantitative prognostic indicator in 60 women with ovarian cancer.[19] Those patients with a PCI lower than 10 had a median survival of 80 months and a 5-year survival of

65%, while those patients with a PCI greater than 10 had a median survival of 38 months and a 5-year survival rate of 29% (p=0.0253).

Look and colleagues studied the CC score as a prognostic indicator.[13] The results showed that a complete cytoreduction had a statistically significant improved survival (p=0.049)(Figure 8).

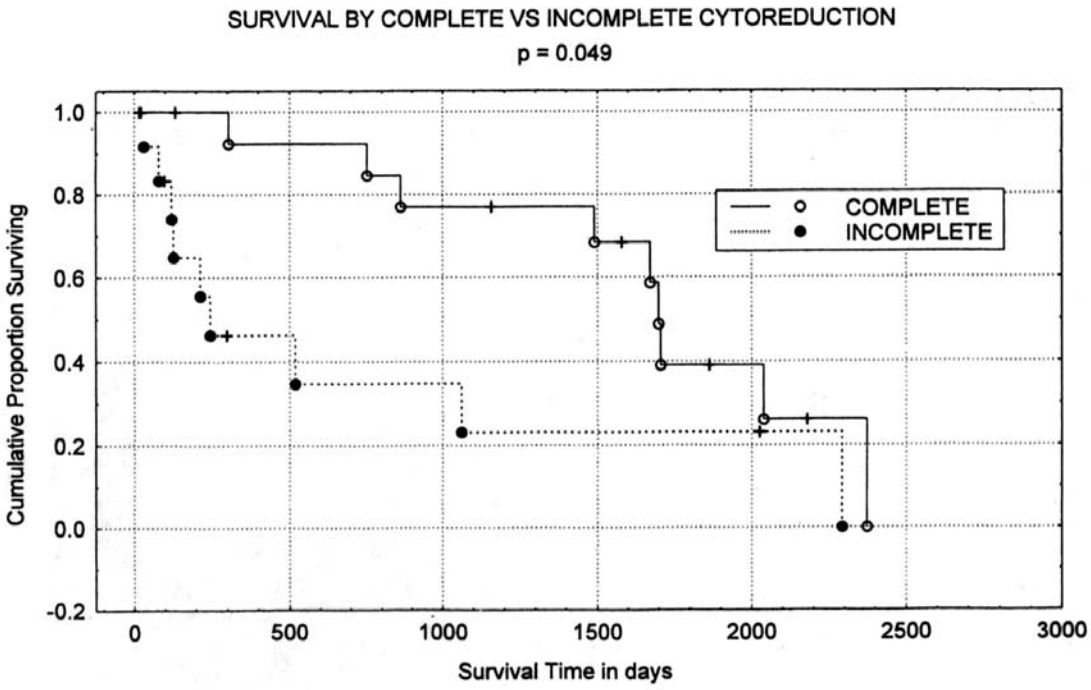

Figure 8. Survival of ovarian cancer by completeness of cytoreduction.

The peritoneum as a first line of defense against carcinomatosis

Our hypothesis regards the peritoneum as the human body's first line of defense against carcinomatosis. Whenever the peritoneum is violated by surgery, residual cancer cells are implanted and then progress beyond the peritoneum. In the abdomen or pelvis with a high prior surgical score, the peritonectomy becomes technically much more difficult and less likely to be complete. Also, tumor growth deep to the peritoneum at crucial anatomic sites increases the likelihood of severe complications; for example, ureteral and vascular injuries will occur more frequently during the cytoreductive surgery and intestinal fistulas occur more often in the postoperative period.

In summary, in all surgery for ovarian cancer involving stripping of peritoneal surfaces there is a high likelihood of malignant seeding deep to the peritoneum. Based on the data from prior surgical score an attempt should be

made at eradicating all tumor to prevent further cancer cell contamination of raw abdominal and pelvic surfaces. This approach employs proper “respect for the peritoneum” in patients with carcinomatosis. Complete cytoreduction and intraperitoneal chemotherapy is an essential part of the strategy to use to achieve that goal.

Morbidity and mortality

The combination of cytoreductive surgery and perioperative intraperitoneal chemotherapy as previously described is associated with a 30% morbidity and 2% mortality.[37,38] The typical postoperative course for these patients implicates an average 21-day hospital stay. They usually have a prolonged ileus lasting for 10 to 14 days. Nasogastric suction is sustained until the bowel function is recovered. These patients need total parenteral nutrition until intestinal function has returned. After the nasogastric tube is withdrawn oral nutrition is gradually restarted. The most common complications are central line infections, pancreatitis and intestinal fistulas. Anastomotic leak rate is 2%. Mortality was often associated with septic neutropenia and cardiovascular events.

Summary

These new concepts regarding the management of the peritoneal surface component of ovarian cancer suggest some major modifications in the surgery for primary disease. First, debulking surgery to resect the ovaries and tubes and greater omentum if it is involved by a large mass of tumor is indicated. This surgery is necessary to achieve an accurate diagnosis and debulk cancer that is easily accessible. By the log-kill hypothesis it may assist in a beneficial systemic chemotherapy response. However, no attempt at aggressive surgical debulking is indicated unless complete cytoreduction to a state of no visible evidence of disease is considered likely. Unless cytoreduction is complete no deeply invasive dissections should occur. Hysterectomy is not indicated. Pelvic peritoneal stripping with or without rectosigmoid colon resection is not indicated. Small or large bowel surgery should only be performed if there is established or impending intestinal obstruction. Retroperitoneal or pelvic sidewall lymph node dissections are contraindicated. Only enlarged lymph nodes should be biopsied and not resected. Following this minimally aggressive primary cancer surgery the most aggressive systemic chemotherapy is necessary.

In those patients who show stable disease or an objective response, our combined treatment should be initiated 6 to 8 weeks after the completion of

systemic chemotherapy. Response must be monitored by CT of chest, abdomen and pelvis and by tumor markers. The patient should be required to vigorously pursue a period of physical conditioning to optimize their recovery from a major intervention of both surgery and perioperative intraperitoneal chemotherapy.

In a physically fit patient who has shown control of a cancer mass as a result of systemic chemotherapy, the comprehensive approach may be considered with curative intent. The goal of the cytoreductive surgery with peritonectomy is complete visible removal of all ovarian cancer. The goal of the perioperative intraperitoneal chemotherapy is to cytoreduce microscopic residual disease, especially small cancer nodules that cannot be completely resected from the small bowel surface.

In approximately one-third of these patients an ostomy may be required to protect a low colorectal anastomosis. If this is required the patient returns after full recovery for an ostomy closure. This third intervention may be used as a third look/ostomy closure and additional cytoreduction and additional perioperative intraperitoneal chemotherapy is appropriate if small volume persistent disease is documented.

This highly specialized treatment needs to be performed by qualified surgeons who are knowledgeable about intraperitoneal chemotherapy toxicity as well as the complications of this aggressive surgical approach. Accepting the fact that a systematic review supports this management strategy, the results with this comprehensive treatment are encouraging for ovarian cancer.[39] A large phase II prospective multiinstitutional study would be needed to validate these results and a phase III study may be required in the future.

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