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Combined Cytoreductive Surgery and Perioperative Intraperitoneal Chemotherapy for the Treatment of Advanced Ovarian Cancer

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1. Introduction

Ovarian cancer is the leading cause of death from gynecologic cancer and the fifth cause of cancer deaths in women in developed countries (Yancik, 1993; Cannistra, 1993). The number of deaths seems to increase the last few years. More than 70% of the patients with ovarian cancer have advanced disease at the time of initial diagnosis because they remain asymptomatic in early stages (Roberts, 1996). Ovarian cancer is the most frequent intraceolomic malignancy presenting with peritoneal spread. In the past debulking surgery combined with systemic chemotherapy offered long-term survival in less than 10% of the patients (Smith & Day, 1979). The standard treatment of advanced ovarian cancer is cytoreductive surgery followed by systemic chemotherapy (Hacker et al, 1983; Neijt et al, 1991; Hoskins et al, 1992). Despite systemic chemotherapy based on platinum and taxanes 5 and 10-year survival rate do not exceed 20% and 10% respectively because the majority of the patients develop recurrence (Mc Guire & Ozols, 1998; Piccart et al, 2000). The disease remains characteristically confined to the peritoneal surfaces for most of its natural course (Bergmann, 1996). Surgical resection of the tumor may not be complete and microscopic or even macroscopic residual tumor may be left behind. In these situations the intraperitoneal route of administration of cytostatic drugs is a logical approach.

Patients with diseases that have similar biological behavior to ovarian cancer are offered significant survival benefit when they are treated with perioperative intraperitoneal chemotherapy integrated in cytoreductive surgery. In pseudomyxoma peritonei (Sugarbaker, 2006), peritoneal sarcomatosis (Rossi et al, 2004), peritoneal mesothelioma (Yan et al, 2007), colorectal cancer with peritoneal dissemination (Elias et al, 2009; Mahteme et al, 2004; Verwaal et al, 2008), as well as in gastric cancer with peritoneal carcinomatosis (Yonemura et al, 1996; Yu et al, 1998) survival is improved with this treatment strategy. The last two decades the method has been used in ovarian cancer with promising results.

2. Prognostic indicators of advanced ovarian cancer

2.1 Peritoneal Cancer Index (PCI)

The clinical utility of the FIGO staging system has been well established since its first report in 1964 (Odicino et al, 2001) but does not provide clear details about the extent and distribution of the peritoneal spread.

In contrast the peritoneal cancer index is a useful clinical variable by which the evaluation of the extent and distribution of the peritoneal malignancy is clear and accurate and has been continuously used in pseudomyxoma peritonei (Sugarbaker, 2006), peritoneal mesothelioma (Yan et al, 2007), colorectal cancer with peritoneal dissemination (Elias, 2001; Sugarbaker, 1999; Gomez-Portilla et al, 1999), and peritoneal sarcomatosis (Rossi et al, 2004; Esquivel & Sugarbaker, 1998).

The calculation of the peritoneal cancer index is possible with the division of the abdomen and pelvis in 13 different regions (Figure 1). Two transverse and two sagittal planes are used to divide the abdomen and pelvis in nine regions. The upper transverse plane is the lowest part of the costal margin and the lower plane is the anterior superior iliac spine. The sagittal planes divide the abdomen in three equal sectors. The abdominopelvic region 0 (AR-0) includes the midline incision, the greater omentum and the transverse colon. The abdominopelvic region 1 (AR-1) includes the superior surface of the right lobe of the liver, the undersurface of the right hemidiaphragm, and the right retrohepatic space. The epigastric fat, the left lobe of the liver, the lesser omentum and the falciform ligament are included in the abdominopelvic region 2 (AR-2). The abdominopelvic region 3 (AR-3) includes the undersurface of the left hemidiaphragm, the spleen, the tail of the pancreas, as well as the anterior and posterior surface of the stomach. The descending colon and the left abdominal gutter are included in abdominopelvic region 4 (AR-4). The left pelvic side wall and the sigmoid colon are included in the abdominopelvic region 5 (AR-5). The abdominopelvic region 6 (AR-6) includes the internal female genitalia, the cul-de-sac of Douglas, and the rectosigmoid colon. The abdominopelvic region 7 (AR-7) includes the right pelvic side wall, the base of the cecum, and the appendix. The abdominopelvic region 8 (AR-8) includes the ascending colon and the right paracolic gutter. The small bowel and its mesentery are divided in four additional regions in upper jejunum (AR-9), lower jejunum (AR-10), upper ileum (AR-11), and lower ileum (AR-12). The peritoneal cancer index is the summation of the tumor volume in each one of the 13 different regions in which the abdomen and the pelvis are divided.

Although the inclusion of the anatomic structures in the abdominopelvic regions is arbitrary the assessment of the distribution and extent of the peritoneal dissemination is detailed.

2.2 Tumor volume

The tumor volume is assessed as LS-0 (lesion size) when no visible tumor is detected, as LS-1 when tumor nodules are < 0.5 cm in their largest diameter, as LS-2 when tumor nodules are 0.5-5 cm in their largest diameter, and as LS-3 when tumor nodules are > 5 cm in their largest diameter, or there are confluent any size nodules. LS-0, LS-1, and LS-2 are considered small volume tumors, and LS-3 large volume tumors (Figure 1) (Jacquet & Sugarbaker, 1996).

The tumor volume is a significant prognostic indicator of survival in advanced ovarian cancer (Tentes et al, 2003; Piso et al, 2004; Raspagliesi et al; 2006, Di Giorgio et al, 2008).

The extent of peritoneal dissemination in ovarian cancer may also be assessed with the use of the Lyon staging system, and the Dutch simplified peritoneal carcinomatosis index (SPCI) (Gilly et al, 2006). The assessment of the extent and distribution of peritoneal carcinomatosis using anyone of the above staging systems is helpful in excluding from surgery those patients who are not expected to be offered any benefit from cytoreductive surgery.

In patients with high-grade tumors and high PCI complete cytoreduction is not feasible. In contrast, patients with low-grade tumors such as pseudomyxoma peritonei, grade I sarcoma and cystic peritoneal mesothelioma may easily undergo complete cytoreduction even if they have very high PCI. Therefore, in these situations the prognosis is related only to the completeness of cytoreduction. In addition, in very aggressive high grade tumors such as unresectable common bile duct cancer or unresectable cancer of the head of the pancreas the peritoneal cancer index is of no prognostic significance, even if it is low. In addition, the lymph node involvement in groups of lymph nodes that have no anatomic relation to the primary tumor the prognosis is poor despite a low PCI, because the favorable PCI is overridden by the systemic disease.

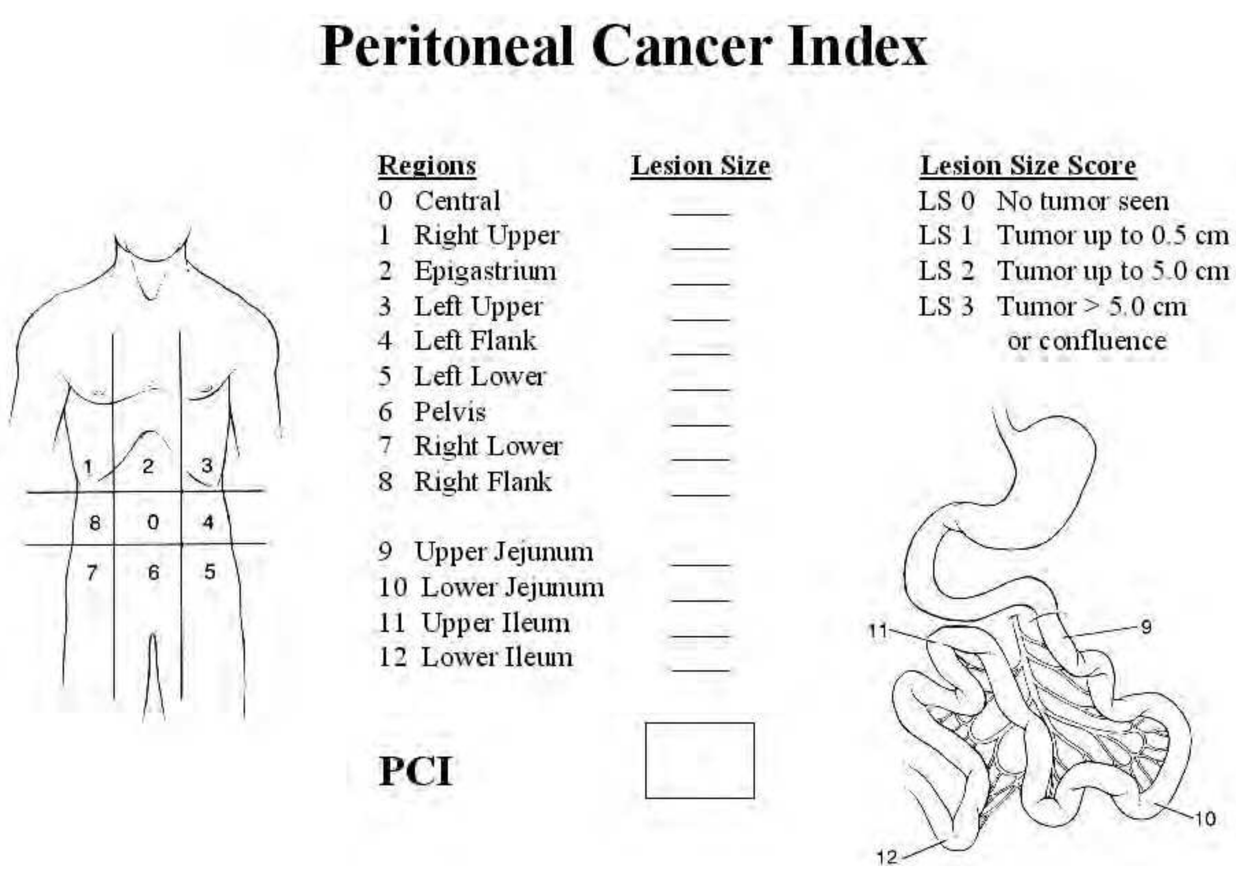

Fig. 1. Assessment of PCI by summation of the lesion size in the 13 regions in which the abdomen and pelvis are divided.

2.3 Prior Surgical Score (PSS)

Prior surgical score is a useful prognostic indicator of survival for patients with peritoneal malignancy. If surgery has not been performed or only biopsy or laparoscopy has been performed then the score is 0 (PSS-0). In patients that have undergone surgery in one abdominopelvic region the score is 1 (PSS-1). For those patients that have undergone surgery in 2-5 abdominopelvic regions the score is 2 (PSS-2) and for those patients that have undergone surgery in > 5 abdominopelvic regions the score is 3 (PSS-3) (Jacquet & Sugarbaker, 1996).

Prior surgical score is a significant prognostic indicator of survival in peritoneal sarcomatosis, appendiceal cancer, and peritoneal mesothelioma (Rossi et al, 2004; Jacquet & Sugarbaker, 1996; Sebbag et al, 2000). The significance of PSS has been questioned by other studies for pseudomyxoma peritonei and peritoneal mesothelioma (Brigand et al, 2006; Deraco et al, 2006; Miner et al, 2005; Baratti et al, 2007). In ovarian cancer PSS has been identified as a significant prognostic indicator of survival in one study (Look et al, 2004). The value of PSS in ovarian cancer is currently under investigation.

2.4 Completeness of cytoreduction score

In ovarian cancer the residual tumor is the most significant indicator for long-term survival (Hacker et al, 1983; Neijt et al, 1991; Hoskins et al, 1992; Eisenkop et al, 2003; Hunter et al, 1992; Bristow et al, 2002; Tentes et al, 2006; Piso et al, 2004; Raspagliesi et al, 2006; Di Giorgio et al, 2008; Look et al, 2004). Gynecologists oncologists use the terms optimal and suboptimal cytoreduction to define the quality of the surgical result. The level of optimal cytoreduction has been arbitrarily set from 5 mm to 3 cm. The Gynecologic Oncology Group has shown that survival progressively decreases as the residual tumor increases from microscopic to 2 cm (Hoskins et al, 1994). As a consequence optimal cytoreduction is defined as the operation with no macroscopic residual disease. Survival is not improved if the residual tumor is more than 2 cm in its largest diameter and these patients do not survive longer than patients with 10 cm residual disease, which means that aggressive surgery such as bowel resection is not indicated if the residual tumor can not be less than 2 cm (Hoskins et al, 1994).

The completeness of cytoreduction is a different approach to residual disease. For gastrointestinal cancer the completeness of cytoreduction score is defined as CC-0 if no macroscopically tumor is left after cytoreductive surgery, as CC-1 if nodules less than 2.5 mm are left after surgery, as CC-2 if the residual nodules are > 2.5 mm and < 2.5 cm, and as CC-3 if tumor nodules > 2.5 cm or a confluence of tumor nodules in the abdomen or in the pelvis are left behind after cytoreductive surgery. For high-grade tumors only CC-0 surgery is considered to be complete cytoreductive surgery. For low-grade tumors CC-0 and CC-1 cytoreductions are considered complete cytoreductive operations.

The completeness of cytoreduction score is the most significant prognostic indicator of survival in patients with pseudomyxoma peritonei (Sugarbaker, 2006; Miner et al, 2005; Baratti et al, 2007) peritoneal mesothelioma (Yan et al 2007; Sebbag et al, 2000; Brigand et al, 2006; Deraco et al, 2006), colorectal cancer with peritoneal carcinomatosis (Sugarbaker, 1999; Gomez-Portilla et al, 1999) gastric cancer with peritoneal carcinomatosis (Yonemura et al, 2003), and peritoneal sarcomatosis (Rossi et al, 2004; Berthet et al, 1999).

The completeness of cytoreduction score in advanced ovarian cancer has been demonstrated to be a significant prognostic indicator of survival (Tentes et al, 2003; Tentes et al, 2006; Piso et al, 2004; Raspagliesi et al, 2006; Di Giorgio et al, 2008).

2.5 Performance status

Long-term survival in ovarian cancer is related to patient's performance status (Tentes et al, 2006). Patients with poor performance status can not tolerate extensive surgery such as cytoreductive surgery because of increased morbidity and hospital mortality. The preoperative performance status and the extent of the peritoneal carcinomatosis are prognostic indicators of hospital morbidity (Reuter et al, 2008)

3. Treatment of advanced ovarian cancer

3.1 Cytoreductive surgery-standard peritonectomy procedures

The most powerful tool in the treatment of the diseases that have already disseminated at the peritoneal surfaces is surgical resection of the macroscopically visible tumor. For this purpose standard peritonectomy procedures have been used. The initially described six peritonectomy procedures (Sugarbaker, 1995) have recently been modified to the: 1) epigastric peritonectomy, 2) right subdiaphragmatic peritonectomy, 3)) left subdiaphragmatic peritonectomy, 4) greater omentectomy ± splenectomy 5) lesser omentectomy, 6) pelvic peritonectomy, 7) cholecystectomy and resection of the omental bursa, 8) right parietal peritonectomy, 9) left parietal peritonectomy, and 10) resection of other organs (antrectomy, colectomy other than low anterior, subtotal colectomy, total gastrectomy, segmental intestinal resection) (Sugarbaker, 1999).

In retrospective studies the residual tumor has been identified as the most significant prognostic indicator of survival (Hacker et al, 1983; Neijt et al, 1991; Hoskins et al, 1992; Eisenkop, 2003). Meta-analyses have documented the same finding (Hunter et al, 1992; Bristow et al, 2002) but no prospective trial has been performed. The feasibility of complete cytoreduction using standard peritonectomy procedures in ovarian cancer is 78.4% (Tentes et al, 2006; Chi et al, 2004).

3.1.1 Patient's position

The patient is placed in modified lithotomy position. This place provides access to the perineum. A hyperthermia blanket is placed on the operating table to warm the patient during surgery. A midline incision from xyphoid process to the symphysis pubis is used for maximal exposure of the abdominal cavity.

3.1.2 Epigastric peritonectomy procedure

Epigastric peritonectomy procedure is used in re-operations and includes wide resection of the old scar with the round and the falciform ligament of the liver. Sometimes resection of the xyphoid process is required for maximal exposure of the subdiaphragmatic areas.

3.1.3 Right subdiaphragmatic peritonectomy procedure

The peritoneum beneath the right hemidiaphragm is stripped until the bare area of the liver is encountered. If tumor has seeded the anterior surface of the liver then it is removed beneath or through the Glisson's capsule until the liver surface free of tumor is encountered. The tumor beneath the right hemidiaphragm, the right subhepatic space and the surface of the liver is removed en-bloc forming an envelope. Laterally on the right the dissection includes the peritoneum that covers the right perirenal fat as well as the anterior surface of the right adrenal. Eventually the vena cava, and the right hepatic vein form the base of the specimen (Figures 2, 3).

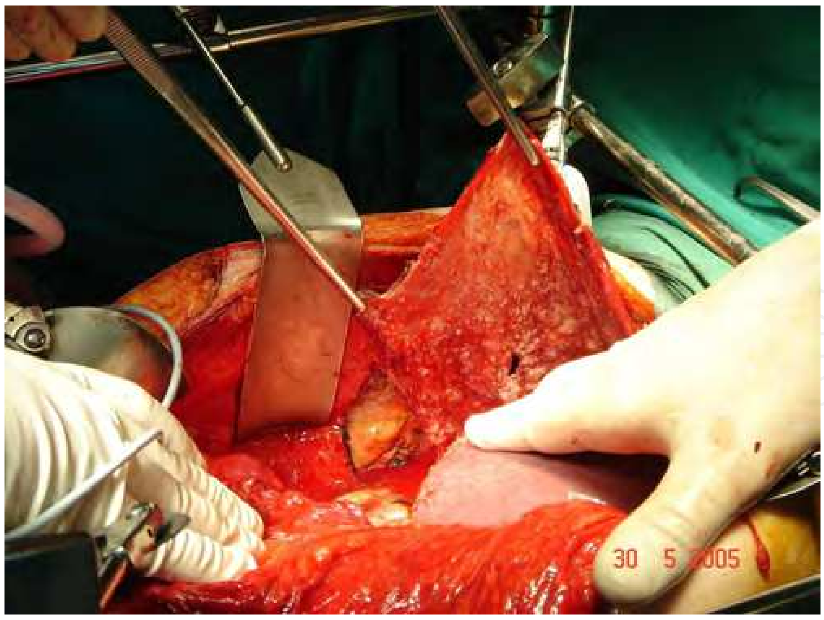

Fig. 2. The peritoneum beneath the right hemidiaphragm with the tumor, and the Glisson's capsule of the right lobe of the liver have been mobilized as an envelope and are ready for resection.

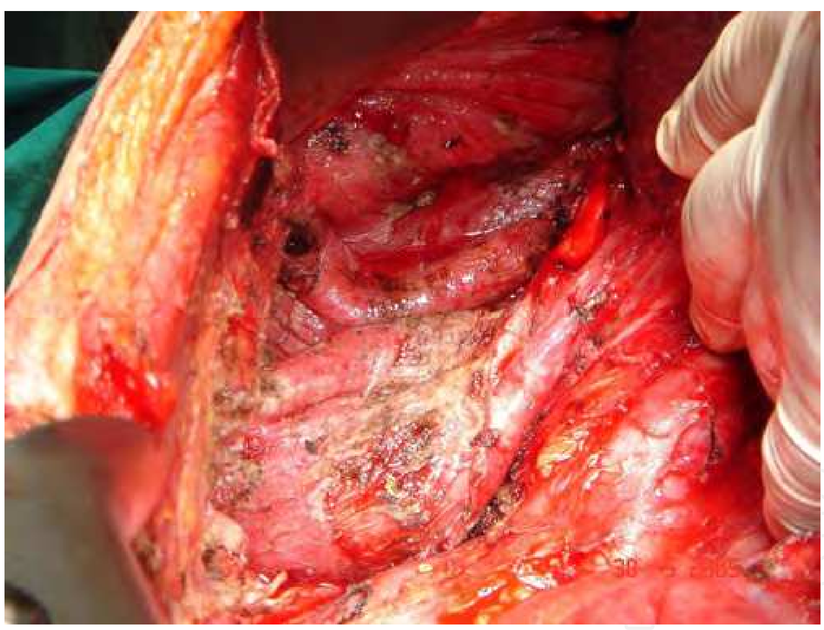

Fig. 3. Specimen of the right subdiaphragmatic peritonectomy procedure. The right lobe of the liver has been turned to the left. The muscular segment of the right hemidiaphragm is exposed free of tumor as well as the anterior surface of the right adrenal and the right kidney. The subhepatic inferior vena cava is visualized.

3.1.4 Left subdiaphragmatic peritonectomy procedure

All the tumor tissue beneath the left hemiaphragm is stripped until the muscular segment of the left hemiaphragm, the anterior surface of the left adrenal, the left kidney, and the tail of the pancreas are visualized free of tumor (Figure 4).

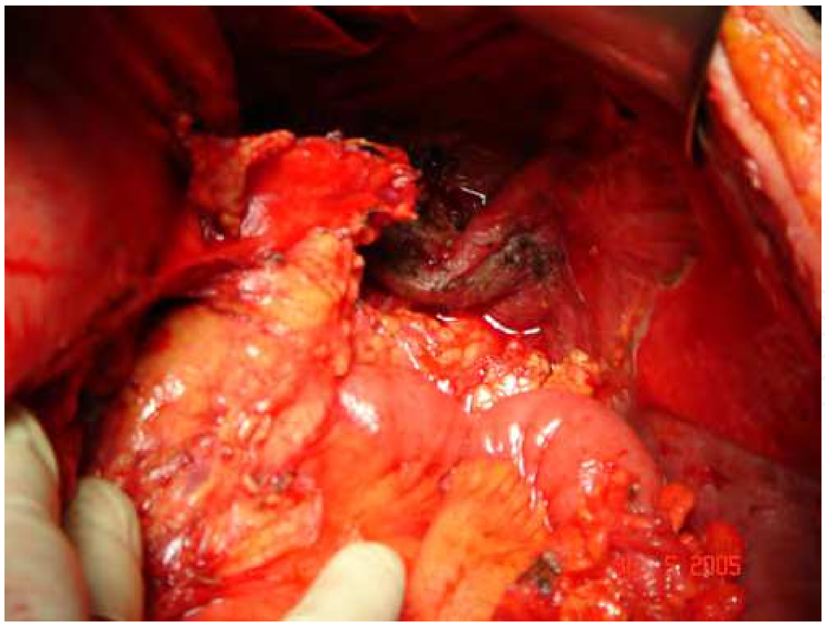

Fig. 4. Specimen of the left subdiaphragmatic peritonectomy procedure. The spleen has been removed. The tail of the pancreas, the undersurface of the left hemidiaphragm, the anterior surface of the left adrenal and the left kidney are exposed.

3.1.5 Greater omentectomy and splenectomy

The greater omentum dissected from the transverse colon and transverse mesocolon permits the exposure of the anterior surface of the body and tail of the pancreas. The branches of the right and left gastroepiploic vessels and the short splenic vessels on the greater curvature of the stomach are clamped and ligated. The splenic artery and vein at the tail of the pancreas are visualized, clamped, divided, and ligated. If the spleen is adherent by tumor of the left hemiaphragm then left subdiaphragmatic peritonectomy procedure must be completed before the spleen and the greater omentum are released (Figure 5, 6).

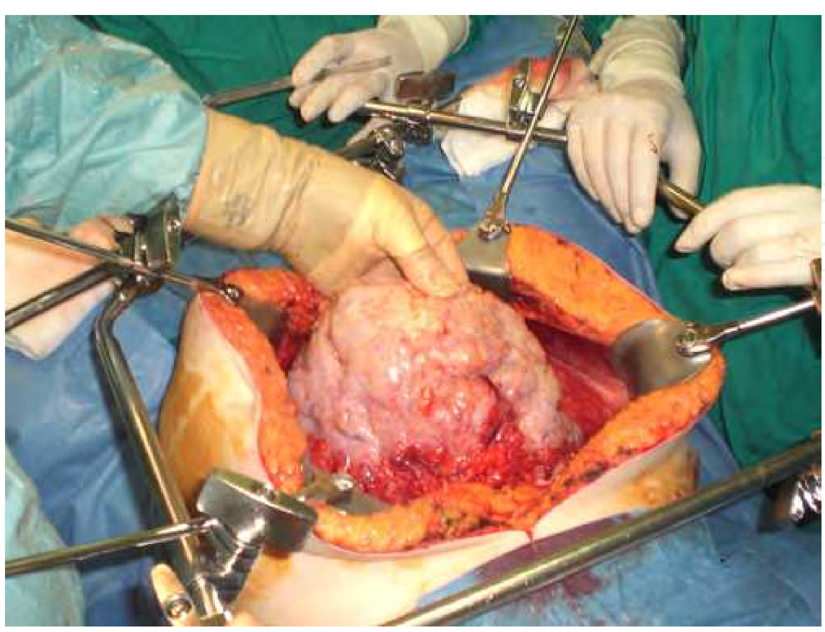

Fig. 5. Omental cake.

Fig. 6. The base of greater omentectomy and splenectomy (greater curvature of the stomach).

3.1.6 Cholecystectomy and resection of the omental bursa

The gallbladder is removed from its fundus toward the cystic artery and the cystic duct which are ligated, and divided. The anatomical structures of the hepatoduodenal ligament are skeletonized and the covering peritoneum is released. The peritoneum that covers the anterior surface of the inferior vena cava is stripped with the tumor that seeds the foramen of Winslow (Figure 7).

Fig. 7. The skeletonized hepatoduodenal ligament and the anterior surface of the inferior vena cava below the portal vein are exposed free of tumor.

3.1.7 Lesser omentectomy

The lesser omentum is released from the fissure between liver segments 1, 2, and 3, and from the arcade of the right to left gastric artery along the lesser curvature of the stomach.

The fat of the lesser omentum with the tumor are separated and released from the vascular arcade. The anterior vagus must be preserved as much as possible. An accessory left hepatic artery originating from the left gastric artery must also be preserved. After the release of the lesser omentum the complete resection of the omental bursa is possible by division of the peritoneal reflection of the liver to the left of the subhepatic vena cava which is stripped from the superior recess of the omental bursa, from the crus of the right hemidiaphragm, and from beneath the portal vein (Figure 8).

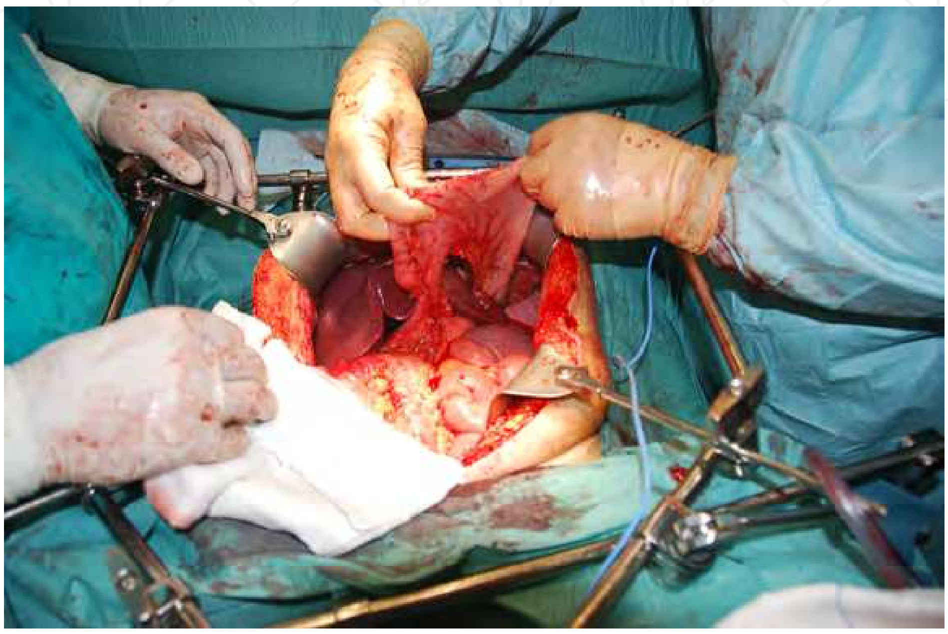

Fig. 8. The base of lesser omentectomy. The arcade of the right gastric and left gastric artery has been preserved.

3.1.8 Pelvic peritonectomy procedure

The peritoneum stripped from the posterior surface of the lower abdominal incision allows the exposure of the posterior muscular wall of the bladder. The urachus is identified, divided, and used for traction of the bladder. In female patients the round ligaments are divided at the point they enter the internal inguinal canal bilaterally. Superiorly the peritoneum is stripped to the duodenum and the ligament of Treitz. The ureters are identified and preserved. In females the ovarian veins are identified and ligated at the lower pole of the kidneys while in males the spermatic veins are preserved. The inferior mesenteric vein is identified and ligated. The inferior mesenteric artery is also identified and ligated just above its origin from the aorta. The colon is divided at the junction of the descending to sigmoid colon and this allows the complete separation of the upper and the lower abdomen. The mesorectum can be easily dissected with the use of a ball-tip electrocautery. The surgeon working in a centripetal fashion may free-up the entire pelvis. The uterine vessels are ligated and divided above the ureters and close to the base of the bladder. The bladder is freed from the cervix and the vagina is encountered. The vagina is divided, the perirectal fat is divided beneath the peritoneal reflection and the tumor occupying the cyl-de-sac of Doudlas is removed en-bloc with the specimen. The mid-rectum is skeletonized and divided (Figure 9).

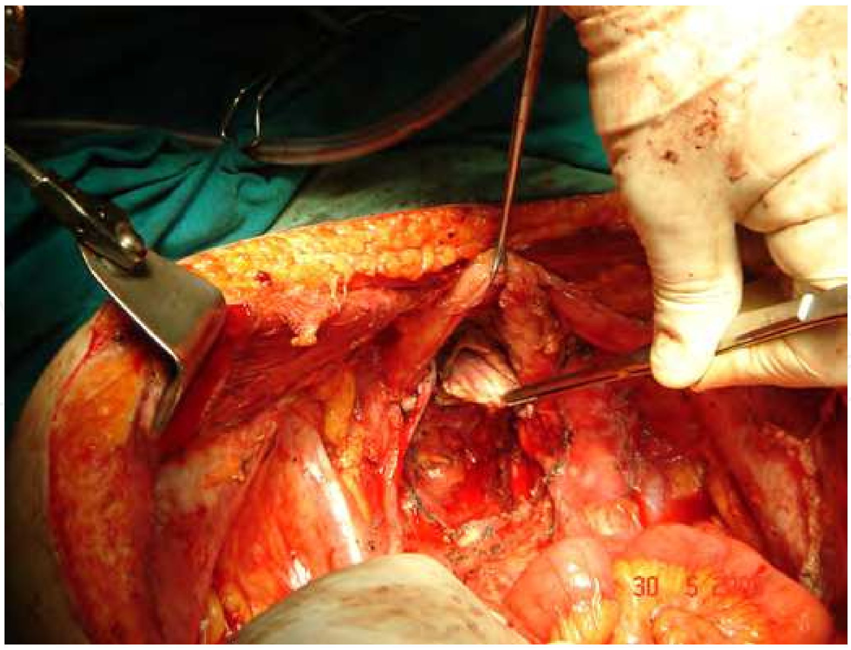

Fig. 9. The base of pelvic peritonectomy procedure. The vaginal stump has not been sutured and is visualized. The bladder is raised by a clamp. The ureters, the sacral bone, and the rectal stump are also visualized.

3.1.9 Bilateral lateral peritonectomy procedure

The peritoneum behind the rectus abdominal muscle is stripped and the base of the specimen is the posterior sheath of the rectus abdominal muscle and the posterior surface of the lateral abdominal muscles.

3.1.10 Resection of other organs

Antrectomy in addition to other peritonectomy procedures is required if the gastric antrum is seeded by tumor. Total gastrectomy is infrequently required in an attempt to achieve complete cytoreduction. Segmental intestinal resection or subtotal colectomy with end-ileostomy may also be performed in order to achieve complete or near complete cytoreduction (Stamou et al, 2003).

3.2 Perioperative intraperitoneal chemotherapy

Even if the macroscopically visible tumor has been completely removed after maximal cytoreductive surgery the microscopic residual tumor will possibly be present at the peritoneal surfaces. The disseminated cancer cells adhere to the peritoneal surfaces and are covered by fibrin, platelets, polymorphonuclear cells, and monocytes that infiltrate fibrin during the healing process. Growth factors released in large amounts stimulate fibroplast proliferation and local collagen production, eventually modulating wound healing promote cancer proliferation and give rise to secondary tumors within 2-3 years after initial surgery (Roberts & Sporn, 1989). In recurrent ovarian cancer it has been demonstrated that in 90% of the patients tumor is found in the vaginal cuff and in 60% tumor is found in the lower part of the abdominal incision (Sugarbaker TA et al, 1996).
The concept about the use of intraperitoneal chemotherapy is based upon the properties of the peritoneal-plasma barrier. Peritoneal plasma barrier is an anatomical and functional

structure. It is consisted by the fluid in the abdominal cavity, the mesothelium, the intervening interstitium, and the blood vessel wall (Jacquet et al, 1994; Sugarbaker, 1991). Most of the cytostatic drugs are large molecular weight substances that are confined for long at the peritoneal surfaces and exert intensively their pharmacologic properties before their absorption into the systemic circulation.
The penetration of intraperitoneal chemotherapy is limited to approximately 1-2 mm into tissues and may result in the eradication of the microscopic residual tumor.

3.2.1 Hyperthermic Intraperitoneal Intraoperative Chemotherapy (HIPEC)

Hyperthermic intraperitoneal intraoperative chemotherapy (HIPEC) enhances cytotoxicity and improves drug penetration. The heat itself has antitumor properties. If HIPEC is performed with the open abdominal technique (Coliseum technique) the surgeon may distribute uniformly the heat and the cytotoxic drugs to the entire peritoneal cavity manually (Figure 10). Renal toxicity of intraperitoneal chemotherapy is avoided by careful monitoring of urine output during perfusion. Side-effects of systemic chemotherapy (nausea, vomiting) are avoided because the patient is under general anesthesia. The time that elapses during hyperthermic perfusion normalizes a number of parameters (hemodynamics, hemostasis, temperature etc) (Sugarbaker, 2005).

Fig. 10. The surgeon distributes heat and cytotoxic drugs manually to all the peritoneal surfaces.

3.2.2 Early Postoperative Intraperitoneal Chemotherapy (EPIC)

Early postoperative intraperitoneal chemotherapy under normothermia (EPIC) is used with the same intent as HIPEC before intra-abdominal adhesions are formed. The method is used during the first five postoperative days (Sugarbaker, 2005), because the formation of adhesions after days 7-8 do not permit uniform distribution of the cytostatic drugs. The distribution of cytostatic drugs is imperfect with EPIC because the undersurface of the right hemidiaphragm, the corresponding surface of the right lobe of the liver, the anterior surface

of the stomach, the folds of small bowel mesentery, and adherent bowel surfaces, the male pelvis, and the abdominal wall are not adequately exposed to cytostatic drugs (Averbach & Sugarbaker, 1996).
The effectiveness of the peritoneal-plasma barrier persists despite extensive stripping of the peritoneal surfaces and the pharmacokinetics of intraperitoneal drug delivery is not changed (Jacquet.& Sugarbaker, 1996a). These results have been reproduced and confirmed by studies on peritoneal transport in experimental animals (Rubin et al, 1988).

3.2.3 Drugs used in HIPEC

The combination of cis-platin (50 mg/m^2) and doxorubicin (15 mg/m^2) is the ideal treatment for both primary and recurrent ovarian cancer. For platinum resistant patients gemcitabine (1000 mg/m^2) or mitomycin-C (10-20 mg/m^2) or oxaliplatin (130 mg/m^2) or melphalan (50-70 mg/m^2) may alternatively be used. The doses are 33% reduced if aggressive chemotherapy has been previously used or the renal function is marginal or the patient is above 60 years of age or there has been extensive intraoperative trauma to the small bowel surfaces or if irradiation has been previously used (Sugarbaker, 2005).

3.2.4 Drugs used in EPIC

5-FU (600 mg/m^2) (maximum dose=1400 mg) with 50 meq sodium bicarbonate or alternatively paclitaxel (20-40 mg/m^2) (maximum dose=80 mg) or docetaxel (20 mg/m^2) (maximum dose=100 mg) are currently in use during EPIC (Sugarbaker, 2005).

4. Patient selection for cytoreductive surgery and perioperative intraperitoneal chemotherapy

The combined treatment with the use of cytoreductive surgery and perioperative intraperitoneal chemotherapy does not offer benefit to all patients. Therefore proper patient selection is required.

4.1 Inclusion criteria

Patients are included for cytoreductive surgery and perioperative intraperitoneal chemotherapy if they meet the following criteria: 1) performance status > 50% according to Karnofsky performance scale, 2) no recent cardiovascular accident, 3) normal hematologic profile, 4) normal hepatic and renal function, 5) absence of a second malignancy at risk for recurrence (except for skin basal-cell carcinoma or in-situ cancer of the cervix adequately treated), 6) absence of chronic or recent acute pulmonary disease, 7) absence of multiple and unresectable extra-abdominal metastases.

4.2 Exclusion criteria

Patients with: 1) performance status < 50%, 2) severe cardiovascular or pulmonary disease, 3) white blood cell count < 4000, 4) platelets < 150.000, 5) urea > 50 mg/dl, 6) creatinine level > 1.5 mg/dl, 7) abnormal hepatic function, 8) presence of a second malignancy at risk for recurrence, 9) pregnancy, 10) drug addiction, 11) presence of tumor at the ligament of Treitz, 12) multiple segmental intestinal obstruction, 13) presence of multiple and unresectable distant metastases, 14) extensive disease at the peritoneal surfaces of the small bowel making impossible a complete or near-complete cytoredution are excluded from treatment for cytoreductive surgery and perioperative intraperitoneal chemotherapy.

Complete hematological and biochemical profile is preoperatively required as well as whole body bone scanning for the exclusion of osseous metastases.

The presence of resectable distant metastases is not an absolute contraindication for cytoreductive surgery combined with perioperative intraperitoneal chemotherapy. It has been demonstrated that patients with colorectal cancer, peritoneal carcinomatosis, and hepatic metastases who may undergo complete cytoreduction, and R_0 resection of the metastatic lesions are offered significant survival benefit although their long-term survival is not equivalent to survival of patients without distant metastases (Elias et al, 2001).

4.3 Imaging modalities used to detect the extent and distribution of peritoneal malignancy

All imaging modalities have been used in the past to detect peritoneal malignancy. Plain films, ultrasound, magnetic resonance imaging, and CT-scan have been used in excess. CT-scan of the abdomen and pelvis with oral and intrarectal contrast plus intravenous contrast has been the state-of-the-art modality for detecting the extent of the implants of peritoneal malignancy (Archer et al, 1996).

4.3.1 Abdominopelvic Ultrasonography (US)

The first imaging evaluation of women with ovarian cancer and suspected peritoneal carcinomatosis was performed with US (Raptopoulos & Gourtsigiannis, 2001). There is a lack of radiation, the examination is easily accepted from the patient and the availability of the modality is wide. The accuracy of the method is high in detecting ascites and/or peritoneal implants especially at the pelvic walls (Raptopoulos & Gourtsigiannis, 2001; Gonzalez-Moreno et al, 2009). The detailed mapping of cancerous implants in entire peritoneal cavity is time consuming with low specificity. The results of the examination are operator – depended and consequently not always reproducible (Gonzalez-Moreno et al, 2009).

4.3.2 Computed Tomography (CT), Computed Tomography-Enteroclysis (CTE)

CT is the established and worldwide most used imaging method in staging and follow-up of patients with peritoneal carcinomatosis because of high image quality, fast throughput of examinations and lower cost, than other imaging modalities (i.e. MRI, PET, PET/CT) (Raptopoulos & Gourtsigiannis, 2001; Gonzalez-Moreno et al, 2009; Woodward et al, 2004; Coakley et al, 2002; Marin et al, 2010). The last few years the development of technology with the multi-detectors CT (MDCT) has improved significantly the ability to obtain in short-image acquisition very thin slices with high spatial resolution including multiplanar or tridimensional reconstructions (Forstner 2007). The ability of CT to detect peritoneal dissemination depends on the size and morphology of the peritoneal implants. The diagnostic accuracy of CT even MDCT for detecting peritoneal implants is decreased dramatically for lesions smaller than 0.5 cm or for those with a “layered – type” form covering the gastrointestinal tube and especially the small bowel (Gonzalez-Moreno et al, 2009; Coakley et al, 2002).

The assessment of the extent and distribution of the peritoneal carcinomatosis is possible with CT which provides sufficient sensitivity and specificity. However, the sensitivity and specificity at the peritoneal surfaces of the small bowel and its mesentery are not sufficient (Raptopoulos & Gourtsigiannis, 2001; Gonzalez-Moreno et al, 2009; de Bree et al, 2004). Disease at the small bowel constitutes a sentinel, limiting criterion in the decision making process involved cytoreduction because sufficient length of small bowel must remain in place to allow for adequate oral nutrition in the future. Once the extent of peritoneal malignancy at the small bowel is the limit of cytoreductive surgery, the evaluation of the small bowel is a crucial component in the preoperative imaging assessment. Experience tells us that even the most sophisticated CT technology usually underestimates actual small bowel involvement revealed at surgical exploration (Gonzalez-Moreno et al, 2009; de Bree et al, 2004).

Implants of less than 1 cm in size are detected with sensitivity 25-50% when helical-CT is used (Gonzalez-Moreno et al, 2009; de Bree et al, 2004). Multi-detectors CT yield a mean sensitivity of 89% for implants larger than 0.5 cm. The sensitivity decreases to 43% for lesions less than 0.5 cm (Marin et al, 2010).

CTE has been defined as "small bowel distention" by administration of high volume of contrast medium via a naso-gastro-jejunal catheter followed by axial CT acquisition (Maglinte et al, 2007). Thus, CTE is a hybrid technique combining the advantages of conventional enteroclysis and those of CT. The cancerous implants attached to the partially distended intestinal loops, sometimes with insufficient quantity of enteral contrast on conventional CT are very difficult to be depicted. Severe involvement of the entire segments of the small bowel manifested as remarkable wall thickness cannot be revealed, if the intestinal loops are not well-distended. Thus, the study of the small bowel and its mesentery could be more accurate, in detail and facilitated having simultaneously information for both the extent and the distribution of cancerous implants within the peritoneal cavity. At the surface of the stretched loops, the tiny or small in size implants may be depicted. Even, the "layered-type" of small bowel involvement may be demonstrated as remarkable thickness of the strongly enhancing intestinal wall. Small bowel loops dilatation allows mesentery unfolding and consequently the easier demonstration of implanted cancerous lesions.

CTE in patients with peritoneal malignancy is currently under extensive investigation. In a prospective study, forty-five consecutive patients (34 women, 11 males, mean age=57.02 years) with peritoneal malignancy of different primaries who were candidates for cytoreductive surgery and HIPEC underwent CTE before surgery. A modified CTE-Peritoneal Carcinomatosis Index (CTE-PCI) was applied to score the lesion size of the nodules at the small bowel surfaces. CTE-PCI was correlated with surgical–PCI. High sensitivities and specificities were estimated for each part of the small bowel. The sensitivity was 87.5%, 91.3%, 92.3%, 90%, and the specificity was 95.2%, 95.4%, 94.7%, 100% for proximal jejunum, distal jejunum, proximal ileum, and distal ileum respectively. The average sensitivity was 90.3±2.1%, and the average specificity was 96.3±2.5% for the entire small bowel. The kappa coefficient of agreement was found to be statistically significant ($p<0.0001$) in all four parts ranging from 0.597 for proximal jejunum, 0.663 for distal jejunum, 0.470 for proximal ileum, to 0.752 for distal ileum (mean kappa=0.621 ± 0.119) (Courcoutsakis et al, 2010a; Courcoutsakis et al, 2010b) (Figures 11, 12).

Fig. 11. CT enteroclysis in a patient with ovarian cancer.

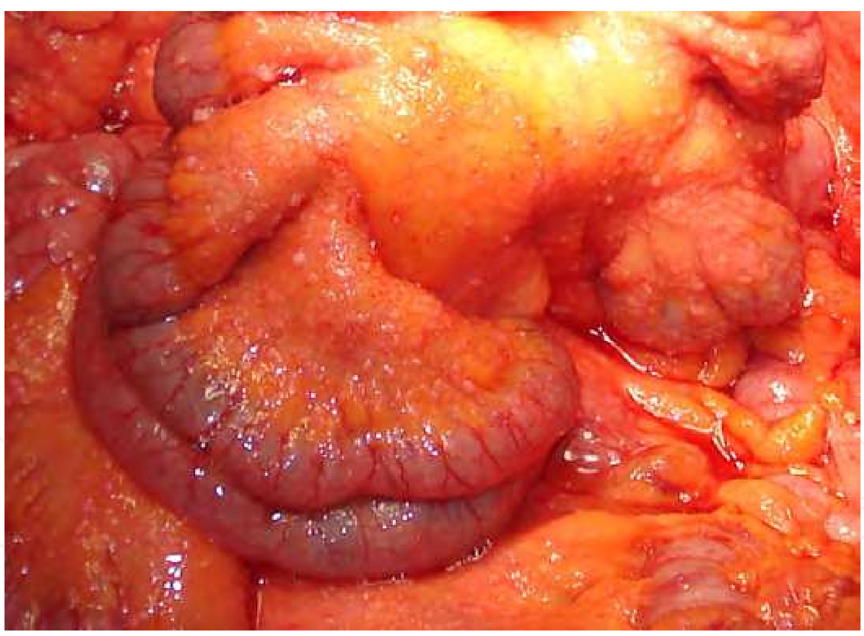

Fig. 12. The corresponding to CT-enteroclysis surgical specimen.

4.3.3 Magnetic Resonance Imaging (MRI)

There are few studies comparing CT to MRI in the peritoneal carcinomatosis evaluation. It has been shown that MRI has significantly improved sensitivity for depicting tumor involving the peritoneum even the subtle peritoneal implants (Forstner, 2007; Low, 2000). In patients with ascites the evaluation of visceral and parietal peritoneum is allowed (Gonzalez-Moreno et al, 2009; Forstner, 2007; Low, 2000). Compared with CT scan, MRI has lower spatial resolution, the acquisition time is longer and influenced by respiratory movement artifacts. On MRI may be obtained multiplanar and tridimensional reconstructions. The clinicians find it harder to interpret, the availability is limited, and the cost is higher. For the evaluation of cancerous implants within the peritoneal cavity specific sequences are needed (i.e. fat-suppression techniques, spoiled-gradient–echo sequence) and the i.v. infusion of gadolinium for tissue enhancement (Gonzalez-Moreno et al, 2009).

The recently introduced MR technique "diffusion-weighted imaging" (DWI) provides quantitative information about tissue cellularity and exploits the restricted water mobility within hypercellular tumors to increase the contrast between these lesions and surrounding tissue. DWI of the peritoneum in patients with ovarian cancer may be helpful for mapping the disease sites, their extent and differentiating tumors from treatment – induced changes (Kyriazi et al, 2010). Larger cohorts are needed to establish the role of the MRI-DWI in peritoneal carcinomatosis.

4.3.4 ^{18} Fluoro Deoxyglucose Positron Emission Tomography (PET), PET/CT

PET has been introduced in the clinical praxis the last decade provoking an innovation in diagnostic oncology. PET uses nuclear medicine in measuring the metabolic assessment of the tumors by counting the selective uptake of the intravenously administrated ^{18} Fluoro-Deoxyglucose. The disadvantages of the method are the poor anatomic resolution, and the non infrequent false positive results. The deficit of the poor spatial resolution is overcome by PET/CT. It has been reported that this hybrid technique is more accurate than PET or CT alone (Gonzale-Moreno et al, 2009, Satoh et al, 2011). This hybrid technique PET/CT may not be commonly used because of disadvantages such as the large size and the high cost of the system, the high cost of the examination, and time expended by the patient (Satoh et al, 2011). There have been only few reports of comparisons of DWI and PET, and the conclusions are controversial (Satoh et al, 2011).

5. Hospital morbidity-mortality

Cytoreductive surgery with perioperative intraperitoneal chemotherapy is associated with high morbidity rate and low mortality rate. The majority of postoperative complications are due to surgery itself. The last decade systemic chemotherapy integrated in this combined treatment has increased the rate of chemotherapy complications which are frequently easily reversed. A large multi-institutional study in patients with peritoneal malignancy of colorectal cancer origin revealed that major complications occurred in approximately 23% of the patients (Glehen et al, 2004). The extent of peritoneal carcinomatosis, and the use of EPIC significantly increase the risk of major complications, as well as the combination of HIPEC and EPIC (Glehen et al 2003; Stephens et al, 1999; Glehen et al, 2003). The most frequent complications are anastomotic leaks or bowel perforation (Glehen et al 2004; Stephens et al, 1999; Glehen et al, 2003; Younan et al, 2005; Kusamura et al, 2006). Other important variables related to postoperative morbidity are the duration of surgery and the number of the performed anastomoses (Stephens et al, 1999). Hematological toxicity is low and does not usually exceed 4% (Stephens et al, 1999).

The rate of postoperative complications in cytoreductive surgery combined with HIPEC does not usually exceed 30-35% although a morbidity rate of 54% has been referred in one study (Elias et al, 2001). The same high rate of morbidity has been recorded in patients with ovarian cancer treated with cytoreduction and perioperative intraperitoneal chemotherapy (Tentes et al, 2003; Tentes et al, 2006; Raspagliesi et al, 2006; Di Giorgio et al, 2008; Tentes et al, 2010).

In properly selected patients the mortality rate is not high and does not exceed 5% (Piso et al, 2004; Raspagliesi et al, 2006; Tentes et al, 2010). However, if the patients are not properly selected the mortality rate increases dramatically (Tentes et al, 2006). In non-properly selected patients the age > 65 years and the performance status were found to be related to mortality, in addition to extensive peritoneal carcinomatosis that was not completely cytoreduced (Table 1).

1st author	No of patients	Hemato-logical toxicity	Bowel perforation-leak	fistula	bleeding	sepsis	mor-tality
Ryu	57	-	7%	-	-	5%	3%
Rufian	33	-	3%	-	3%	-	0%
Di Giorgio	47	NR	-	7%	4%	NR	4.2%
Ras-pagliesi	40	7.5%	2.5%	-	-	-	8%
Piso	19	-	10%	-	5%	5%	5%
Zanon	30	6%	6%	-	5%	-	3.3%
de Bree	19	0%	-	-			10%
Bae	67	13%	NR	NR	NR	NR	0%
Tentes	29	.9%	10.3%	0%	0%	0%	3.4%
Ceelen	42	NR	NR	NR	NR	NR	0%

NR=not reported

Table 1. Major morbidity and mortality rates in cytoreductive surgery combined with HIPEC in patients with primary or recurrent ovarian cancer.

6. Survival

Several clinical variables have been identified to be related to long-term survival. The completeness of cytoreduction, and the extent of peritoneal dissemination are consistently found to be significant prognostic indicators of survival (Tentes et al, 2003; Piso et al, 2004; Gilly et al, 2006; Di Giorgio et al, 2008; Tentes et al, 2010; Zanon et al, 2004; Rufian et al, 2006). Prior surgical score has been identified as a prognostic indicator of survival in one study (Look et al, 2004).

Median and 5-year survival rate varies from 18-54 months and 12-66% respectively (Piso et al, 2004; Raspagliesi et al, 2006; Di Giorgio et al, 2008; Tentes et al 2010, Ryu et al, 2004; Zanon et al, 2004; Rufian et al, 2006; de Bree et al, 2003; Bae et al, 2007; Ceelen et al, 2009) (Table 2). All these studies are prospective but not randomized (evidence level 4) and demonstrate that the method is feasible, well tolerated by the patients, and the results are equivalent or even improved if compared to historical data.

1st author	year	Patients No	Median FU	Median survival	5-year survival
Ryu	2004	57	47	NR	54
Rufian	2006	33	NR	48	37
Di Giorgio	2008	47	NR	24	16.7
Raspagliesi	2006	40	26	32	12
Piso	2004	19	24	18	15
Zanon	2004	30	19	28	12
de Bree	2003	19	30	54	42
Bae	2007	67	NR	NR	66
Tentes	2010	29	34	34	30
Ceelen	2009	42	NR	37	41.3%

NR=not reported

Table 2. Median follow-up, median and 5-year survival rate in cytoreductive surgery combined with HIPEC for ovarian cancer.

7. Recurrence

The incidence of recurrence is high in ovarian cancer and varies from 42-48% (Di Giorgio et al, 2008; Tentes et al, 2010). The majority of recurrences are loco-regional. The extent of peritoneal carcinomatosis is a prognostic indicator of recurrence (Tentes et al, 2010), and less than 30% of patients with low PCI (<13) develop recurrence.

8. Conclusions

Maximal cytoreductive surgery using standard peritonectomy procedures combined with perioperative intraperitoneal chemotherapy is an effective and promising treatment strategy in women with locally advanced epithelial ovarian cancer. The extent of peritoneal carcinomatosis and the completeness of cytoreduction are the most significant prognostic variables of survival. Proper patient selection is required for women with primary or recurrent ovarian cancer because only those women with limited peritoneal carcinomatosis may undergo complete cytoreduction and may be offered significant survival benefit. A useful tool in patient selection is CT-enteroclysis that shows to have higher sensitivity and specificity in the detection of peritoneal malignancy at the peritoneal surfaces of the small bowel compared to CT-scan.

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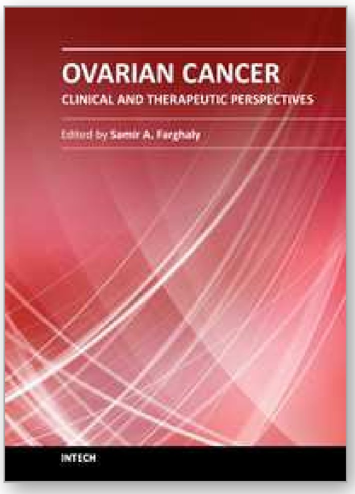

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