Cytoreduction and Hipec in the treatment of OvaRIaN cancEr

CHORINE Study

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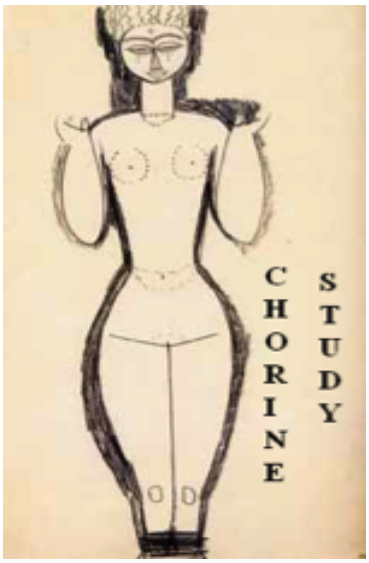

Stage IIIC unresectable epithelial ovarian/tubal cancer with partial or complete response after 1st line neoadjuvant chemotherapy (3 cycles CBDCA+Paclitaxel): a phase 3 prospective randomized study comparing cytoreductive surgery + hyperthermic intraperitoneal chemotherapy (CDDP+Paclitaxel) + 3 cycles CBDCA+Paclitaxel vs cytoreductive surgery alone + 3 cycles CBDCA+Paclitaxel.

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Spontaneous study

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BACKGROUND

Ovarian cancer is the third commonest and most lethal gynecological neoplasm[1]; it is the nineth most commonly diagnosed type of cancer among women, accounting for 5% of all female cancer deaths.

Epithelial ovarian cancer (EOC) account for majority (>70%) of all ovarian cancers.

It typically presents with unclear gastrointestinal and constitutional symptoms, like abdominal bloating, distension, weight loss, and fatigue[2].

Due to heterogeneity of these clinical symptoms, early diagnosis is often delayed, resulting in the majority of patients being diagnosed with advanced disease (stage III/IV).

5-year survival rate of patients with advanced ovarian cancer is <25%[3]. In the final stages of this disease, patients suffer from severe anorexia, dyspnea and pain from malignant bowel obstruction, ascites, and pleural effusion as a result of the extensive burden of tumor.

EOC arises from the serosal lining of the ovary that communicates with the serosal lining of the abdominopelvic cavity, i.e. the peritoneum. During its growth the tumor exfoliates neoplastic cells into the peritoneal fluid, that circulate freely and typically implant in the pelvis and subdiaphramatic recesses owing to gravity and the incumbent position. The spread of tumor within the peritoneum is termed peritoneal carcinomatosis[4].

Intraoperatively, it is characterized by the widespread presence of macroscopic whitish neoplastic nodules of variable sizes and consistency, that may join together to form plaques or masses inside the abdominopelvic cavity.

Neoplastic dissemination from the peritoneal cavity into the pleural cavity may also occur, through the lymphatic lacunae within the diaphragmatic peritoneum[5] [6]. This results in severe pleural effusion, which compromises lung and cardiac function.

In the past, peritoneal carcinomatosis was regarded as a terminal condition and patients were treated symptomatically. However, as this disease is largely confined to the peritoneal surfaces, it is now considered to be a loco-regional disease.

Actually, Neoadjuvant Chemotherapy (NACT) followed by Interval Cytoreductive Surgery (ICS) is a good option for patients deemed to have unresectable disease (stage IIIC/IV ovarian, fallopian tube, or primary peritoneal cancer). However, optimal debulking to microscopic disease should be achieved at the time of ICS.

From several retrospective and prospective case–control studies of NACT-ICS compared to Primary Cytoreductive Surgery (PCS), along with recent metaanalises, it appears that NACT-ICS offers less morbidity to patients[7] [8].

Preliminary results of the prospective randomized controlled trial EORTC 55971 are consistent with the majority of the previous studies, suggesting that neoadjuvant chemotherapy followed by interval debulking results in the same survival but fewer complications than primary debulking surgery, in patients with stage IIIC/IV ovarian, fallopian tube, or primary peritoneal cancers[9].

Patients with optimal disease cytoreduction should be offered adjuvant chemotherapy for the potential survival benefit. Chemotherapy for EOC is usually given as an intravenous infusion repeatedly over 5 to 8 cycles.

EOC tends to be chemosensitive and confine itself to the surface of the peritoneal cavity for a long time during its natural history. These features have made it an obvious 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.

Intraperitoneal chemotherapy has the potential to improve cure rates from EOC. However, it is not known who specifically will benefit from it, nor is clear how and when it is best administered. The optimal drug, dose, modality and combination are also unknown[10].

Adequate surgical cytoreduction is necessary for optimal results of intraperitoneal chemotherapy, because the outcome of intraperitoneal chemotherapy can be impaired by limited tumour penetration. In addition, comprehensive adhaesiolysis, mobilization of the bowel and intraoperative peritoneal cavity expansion may overcome the problem of incomplete exposure of the seroperitoneal surface to the chemotherapeutic agents during simple instillation intraperitoneal chemotherapy.

To optimize drug distribution, intraperitoneal chemotherapy has also been applied immediately after CRS. Different techniques have been used for intraoperative intraperitoneal chemotherapy. An advantage of intraoperative use is that intraperitoneal chemotherapy can be 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 intraperitoneal chemotherapy (HIPEC) as a treatment for peritoneal carcinomatosis was first demonstrated by Spratt et al. in the early 1980s[11]. Its development

continued under Dr. Sugarbaker from the Washington Cancer Institute in the mid-1990s, who advocated this combined procedure of surgical resection and hyperthermic chemoperfusion, to achieve complete intraoperative cytoreduction. This procedure involves 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[12].

The results of this treatment have been shown to be beneficial for patients with peritoneal carcinomatosis from appendiceal cancer[13], colorectal cancer[14] and peritoneal mesothelioma[15].

There has been increasing attention within the surgical oncology community for this approach, that combines aggressive cytoreduction and regional anti-neoplastic drug delivery in the management of cancers (like ovarian cancer) which remain principally localized to the peritoneal cavity.

The rationale to use CRS and HIPEC in EOC stands on some considerations.

First, phase 3 randomized controlled trials (RCTs) have established the superiority (improved progression-free and overall survival) of intraperitoneal cisplatin-based chemotherapy compared to the systemic delivery of the agent in the treatment of small-volume residual advanced ovarian cancer[16 17 18].

Second, a number of prospective phase 2 studies and retrospective institutional experiences have shown the feasibility of employing a particular technically demanding regional therapeutic approach, HIPEC[19 20 21 22 23 24], when complete macroscopic cytoreduction is achieved prior to the delivery of the anti-neoplastic agents.

Finally, reports have suggested improved patient outcome in a variety of settings, compared to either non-randomized contemporary or historical control populations.

Unfortunately, there is no evidence from prospective phase 3 RTCs to confirm any claimed overall survival benefit associated with aggressive surgical resection of intraperitoneal metastatic cancer in combination with HIPEC.

It is reasonable to state that existing data regarding the utility of this strategy can be interpreted as revealing: (a) the benefits of aggressive surgery alone (without HIPEC); (b) simply reflecting the natural history of disease in carefully selected good performance status patients with advanced, but relatively indolent, intraperitoneal cancers; or (c) a combination of these two factors, independent of any influence of HIPEC.

In the single available randomized phase 3 trial, that is frequently referenced as demonstrating the

superiority of this multi-modality approach, patients with peritoneal carcinomatosis from colorectal cancer either underwent aggressive surgery followed by HIPEC plus "standard intravenous chemotherapy" (5-fluorouracil-leucovorin), or the same intravenous chemotherapy plus (in selected situations) "palliative surgery"[25]. Unfortunately, this study failed to address the specific clinical value of regional chemotherapy. As a result, the trial may simply have shown the utility of an appropriately aggressive surgical procedure, performed in a carefully selected patient population in this specific clinical setting. What would this study have revealed if the randomization had compared an attempt at maximal surgical cytoreduction (alone) versus such a surgical approach plus HIPEC?

Recently, investigators have begun to report their non-randomized experience adopting this general strategy in women with advanced EOC, in both primary and recurrent disease settings[26 27 28 29 30 31 32 33].

In the absence of any evidence-based (RCTs) data, rather striking claims have been made in the peer-reviewed literature regarding the utility of this strategy. For example, one paper concluded that "considering the high recurrence rates after standard treatment for advanced ovarian cancer, and the good results the combined procedures achieved in our series and in others, we suggest that maximal cytoreduction (peritonectomy procedures) plus HIPEC should now be the up-front treatment for selected patients with ovarian carcinomatosis who have diffuse peritoneal spread"[34].

Such conclusions must be vigorously challenged. In the absence of results from phase 3 RCTs, any suggestion of a more favorable survival associated with surgery plus HIPEC in these patient populations can be completely explained by the documented utility of non-hyperthermic intraperitoneal platinum in ovarian cancer [35 36 37], appropriate (and even "highly aggressive") CRS without HIPEC [38 39], and the well-recognized impact of selection bias or, in the context of the specific unique medical care being provided to these individuals, clinical judgment.

Of major importance in this discussion, the decision by a competent physician to employ an intensive and potentially highly morbid management strategy will certainly include consideration of relevant existing co-morbidity and overall performance status, factors that may substantially impact overall survival, independent of the specific selected treatment plan.

The outcomes of combined procedure of surgical resections and hyperthermic chemoperfusion to achieve complete intraoperative cytoreduction have been recently evaluated even in a sytematic review by Chua et al[40]. The authors conclude that despite the lack of quality (level I evidence) data, even if the results of their review suggest that there is an overall survival advantage associated with

CRS and HIPEC in patients that are at various stages of their disease process, who have been heavily treated with both surgery and chemotherapy and with issues of chemoresistance, it is only through the conduct of prospective phase 3 randomized clinical trials that an apparent "favorable impact" of a new/novel therapeutic strategy (e.g., HIPEC) can be distinguished from the selection bias associated with the inclusion of particular patients within the "study population".

Based on the current absence of such evidence-based data, it is sensible to state that considering the costs, documented morbidity, and potential mortality associated with aggressive surgery plus HIPEC in ovarian cancer, compared to alternative and far more established management strategies, it is mandatory to formally document its merits through the conduction of an appropriately designed randomized phase 3 trial[41].

Specifically, trials should be set in the context of HIPEC use according to the various time-points as previously proposed[42]. Particularly, there are five time-points in the natural history of EOC at which discussion of treatment with HIPEC and research can usefully be directed:

1. front-line,
2. interval debulking following initial neo-adjuvant chemotherapy,
3. consolidation following complete response to front-line therapy (surgery and chemotherapy),
4. at the time of recurrence,
5. "salvage" therapy.

Among all of these situations, at least at points 2 and 3, it is possible to establish a "clinical" chemosensibility of the neoplasm which makes particularly attractive the hypothesis of HIPEC use.

A retrospective study among 42 patients with EOC where HIPEC was used during the consolidation phase (point 3) registered very flattering results, showing an 8-year progression-free survival rates of 63.16% in the HIPEC group and 29.17% in the control group without HIPEC (p=0.027) and an 8-year overall survival rates of 84.21% in the HIPEC group and 25% in the control group (p=0.0004).

Our group is more interested in investigating the HIPEC use in a cohort of patients with advanced EOC where chemosensibility was tested by neoadjuvant therapy, selecting the patients who responded to treatment.

Actually there are no phase III trial data documenting the equivalence or the superiority of CRS plus HIPEC (CDDP and Paclitaxel) compared to CRS alone in patients with EOC. Therefore it

looks reasonable to compare HIPEC in patients where the platinum and Paclitaxel chemosensibility were already proved. The initiation of such a study, perhaps through the collaboration of an international consortium of interested oncologic surgeons, should be strongly encouraged by the surgical and gynecologic cancer research community.

The reasons for the absence of an RCT in this field are certainly the technical difficulty in carrying it on, but also the relative lack of motivation and study acceptability by patients resulting in little chance of recruitment.

Indeed, cytoreductive surgery followed by chemotherapy with platinum and taxanes, which is now the standard treatment for this disease, can provide a clinical response in 60-80% of patients, but a long-term survival in only 20-30% of cases. For this reason, these patients should be made aware and mindful that, even if the results of standard treatment of EOC are encouraging in the short term, new therapeutic strategies to treat this cancer are still necessary and desirable.

In this context of probable and possible recruitment difficulties, particular attention will be devoted to two groups of patients: (1) those who refuse randomization and (2) those who withdraw from the study after randomization (dropouts).

Patients who refuse randomization will receive the standard treatment, ie the CRS and systemic chemotherapy completion.

Regarding dropout, we have two cases: patients randomized for standard treatment (CRS only with chemotherapy completion) who require HIPEC and patients randomized for CRS + HIPEC who reject HIPEC and instead receive CRS with only consolidation chemotherapy.

In general, the behavior of dropouts may be different for reasons of illness (severity) or treatment (tolerability, toxicity, etc.). In fact, treatment may be very effective, but also produce a high number of dropouts because of side effects, so that its overall effectiveness and applicability would be then resized.

For this reason, analysis according to the "intention to treat" principle is particularly important, analyzing the subjects according to group randomization (intention to treat) and not according to the treatment received (per protocol analysis).

Analysis according to the intention to treat principle has some advantages: it is a conservative analysis, which softens the differences between groups, reflecting more accurately what will happen in daily practice, allowing to respect and maintain allocation by randomization.

For this reason, data analysis will be performed according to the intention to treat principle and only

secondarily according to the Protocol group.

AIM

To compare two-years disease-free survival of CRS and HIPEC (CDDP+Paclitaxel) vs CRS alone in Stage IIIC unresectable epithelial tubal/ovarian cancer with partial or complete response after 3 cycles of 1st line chemotherapy (CBDCA +Paclitaxel).

DESIGN

The study project is a multicentre phase 3 prospective randomized trial, comparing CRS + HIPEC (CDDP+Paclitaxel, CYHI) vs CRS alone (CYALONE) in Stage IIIC unresectable epithelial tubal/ovarian cancer with partial or complete response after 3 cycles CBDCA+Paclitaxel (neoadjuvant chemotherapy), followed by further 3 cycles of CBDCA+Paclitaxel (adjuvant chemotherapy)**.**

The outcomes measured are the following:

- two-years disease-free survival;
- one-year, three- and five-years disease-free survival;
- one month, one-year, three- and five-years overall survival;
- toxicity induced by HIPEC using the NCI CTC criteria;
- one month and six months morbidity using the Common Terminology Criteria for Adverse Events v4.03 (CTCAE 4.03);
- duration of operation (minutes), defined as operating time, anesthesia time, or operating room time;
- return of bowel function (days), subdivided in: time until first stool, introduction of liquid or solid diet;
- length of hospital stay (days);
- return to normal activity (days), i.e. return to full activity, work, or sport;
- six months and one year QOL, using the Standard Form 36 (SF-36 v1.0);
- percentage of patients in both arms completing the scheduled postoperative chemotherapy;
- correspondence between pre-randomization clinical/radiologic/laboratory evaluation and intraoperative findings.

The study will be multicentric (4-6 Centres involved), with the participation of oncologists,

surgeons and gynecologists who will accept to standardise the medical and surgical procedures and follow-up.

Only centres having performed at least 10 CRS + HIPEC procedures in the last 2 years can join the trial: their data will be considered in the final analysis and report only in case that they have provided 10 or more included cases in the study period of two years. Two scientists in each centre will be the responsibles of the study (Local Co-ordinators, see Organization) and the others will be mentioned as participants.

Patients with suspected diagnosis of advanced ovarian carcinoma will be submitted to a diagnostic laparoscopy, to evaluate the possibility of optimal debulking surgery with no residual disease at the end of the procedure. Laparoscopy will be performed by trained gynecologists and surgeons and a detailed pattern of diffusion of the disease will be drawn on a specific sketck (**APPENDIX 0**); in presence of ascitic fluid, a sample for cytology will be obtained; otherwise, a lavage of the peritoneal cavity will be performed; biopsy of eventual pelvic and peritoneal masses will be obtained.

A scoring system to assess the feasibility of resection with zero residual tumor will be applied (**APPENDIX 1**). Patients with a score ≥4 are not candidate for debulking surgery: a score ≥4 is choosen as a compromise to warrant adequate accrual, because the higher risk of inappropriate lack of exploration (26%) is likely to be balanced by the documented efficacy of neoadjuvant chemotherapy in this type of tumor.

Patients not candidate for upfront debulking surgery are submitted to neoadjuvant chemotherapy: 3 cycles of carboplatin AUC-5 and Paclitaxel 175 mg/m^2 are administered every 21 days. After 3 cycles of chemotherapy, patients are re-assessed by clinical, radiologic (CT scan) and laboratory (CA 125) evaluation and assigned to one of four subgroups (**APPENDIX 2**): complete clinical response (cCR), partial clinical response (cPR), clinically with stable disease (cSD), clinically disease progression (cDP)[43].

If the response is considered cCR or cPR, patients are included in the study**.** Patients with cSD or cDP are not eligible.

In summary, only patients with complete clinical response (cCR) or partial clinical response (cPR) after 3 cycles of neoadjuvant theraphy will be eligible for the Study.

After signing the informed consent form, patients will be submitted to CRS with radical intent.

CRS will be as follows: hysterectomy, bilateral salpingoophorectomy, pelvic and peri-aortic lymphadenectomy, radical omentectomy, random biopsy of peritoneal surfaces, associated to any surgical procedure needed to obtain a ≤ 2.5mm residual tumor (peritonectomy, bowel resection, diaphragmatic stripping, gastric resection, etc.). Pelvic and peri-aortic lymphadenectomy is not

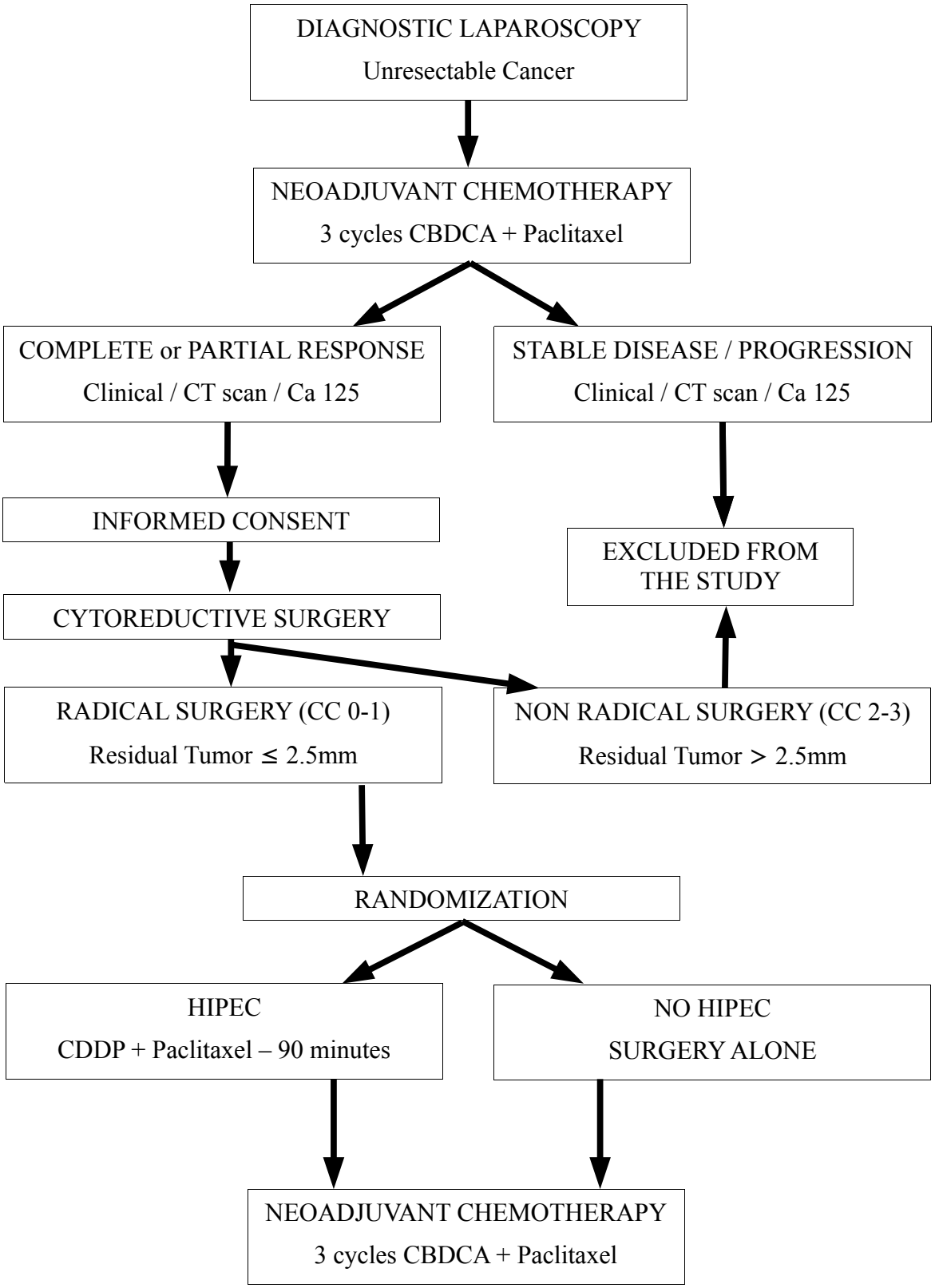
choosen as a standard procedure: anyway, an adequate number of lymph nodes should be harvested to warrant correct staging of the neoplasia.

After CRS, only patients with adequate cytoreduction (CC 0-1, residual tumor $\leq$ 2.5mm) will be randomized. Patients with suboptimal cytoreduction (CC 2-3, residual tumor $>$ 2.5mm) are not suitable for randomization.

Randomization will be: CRS and hypertermic endoperitoneal chemotherapy (HIPEC) vs. CRS alone.

Hyperthermic intraperitoneal chemotheraphy (HIPEC) will be as follows: after CRS, 1 Tenckhoff and 4 Jackson-Pratt catheters will be placed in the abdominal cavity. Two inflow catheters (1 JP and 1 Tenckhoff) will be placed in the right subphrenic cavity and at deep pelvic level, respectively; three JP outflow catheters will be placedin the left subphrenic cavity and in the superficial pelvic site.

The HIPEC requires the employment of a device comprised by a roller pump, a thermostat, a heat exchanger and an extra corporeal circuit. The perfusate flow will be controlled as well as the heat exchanger adjusts the temperature of perfusate, by circulating water at a desired temperature in the inflow phase of circuit. The extra corporeal circuit consists of interconnected tubes which has: a) an input section (inflow); b) an output section (outflow); c) an axis of rapid filling up; d) a central body connected with a filter; e) a deflow section; f) a series of multiperforated catheters in their extremities. The priming, defined as the liquid filling the circuit, will be a peritoneal dialysis solution. The priming volume should be abundant enough to achieve homogeneity and constancy of heating, but not excessive, in order to avoid bodily thermo-dilution. For an optimal working of circuit, 3-4 litres of perfusate for opened technique are usually sufficient. The drug schedule elected in the current study is Cisplatin (CDDP) (100 mg/m^2 of body surface area) and Paclitaxel (175mg/m^2 of body surface area) (**APPENDIX 3**)[44 45 46].


DIAGNOSTIC LAPAROSCOPY
Unresectable Cancer
NEOADJUVANT CHEMOTHERAPY
3 cycles CBDCA + Paclitaxel
COMPLETE or PARTIAL RESPONSE
Clinical / CT scan / Ca 125
STABLE DISEASE / PROGRESSION
Clinical / CT scan / Ca 125
INFORMED CONSENT
EXCLUDED FROM THE STUDY
CYTOREDUCTIVE SURGERY
RADICAL SURGERY (CC 0-1)
Residual Tumor ≤ 2.5mm
NON RADICAL SURGERY (CC 2-3)
Residual Tumor > 2.5mm
RANDOMIZATION
HIPEC
CDDP + Paclitaxel – 90 minutes
NO HIPEC
SURGERY ALONE
NEOADJUVANT CHEMOTHERAPY
3 cycles CBDCA + Paclitaxel

RANDOMIZATION

Randomization will be obtained through computer-generated schedule at http://www.randomization.com/.
Randomization will be done in blocks of 6. The results of randomization will be enclosed in envelopes and distributed to the participating centres in blocks of 6.
In case that a patient will fulfill the inclusion criteria and will accept to participate to the study (signing the informed consent), the surgeons of each centre will disclose from the envelope the surgical procedure (either CYHI, either CYALONE) that has to be performed.
The patient's name and the assigned progressive number will be recorded in the case report form (CRF, part one), together with preoperative and intraoperative data.
All the postoperative data and the outcomes evaluations will be recorded in the second part of the CRF, by a researcher aware of the type of surgical procedure performed (researcher unblinded).

SAMPLE SIZE

The sample size will be 41 patients for each group (82 patients for the whole study).

We estimate that the four centres will provide 11 patients every year (44 patients per year with a total of 88 patients in two years).

POWER CALCULATION

Sample size has been calculated to reach a confidence level of 95% with a power of 80%, considering a 45% and 75% disease-free survival at two years of follow-up in CYALONE and CYHI group respectively (**APPENDIX 4**).
Sample size will be 41 patients for each group, calculated by a Power/Sample Size Calculator that uses the usual sample-size formula based on the normal approximation to the binomial distribution.

INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria will be the following:

- Female adult women (18 to 70 years old) patients, with EOC (FIGO stage IIIc, **APPENDIX 5**) with a Fagotti modified Laparoscopic Scoring System ≥ 4 who will show a complete clinical response (cCR) or partial clinical response (cPR) after 3 cycles (Carboplatin+Paclitaxel) of neoadjuvant chemotherapy;
- performance status (ECOG) 0, 1 or 2 (**APPENDIX 6**);
- signed informed consent.

Exclusion criteria will be the following:

- refusing to sign an informed consent;
- age > 70 years and age <18 years;
- BMI > 35;
- impossibility of an adequate follow-up;
- presence of other active neoplasms;
- active infection or other concurrent medical condition that could interfere in the ability of patients to receive the proposed treatment according to protocol;
- extraabdominal metastases (Stage IV) ;
- performance status (ECOG)>2;
- complete bowel obstruction;
- Abnormal bone marrow indices or renal and liver function;
- ASA IV or V.

In case of intraoperative finding of unresectable disease (ie. PCI > 20 or extensive involvement of small bowel/mesentery or tumor infiltration in the porta hepatis and pancreas) CRS will be performed as choosen by the surgeon and HIPEC will be not performed.
In patients with suboptimal cytoreduction (> 2.5mm) HIPEC will be not performed**.**

PERIOPERATIVE STRATEGY

If the patient with unresectable EOC, after 3 cycles of Carboplatin and Paclitaxel is classified by clinical-radiological-laboratory evaluation as having an optimally cytoreducible disease, she will be randomly assigned to one of treatments arms: the CYHI or CYALONE arms.

Otherwise the patient will be referred for other study protocols: the reason for exclusion lies in the fact that maximization of HIPEC effectiveness can be attained in patients with minimal residual disease. Furthermore, an unresectable carcinomatosis even after 3 cycles of neoadjuvant chemotherapy must be classified as refractory and progressive disease, and a cytoreduction under this condition is not always advisable.

The CYHI arm will comprise the CRS followed by HIPEC (CDDP+Paclitaxel) and 3 cycles CBDCA+Paclitaxel as postoperative systemic chemotherapy (total 6 cycles of perioperative chemotherapy). The CYALONE arm will comprise the CRS alone and 3 cycles CBDCA +Paclitaxel as postoperative systemic chemotherapy (total 6 cycles of perioperative chemotherapy).

Preoperative

Patient allocated to both arms must have been submitted to:

- general and gynaecological examination;
- imaging assessment: thoracoabdominopelvic CT scan or abdominopelvic CT scan + Chest X ray and abdominopelvic sonography;
- laboratory exams: serum Ca-125, complete blood cell count, serum albumin, creatinine clearance.

During the week before surgery, patients will be always submitted to ureteral stenting, to easen pursuing of the urethers during surgery and reduce the risk of uretheral fistula.

Two days before the procedure, patients will start colon clearance; in the same day, a central venous access is obtained. Prevention of venous thromboembolism and of surgical site infection will be done according with each centres' protocols.

Intraoperative

Some general rules should be respected during anesthesia:

- Fluid restriction during the resective phase of the operation (≈5-6 ml/Kg/h).
- Hyperhydration (≈12 ml/kg/h) and forced dyuresis (≈2 ml/Kg/h) during HIPEC, to prevent platinum-induced nephrotoxicity.
- Replace blood loss in order to keep hematocrit ≈ 27% and hemoglobin ≈ 8.5 gr/dL.
- Good control of the patient's temperature and pH, to avoid coagulative disorders: fluids and the patient should be warmed during the resective phase and cooled during HIPEC.
- Optimal pain control: it is advisable to place an epidural catheter before operation, to reduce the need for endovenous opioids.

Standard surgery:

Cytoreductive Surgery (CRS) will comprehend: radical bilateral hysteroannessiectomy with pelvic peritonectomy, radical omentectomy, and pelvic and aortic lymphadenectomy.
The peritonectomy procedures that eventually will be performed are described by Sugarbaker, and will be adopted only in presence of macroscopic neoplastic nodules.
When macroscopic carcinomatosis outside of the pelvis is not present and the peritoneum is smooth, random biopsies are performed for frozen section procedure and intraoperative consultation by the pathologist: if biopsies are negative, the peritoneum is then left untouched.
In the operating room, the patient will be placed supine, with gluteal folds advanced to the break on the operating table to allow full access to the perineum during the surgical procedure. This position is essential to avoid intraoperative skin or muscle necrosis. The weight of the legs must be directed to bottom of the feet, by positioning footrests so that minimal weight is borne by the calf muscles. Myonecrosis within the posterior compartment of the leg may occur unless the legs are protected properly.
A 3-way bladder catheter and a large-bore silastic nasogastric tube are positioned.
Abdominal skin preparation will be from mid chest to mid thigh, as well as the external genitalia, including the vagina.
The abdomen will be opened from xyphoid to pubis. Generous abdominal exposure will be achieved through the use of a Self-Retaining Retractor.

A ball-tip electrosurgical handpiece will be used to dissect the tumour on peritoneal surfaces from normal tissue. Electrosurgery will be used on pure cut at high voltage. The 2 mm ball-tip electrode is used for dissecting on visceral surfaces, including stomach, small bowel, and colon. When more rapid tumour destruction is required, the 5 mm ball-tip can be used.
The peritonectomy technique requires an ordered sequence of surgical maneuvers, to create an optimum cytoreduction. One or more of following steps can be performed depending on the extension of primary surgical staging or disease extension at the time of CRS, in order to achieve optimal residual status (residual tumor $\leq$ 2.5mm):

- greater omentectomy, right parietal peritonectomy and right colon resection
- left upper quadrant peritonectomy, splenectomy and left parietal peritonectomy
- right upper quadrant peritonectomy and Glissonian's capsule resection
- lesser omentectomy, colecystectomy, stripping of omental bursa and antrectomy
- pelvic peritonectomy with sigmoid colon resection with or without hysterectomy and bilateral salpingo-oophorectomy;
- other intestinal resection and/or abdominal mass resection.
- bowel anastomosis (this step will be performed after the completion of HIPEC).
- loop ileostomy (this step will be performed in case of rectal anastomosis).

After CRS HIPEC will be performed as described before.
The priming solution, defined as the liquid filling the circuit, will be a peritoneal dialysis solution. The priming volume should be abundant enough to achieve homogeneity and constancy of heating, but not excessive, in order to avoid abdominal distension and bodily thermo-dilution. For an optimal working of the circuit, the amount of perfusate for open technique will be calculated with the following formula: body surface area in m^2 x 100 / 43.
The drug schedule elected in the current study is Cisplatin (CDDP) (43.0 mg/l of perfusate or 100mg x m^2 of body surface area) and Paclitaxel (175mg x m^2 of body surface area).
If a closed technique is choosen, the skin will be temporary closed with a running suture and the catheters connected to the circuit, in order to initiate HIPEC.
If an open modality is choosen (also known as Coliseum technique), the abdomen will be covered with a plastic sheet and drug vapour is evacuated to protect the operating room personnel.
The catheters will be connected to the extra-corporeal circuit and the preheated perfusate containing Cisplatin and Paclitaxel will be instilled in the peritoneal cavity using the heart-lung pump at a mean flow of 600-1000 ml/min for 90 minutes.

In order to achieve intrabdominal temperature of 42.5°C, an inflow temperature of approximately 44°C will be maintained. Throughout the perfusion, if the opened technique is adopted, the surgeon will continuously manipulate the viscera to distribute both heat and chemotherapy. Following perfusion, the perfusate will be quickly drained, eventual bowel anastomoses will be done and the abdomen closed after careful intraperitoneal inspection.
The main intraoperative potential complication is generalized hyperthermia, that can be avoided submitting the patient to hypothermia. This can be obtained by the eventual application of cooling packages in the flexing faces of joints and in the head. The bladder will eventually be instilled with cooling physiologic solution during hyperthermia to avoid mucosal damage. The optimal temperature expected for the patient before the beginning of HIPEC is 32-33°C; and this can be achieved passively just maintaining the abdomen opened during the surgery, without any heating. During HIPEC, continuous peritoneal temperature monitoring will be performed by 3 thermocouples placed in the abdominal cavity, peritoneal site and rhino pharynx for core temperature.
Cardiovascular parameters, such as central venous pressure and mean arterial pressure will be continuously monitored. In the same way, haemoglobin level, coagulation system parameters and arterial partial oxygen and carbonic gases pressures as well as arterial pH will be determined every 30 minutes.

Postoperative treatment

In the postoperative period, patients submitted to LRT will be assisted in an Intensive Care Unit for at least 72 hours. Based on reported results [176-178] which showed significant changes in proteins levels, due to haemodilution induced by the perfusion, all patients will receive preventive treatment with 10-20 g/day of albumin (D0 - D+7) and 250 ml of fresh plasma (D0 - D+3). In order to prevent possible renal failure due to the high dose administration of CDDP patients will be treated with dopamine (3mcg/kg/min) for 72 hours postoperatively and almost 3,500 ml/day of polysaline solution (D0 - D+7). They will be evaluated with laboratory exams to assess haematological, renal and hepatic function as detailed in **APPENDIX 11**.

INFORMED CONSENT

In the informed consent form (**APPENDIX 7**), patients will receive all the information about the study protocol, the confidential nature of personal data ("information sheet") and will fill up a questionnaire before signing for acceptance or refusal ("informed consent form").
There will be not inconveniences caused to patients, if they refuse. Patients who refuse randomization will receive the standard treatment, ie the CRS and systemic chemotherapy completion.
All the medical informations obtained from the patients will be kept confidentially among the research scientists conducting the study. The patients will be free to withdraw from the study, whenever they want, without any obligation.

ETHICAL APPROVAL

The study protocol will be approved by the Ethical Committee of the "Ospedali Riuniti di Bergamo" Hospital - Bergamo, Italy.

STOPPING RULES

The procedures compared in this study are both well known and in widespread use. So we don't expect to discover new adverse events related to them. However, the study will be stopped if one month and six months mortality exceeds 10% or one month and six months severe morbidity (requiring reoperation) exceeds 50% in the CRS + HIPEC study arm.
The study will also be stopped in case that at the interim analysis done after the inclusion of the first 42 patients the primary endpoint is significantly different, or at least 5 end points will be already significantly different in the same direction.

PRIMARY ENDPOINT

The present study will compare CRS + HIPEC (Cisplatin+Paclitaxel, CYHI) vs CRS alone (CYALONE) in Stage IIIC inoperable epithelial tubal/ovarian cancer with partial or complete response after neoadjuvant chemotherapy (3 cycles CDDP+Paclitaxel), followed by adjuvant chemotherapy in terms of two-years disease-free survival from the date of randomization.

SECONDARY ENDPOINTS

The secondary outcomes measured are the following:

- to evaluate one-year, three- and five-years disease-free survival from the date of randomization after CRS + HIPEC (Cisplatin+Paclitaxel, CYHI) vs CRS alone (CYALONE);
- to evaluate one month, one-year, three- and five-years overall survival from the date of randomization after CRS + HIPEC (Cisplatin+Paclitaxel, CYHI) vs CRS alone (CYALONE);
- to evaluate toxicity induced by HIPEC using the NCI CTC criteria (**APPENDIX 8**).
- to evaluate one month and six months morbidity induced by the CRS + HIPEC (Cisplatin+Paclitaxel, CYHI) vs CRS alone (CYALONE) using the Common Terminology Criteria for Adverse Events v4.03 (CTCAE 4.03 - http://evs.nci.nih.gov/ftp1/CTCAE/About.html);
- to evaluate the duration of operation (minutes) CRS + HIPEC (Cisplatin+Paclitaxel, CYHI) vs CRS alone (CYALONE), defined as operating time, anesthesia time, or operating room time;
- return of bowel function (days) after CRS + HIPEC (Cisplatin+Paclitaxel, CYHI) vs CRS alone (CYALONE), subdivided in: time until first stool, introduction of liquid or solid diet;
- length of hospital stay (days) of CRS + HIPEC (Cisplatin+Paclitaxel, CYHI) vs CRS alone (CYALONE);
- return to normal activity (days), after CRS + HIPEC (Cisplatin+Paclitaxel, CYHI) vs CRS alone (CYALONE) i.e. time until return to full activity, work, or sport;
- six months and one year QOL, using the Standard Form 36 (SF-36 v1.0, **APPENDIX 9**);
- percentage of patients in both arms completing the scheduled postoperative chemotherapy;
- correspondence between pre-randomization clinical/radiologic/laboratory evaluation and intraoperative findings.

PLANNED SUBGROUP ANALYSES

Because therapeutic advantages of HIPEC approach are seemingly larger in patients with lower PCI, a subgroup analysis of all outcomes will be performed in patients with PCI $\leq$ 15.
Subgroup analysis will be also performed in young women, with an age between 18 and 40 years.

SIDE EFFECTS QUANTIFICATION

Treatment-related death is defined as death due to toxicity following cytoreduction and HIPEC without time interval restrictions.
Toxicity will be recorded in accordance to the National Cancer Institute Common Toxicity Criteria (NCI CTC). Surgical complications are seen as a component of the total toxicity and also registered in accordance of the NCI CTC.
Surgical failure is defined as any bowel fistulae resulting in abdominal infection for which invasive therapy is needed.

ANALYSIS PLAN

During surgery, detailed evaluation of peritoneal carcinomatosis index (PCI) will be conducted, taking into consideration the size and distribution, according to the principle of Sugarbaker.
PCI < 20 is defined as low PCI, while PCI ≥ 20 is defined as high PCI (**APPENDIX 0**).
The characteristics of ascites will be also recorded (sample evaluated fo citology).
After evaluation, maximal CRS will be performed, according to the peritonectomy procedure developed by Sugarbaker.
The extent of CRS is determined by Sugarbaker's criteria on the completeness of cytoreduction (CC). A score of CC-0 indicates no residual peritoneal disease after CRS; CC-1, less than 2.5 mm of residual disease; CC-2, residual tumor between 2.5 mm and 2.5 cm; and CC-3, more than 2.5 cm of residual tumor or the presence of a sheet of unresectable tumor nodules.

The analysis plan for the individual patient and the whole study are reported in **APPENDIX 11**.
Data will be collected in a digital database, which will be created for the purpouses of the study.

INTERIM ANALYSIS

An interim analysis is planned after half of all patients have been included (i.e. after the first 42 patients). The study will be stopped in case that at the interim analysis the primary endpoint is significantly different, or at least 5 secondary end points will be already significantly different in the same direction. Furthermore, the study will be stopped if one month and six months mortality exceeds 10% or one month and six months severe morbidity (requiring reoperation) exceeds 50%

in the CRS + HIPEC study arm.

DATA-MONITORING COMMITEE - DATA MANAGEMENT - TYPE OF ANALYSIS - STATISTICS TESTS

The Trial Steering Committee will be responsible for the data monitoring during the whole period of the study.

Data progressively collected will be sent by each centre to the Organising Centre located in the Gynecology Unit of the "Ospedali Riuniti di Bergamo" Hospital of Bergamo. Here the data will be kept in a database of clinical records, surgical reports, medical imaging reports, laboratory and pathology reports, and follow-up records, and later analysed by Statistical Software under the responsibility of the Project Management Group.

All patients will be regularly followed up for detailed monitoring of disease status (see **APPENDIX 11**). Patients lost to follow up will be considered as disease progression, and DFS calculated at the date of the last follow up.

DFS and OS will be estimated by the Kaplan–Meier method, stratified by PCI and CC, and tested with the log-rank test.

This trial was designed to detect a 30% absolute difference in DFS. With a statistical power of 80% to detect such difference and 5% significance level, at least 41 patients are needed for each arm of the Study.

Categorized variables in the two groups will be compared by chi-square test or Fisher’s exact test. The Kaplan–Meier method will be used to compare the survival, with log rank test. Data will analyzed by the Statistical Package for Social Sciences (SPSS, Chicago, IL), and "R" software.

INDEMNITIES SPECIFIED

No incentives are planned for the patients regarding the operations or the follow-up. All the centres and the medical personnel involved in the study will not receive any incentives or sponsorship related to the study itself. No benefits in any form will be received in particular from any commercial party related directly or indirectly to the subject of this study.

TIME FRAME - FINISHING DATE - REPORTING DATE

Time frame with the duration of the study, the finishing and reporting dates are shown in the **APPENDIX 13**.

ORGANIZATION

Trial Steering Committee (TSC)

The TSC comprises:

Luca Ansaloni, Surgeon (Chairman);

Luigi Frigerio, Gynecologist;

Roberto Labianca, Oncologist;

Fausto Catena, Surgeon;

Pierandrea De Iaco, Gynecologist;

Claudio Zamagni, Oncologist;

Elio Campagnutta, Gynecologist, SICHIG Representative;

To be appointed, Surgical, Gynecological and/or Oncological Societies Representatives.

The specific tasks of the Steering Committee will be:

(a) to approve the main study protocol;

(b) to approve necessary changes in the protocol based on considerations of feasibility and practicability;

(c) to receive reports from the Local Coordinators;

(d) to resolve problems brought to it by the Project Management Group;

(e) to approve study reports and papers for publication.

Within the Trial Steering Committee a small group will continue to work closely on a day-to-day basis to enable the smooth and efficient running of the trial: this will be the Project Management Group & Data Monitoring Committee (PMG&DMC).

Project Management Group and Data Monitoring Committee

The PMG&DMC will include: Marco Lotti (Surgeon and Trials Co-ordinator), Federico Coccolini (Surgeon and Trials Co-ordinator), Michele Pisano (Surgeon), Giuseppe Grosso (Gynecologist), Marco Carnelli (Gynecologist), Diego Rossetti (Gynecologist).

The responsibilities of the PMG&DMC include:

(a) recruitment of participating centres;

(b) distribution and supply of data collection forms and other appropriate documentation for the trial;
(c) data collection and management;
(d) data entry and cleaning;
(e) data analysis;
(f) collection of adverse event data;
(g) organising and providing information for the TSC and the Ethical Committee of the participating centres.

Local co-ordination

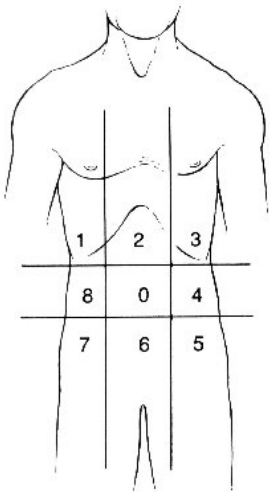
Each participating centre will identify almost two local surgeon/gynecologist/oncologist acting as co-ordinators.
For the "Ospedali Riuniti di Bergamo" Hospital, the local co-ordinators are Lotti Marco (Surgeon), Michele Pisano (Surgeon), Roberto Manfredi (Surgeon), Elia Poiasina (Surgeon), Federico Coccolini (Surgeon), Giuseppe Grosso (Gynecologist), Marco Carnelli (Gynecologist), Gaetano Trezzi (Gynecologist), Daniela Bornaghi (Gynecologist), Diego Rossetti (Gynecologist).

The responsibility of the local co-ordinators will be to:
(a) be familiar with the trial;
(b) liaise with the PMG&DMC and the Trial Co-ordinating centre in Bergamo;
(c) ensure that all medical and nursing staff involved in the care of patients are informed about the trial;
(d) ensure that mechanisms for recruitment of eligible patients (including information material) are in place, monitor their effectiveness, and discuss reasons for the non-recruitment of any eligible patient with relevant staff;
(e) ensure that supplies of data collection forms are always available, that they are completed and returned to the Trial Co-ordinating centre promptly (through the Web-Site), and to deal with any queries arising;
(f) notify the trial co-ordinating centre of any serious adverse events;
(g) facilitate other aspects of local collaboration as appropriate;
(h) make all data available for verification, audit and inspection purposes as necessary;
(i) ensure that the confidentiality of all information about trial participants is respected by all persons.

APPENDIX 0

Peritoneal Cancer Index (PCI). The index will be calculated as the sum of the lesion size of the tumour in all the abdominopelvic regions involved by carcinomatosis. The score of the PCI ranged from 1 to 39 and will be calculated for each patients.

Peritoneal Cancer Index

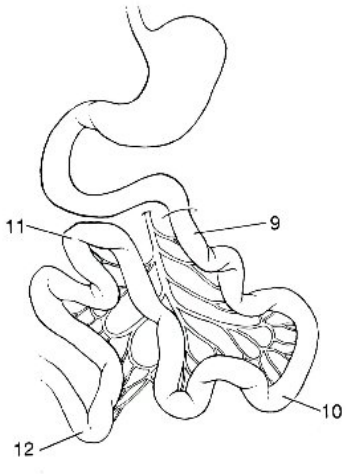


Regions	Lesion Size
0 Central	____
1 Right Upper	____
2 Epigastrium	____
3 Left Upper	____
4 Left Flank	____
5 Left Lower	____
6 Pelvis	____
7 Right Lower	____
8 Right Flank	____
9 Upper Jejunum	____
10 Lower Jejunum	____
11 Upper Ileum	____
12 Lower Ileum	____

PCI ☐

Lesion Size Score

LS 0 No tumor seen
LS 1 Tumor up to 0.5 cm
LS 2 Tumor up to 5.0 cm
LS 3 Tumor > 5.0 cm or confluence



APPENDIX 1

Laparoscopic scoring system

to assess the possibility of tumor resection to zero residual (from Fagotti A, et al. Ann Surg Oncol. 2006 Aug;13(8):1156-61; modified).

Peritoneal carcinosis:	score 0:	carcinosis involving limited araea
	score 2:	patients with unresectable massive peritoneal involvemente as well with miliary pattern of distribution
Diaphragmatic disease:	score 0:	small isolated nodules
	score 2:	widespread infiltrating carcinosis or confluent nodules to the most part of the diaphragmatic surface
Mesenteric disease:	score 0:	small nodules
	score 2:	large infiltrating nodules or an involvement of the root of the mesentery are supposed on the basis of limited movements of the varius intestinal segments
Omental disease:	score 0:	isolated localization
	score 2:	large infiltrating nodules or an involvemt of the root of the mesentery are supposed on the basis of limited movements of the various intestinal segments
Bowel infiltration:	score 0:	disease free
	score 2:	bowel resection is assumed or when miliary carcinosis on the ansae is observed
Stomach infiltration:	score 0:	disease free
	score 2:	obvious neoplastic involvement of the gastric wall is observed.
Liver metastasis:	score 0:	disease free
	score 2:	surface lesions

APPENDIX 2

Evaluation of treatment response

Type of response	Description
Clinical response	
Complete response (cCR):	100% disappearance of all objectives signs of cancer, by clinical, Ca 125 and radiologic criteria, for minimum period of 1 month.
Partial response (cPR)	Tumour regression ≥50% in the product of the two perpendicular diameters of main measurable lesions and the absence of appearance of new lesions or tumour progression elsewhere, for a minimum period of 1 month.
Stable disease (cSD)	<25% increase and <50% regression in the product of the two perpendicular diameters of main measurable lesions
Disease progression (cDP)	≥25% increase in the product of the two perpendicular diameters of main measurable lesions (despite the simultaneous regression of other lesions) or appearance of new lesions elsewhere

APPENDIX 3

Pharmacokinetic profile of chemotherapiesscheduled in the present study when delivered intraperitoneally associated with hyperthermia

Drug	AUCpe/ AUCpl	Tumour penetration	Mechanism of hyperthermic modulation
Cisplatin	14	2-2.5 mm	Enhanced tissue absorption; increased DNA adduct formation; increased activity at low pH; Increased production of O2 radicals; reduction of cisplatin resistance
Paclitaxel	1000*	NA	Increased disruption of microtubules system and apoptosis

NA: data not available in the current literature;

*under normothermic condition;

AUC, area under the concentration-time curve in peritoneal cavity (AUCpe) and plasma (AUCpl). The AUC is calculated integrating the concentration curve over time and reflects the total amount of drug present in peritoneal cavity of plasma.

APPENDIX 4

Sample Size Calculation

Proportion Difference Power / Sample Size Calculation

(Revised 10/30/2009 - Also display results of uncorrected ("classical") calculation.)

This screen computes the sample size required to detect a difference between two proportions. Note: Before using this page for the first time, make sure you read the JavaStat user interface guidelines for important information about interacting with JavaStat pages.

Significance Level (alpha):	0.05	(Usually 0.05)
Power (% chance of detecting):	80	(Usually 80)
Group 1 Population Proportion:	.45	(Between 0.0 and 1.0)
Group 2 Population Proportion:	.75	(Between 0.0 and 1.0)
Relative Sample Sizes Required (Group 2 / Group 1):	1.0	(For equal samples, use 1.0)

Sample Size Required

	Group 1	Group 2	Total
"Classical" Calculation:	41	41	81
With Continuity Correction:	47	47	94

Note: This page incorporates a continuity correction to the usual sample-size formula based on the normal approximation to the binomial distribution. This correction increases the sample size (for each group) by an amount approximately equal to 2/abs(p1-p2), where p1 and p2 are the population proportions for the two groups. For a good discussion of this, see: *Statistical Methods for Rates and Proportions* by Joseph L. Fleiss (2nd ed., 1981, John Wiley & Sons, NY), chapter 3. This web page produces values consistent with those in Table A3 of that book.

APPENDIX 5

Ovarian Cancer FIGO Surgical Staging System

The full FIGO -- International Federation of Gynecology and Obstetrics -- ovarian cancer surgical staging system is based on Roman numerals as well as letters to designate sub-stages. In general, prognosis depends more upon the main Stage. However, the sub-stages can also be important in deciding between treatment recommendations. Read

Stage I - The cancer is limited to the ovaries

IA - Limited to one ovary and the outer ovarian capsule is not ruptured. There is no tumor on the external surface of the ovary and there is no ascites and/or the washings are negative.

IB - Cancer is present in both ovaries, but the outer capsule is intact and there is no tumor on external surface. There is no ascites and the washings are negative.

IC - The cancer is either Stage IA or IB level but the capsule is ruptured or there is tumor on the ovarian surface or malignant cells are present in ascites or washings.

Stage II - Cancer involves one or both ovaries with spread to other pelvic organs or surfaces.

IIA - Extension or implants onto the uterus and/or fallopian tube. The washings are negative washings and there is no ascites.

IIB - Extension or implants onto other pelvic tissues. The washings are negative and there is no ascites.

IIC - Pelvic extension or implants like Stage IIA or IIB but with positive pelvic washings

Stage III - Cancer spread outside the pelvis to the abdominal area, including metastases to liver surface.

IIIA - Tumor is grossly confined to the pelvis but with micro-scopic peritoneal metastases beyond pelvis to abdominal peritoneal surfaces or the omentum.

IIIB - Same as IIIA but with macro-scopic peritoneal or omental metastases beyond pelvis less than 2 cm in size

IIIC - Same as IIIA but with peritoneal or omental metastases beyond pelvis, larger than 2 cm or lymph node metastases to inguinal, pelvic, or para-aortic areas.

Stage IV - Metastases or spread to the liver or outside the peritoneal cavity to areas such as the chest or brain.

APPENDIX 6

ECOG PERFORMANCE STATUS

These scales and criteria are used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. They are included here for health care professionals to access.

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

APPENDIX 7

INFORMED CONSENT FORM

USC OSTERICIA e GINECOLOGIA, USC CHIRURGIA GENERALE 1

CONSENSO INFORMATO
Versione 3.0; 18 luglio 2011

TITOLO:	PROTOCOLLO PER LO STUDIO SPERIMENTALE CHORINE, RIGUARDANTE INTERVENTI DI PERITONECTOMIA (PC) ASSOCIATA A CHEMIO IPERTERMIA INTRA PERITONEALE (HIPEC) PER CARCINOSI PERITONEALE DA NEOPLASIA EPITELIALE TUBO/OVARICA IN STADIO AVANZATO. Studio di fase III con l'intento di definire l'efficacia della chemio-ipertermia intraperitoneale associata a chirurgia citoriduttiva nell'aumentare la sopravvivenza libera da malattia, valutandone inoltre l'impatto in termini di morbi-mortalità perioperatoria.
PROTOCOLLO CHORINE:	Stage IIIC unresectable epithelial ovarian/tubal cancer with partial or complete response after 1st line neoadjuvant chemotherapy (3 cycles CBDCA+Paclitaxel): a phase 3 prospective randomized study comparing cytoreductive surgery + hyperthermic intraperitoneal chemotherapy (CDDP+Paclitaxel) + 3 cycles CBDCA+Paclitaxel vs cytoreductive surgery alone + 3 cycles CBDCA+Paclitaxel.
PROMOTORE:	USC OSTETRICIA e GINECOLOGIA, USC CHIRURGIA 1.
SPERIMENTATORE:	Dott. Luca Ansaloni, (USC Chirurgia 1, Largo Barozzi, 1 - 24128 Bergamo, Tel.: 035269368, Fax 035266567, e-mail: lansaloni@ospedaliriuniti.bergamo.it; Dott. Luigi Frigerio (USC Ostericia e Ginecologia), Dott. Marco Lotti (USC Chirurgia 1). (Collaboratori: Dott. Luca Campanati, Dott. Federico Coccolini, Dott. Nicola Colaianni, Dott. Stefano Magnone, Dott. Roberto Manfredi, Dott. Dario Piazzalunga, Dott. Michele Pisano, Dott. Elia Poiasina, Dott. Eugenio Poletti).

1. Confermo di aver letto e compreso il foglio informativo per i pazienti (versione 1, maggio 2011) per lo studio sopracitato e di aver avuto ampio tempo ed opportunità di porre domande ed ottenere risposte soddisfacenti. ☐

2. Ho compreso che la mia partecipazione è volontaria e che posso ritirarmi dallo studio in qualsiasi momento, senza dover dare spiegazioni e senza che le mie cure mediche ed i miei diritti ne risentano. ☐

3. Ho compreso che parti delle mie cartelle, dalle quali risulta che sto partecipando ad una ricerca clinica, possono essere visionate dalle Autorità Regolatorie, dai consulenti, dai comitati etici e dalle amministrazioni sanitarie locali. Acconsento che queste persone abbiano accesso ai miei dati. ☐

4. Accetto che i miei dati personali siano trasferiti in altri Paesi Europei ed anche non Europei (l'ottenimento ed il trasferimento di qualsiasi dato dovrà essere in accordo alle Leggi No. 675 del 31/12/1996, D.M. 15 Luglio 1997 e No. 196 del 30/06/2003 e successivi aggiornamenti relativi alla legge sulla privacy ed alla normativa europea in materia). In particolare, i miei dati potranno essere inviati ad altri uffici del Promotore e ad altre Autorità Regolatorie, consulenti, comitati etici ed amministrazioni sanitarie locali che hanno un interesse rilevante in questo studio. ☐

5. Acconsento che il mio Medico di famiglia sia informato che sto partecipando a questo studio. ☐

6. Acconsento a partecipare a questo studio. ☐

Nome della Paziente	Data (GG/MM/ANNO)	Firma

Nome della persona che raccoglie il consenso informato *(*Sperimentatore o altra persona designata*)*	Data (GG/MM/ANNO)	Firma

USC OSTERICIA E GINECOLOGIA, USC CHIRURGIA GENERALE 1

CONSENSO INFORMATO ALL'INTERVENTO DI PERITONECTOMIA (PC) ASSOCIATA A CHEMIO IPERTERMIA INTRA PERITONEALE (HIPEC) PER CARCINOSI PERITONEALE DA NEOPLASIA EPITELIALE TUBO/OVARICA IN STADIO AVANZATO

Io Sottoscritta, ……., nata il ……..…….., dichiaro di essere a conoscenza che l'intervento a cui sarò sottoposta in data …....., consisterà in una laparotomia mediana (incisione centrale) con eventuale asportazione delle precedenti cicatrici chirurgiche e, quindi, nell'asportazione della neoplasia peritoneale.

Tale procedura potrà richiedere:

- ☑ la resezione di tratti dello stomaco, di ileo e del colon fino al retto,
- ☑ la splenectomia
- ☑ l'isteroannessiectomia
- ☑ la linfoadenectomia pelvica e lomboaortica
- ☑ l'escissione della cicatrice ombelicale
- ☑ la resezione parziale o totale del diaframma
- ☑ la colecistectomia, eventualmente associata a resezione epatica
- ☑ il confezionamento di ileostomia o colostomia
- ☑ altro

  (specificare……)

A completamento delle suddette resezioni, sarà eseguita l'asportazione delle localizzazioni peritoneali, mediante asportazione (peritonectomia) del peritoneo invaso da malattia.

Eseguita la fase di asportazione della neoplasia, qualora l'asportazione delle localizzazioni di malattia fosse ottimale (noduli residui non superiori a 2.5mm), verrà eseguita una estrazione a sorte

(Randomizzazione) che determinerà se sarò o non sarò quindi sottoposta ad un trattamento consistente in: perfusione ipertermico-antiblastica del peritoneo con Cisplatino (CDDP, 43.0 mg/l di perfusato o 100 mg/m^2 di superficie corporea) e Paclitaxel (175 mg/m^2 di superficie corporea).
Sono cosciente che la decisione in merito ad eseguire la procedura di perfusione ipertermico-antiblastica del peritoneo sarà stabilita solo dal caso e non determinata dai Chirurghi: questa assegnazione casuale è parte fondamentale del protocollo a cui ho deciso di aderire.
La procedura di perfusione ipertermico-antiblastica del peritoneo consisterà nel far circolare in peritoneo una soluzione per dialisi peritoneale contenente i farmaci, con temperatura di ingresso di circa 42,5 gradi ed uscita di circa 40 gradi per 90 minuti. Tale trattamento ipertermico antiblastico si rende necessario per controllare la eventuale presenza di malattia microscopica peritoneale (cellule tumorali non visibili ad occhio nudo).

Sono al corrente che la adozione di tale procedura di "perfusione ipertermica antiblastica intraperitoneale":

1. allungherà i tempi della procedura chirurgica;
2. mi esporrà ad un possibile maggior numero di complicanze post-operatorie che in conseguenza di una procedura standard (fino al 23%) e ad una possibile mortalità (fino al 2%).
3. al fine di non rischiare la deiscenza ("cedimento") delle possibili suture intestinali, potrà essere indicato il confezionamento di una derivazione intestinale temporanea o definitiva (ileostomia o colostomia) e, talvolta, di una digiunostomia per alimentazione enterale.
4. i risultati della metodica sono descritti nella letteratura internazionale come positivi anche se non esistono ancora studi che abbiano una sicura valenza scientifica statistica.
5. richiederà con alta probabilità la trasfusione di emazie concentrate e/o di plasma fresco.
6. dati i precedenti chirurgici e la tipologia di diffusione della malattia, potrà essere necessario variare l'approccio proposto, tale valutazione potrà essere effettuata soltanto al tavolo operatorio, non essendo possibile soltanto in base agli esami strumentali eseguiti.

Sono stata informata circa le procedure che verranno messe in atto, dal Dott. .....
……., che controfirma questo mio "Consenso Informato" all'intervento.

Firma

La paziente Il medico

INFORMATIVA E MANIFESTAZIONE DEL CONSENSO AL TRATTAMENTO DEI DATI PERSONALI[1]

(ai sensi del D.lgs n. 196/2003 e Provvedimento del Garante per la Privacy del 24 luglio 2008- Sperimentazioni cliniche di medicinali)

Titolari del trattamento e relative finalità

Il Centro di sperimentazione A.O. Ospedali Riuniti di Bergamo, con sede legale in Largo Barozzi, 1 (di seguito il "**Centro di sperimentazione**"), rappresentato dal Coordinatore dello Studio Dr. Luca Ansaloni [Studio spontaneo], per gli ambiti di propria competenza e in accordo alle responsabilità previste dalle norme della buona pratica clinica (Decreto Legislativo 211/2003 e D.M. 17/12/2004), tratterà i Suoi dati personali, in particolare la Sua storia clinica e le informazioni che verranno raccolte sottoponendoLa agli esami e agli accertamenti medici illustrati nello stesso consenso informato al trattamento sanitario. Altri dati relativi alla Sua origine, ai Suoi stili di vita e alla Sua vita sessuale verranno trattati solo ove indispensabili per la realizzazione dello studio o per fini di farmacovigilanza.

A tal fine, i dati indicati saranno raccolti e conservati presso il Centro di Sperimentazione.

Obbligatorietà/Facoltatività del conferimento del dato

Il trattamento dei dati personali relativi al Suo stato di salute ed alla Sua storia clinica è indispensabile per lo svolgimento dello studio: il rifiuto di conferirli non Le consentirà di parteciparvi

Natura dei dati

Il medico che La seguirà nello studio La identificherà con un codice: i dati personali e sensibili che La riguardano raccolti nel corso dello studio, ad eccezione del Suo nominativo, saranno trasmessi al Cordinatore dello studio, registrati, elaborati e conservati unitamente a tale codice, a Soltanto il medico e i soggetti autorizzati potranno collegare questo codice al Suo nominativo.

I campioni biologici che Le sono stati prelevati verranno trattati nel rispetto delle misure di sicurezza descritte nel consenso informato al trattamento.[3]

Modalità del trattamento

I dati, trattati mediante strumenti anche elettronici, saranno diffusi solo in forma rigorosamente anonima, ad esempio attraverso pubblicazioni scientifiche, statistiche e convegni scientifici. La Sua partecipazione allo studio implica che, in conformità alla normativa sulle sperimentazioni cliniche dei medicinali, il personale del Centro di sperimentazione, il Comitato etico e le autorità sanitarie italiane e straniere potranno conoscere i dati che La riguardano, contenuti anche nella Sua documentazione clinica originale, con modalità tali da garantire la riservatezza della Sua identità.

Esercizio dei diritti

Potrà esercitare i diritti di cui all'art. 7 del Codice (es. accedere ai Suoi dati personali, integrarli, aggiornarli, rettificarli, opporsi al loro trattamento per motivi legittimi, ecc.) rivolgendosi direttamente al Centro di sperimentazione nella persona del Dottor Luca Ansaloni.

Potrà interrompere in ogni momento e senza fornire alcuna giustificazione la Sua partecipazione allo studio:

in tal caso, i campioni biologici a Lei correlati verranno distrutti. Non saranno inoltre raccolti ulteriori dati che La riguardano, ferma restando l'utilizzazione di quelli eventualmente già raccolti per determinare, senza alterarli, i risultati della ricerca.

CONSENSO

Sottoscrivendo il presente modulo acconsento al trattamento dei miei dati personali per gli scopi della ricerca nei limiti e con le modalità indicate nell'informativa fornitami con il presente documento.

Nome e Cognome dell'interessata *(in stampatello)* _____

Firma dell'interessata _____

Data _____

USC OSTETRICIA E GINECOLOGIA
Direttore: Prof. Luigi Frigerio

USC CHIRURGIA GENERALE I
Direttore: Dott. Luca Ansaloni

STUDIO SPERIMENTALE CHORINE

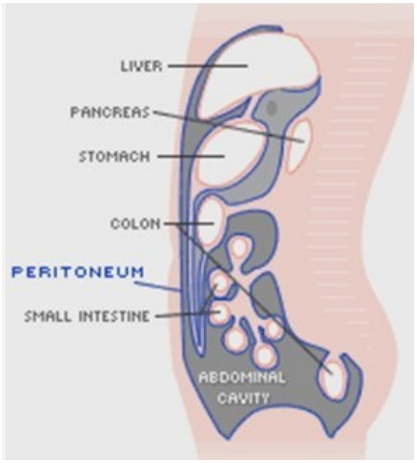
PERITONECTOMIA ASSOCIATA A CHEMIOIPERTERMIA INTRAPERITONEALE PER CARCINOSI PERITONEALE DA NEOPLASIA EPITELIALE TUBO/OVARICA IN STADIO AVANZATO. Studio di fase III con l'intento di definire l'efficacia della chemio-ipertermia intraperitoneale associata a chirurgia citoriduttiva nell'aumentare la sopravvivenza libera da malattia, valutandone inoltre l'impatto in termini di morbi-mortalità perioperatoria.

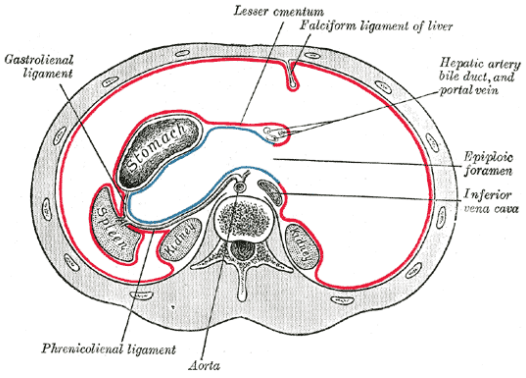
Foglio informativo per le Pazienti

LA CARCINOSI PERITONEALE: cos'è e come si cura

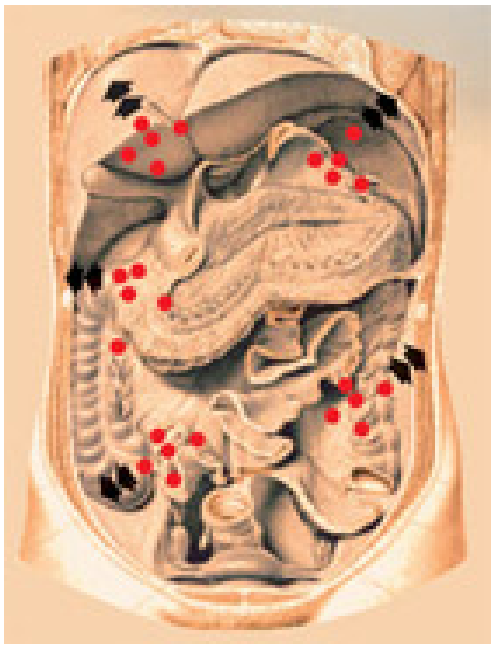
IL PERITONEO

Il **peritoneo** è una sorta di membrana, sottile e trasparente che ricopre la parete interna della cavità addominale e pelvica e tutti i visceri che vi sono ospitati (fegato, milza, intestino, utero e ovaie). Questa membrana è composta di due "foglietti": uno che riveste la faccia interna delle pareti della cavità addominale (detto parietale), l'altro che riveste gli organi interni fissandoli alle pareti addominali (viscerale). Tra i due foglietti peritoneali esiste uno spazio virtuale chiamato cavità peritoneale. In questa cavità è presente un liquido che agisce come lubrificante, permettendo ai due foglietti di "scorrere" l'uno sull'altro, semplificando i movimenti attivi e passivi degli organi addominali.





LA CARCINOSI PERITONEALE - COME ORIGINA



La **Carcinosi Peritoneale** rappresenta lo stadio evolutivo avanzato di molti tumori che si sviluppano in organi addominali, come colon, ovaio, appendice, stomaco, pancreas e fegato. Esistono inoltre, anche se sono per fortuna rari, tumori che si sviluppano direttamente dal peritoneo (mesoteliomi e pseudomixoma del peritoneo).

Il fattore di rischio principale per il tumore dell'**OVAIO** è la familiarità, causa del 5-10% del totale. Le donne che hanno una parente di primo grado (madre, sorella o figlia) affetta da carcinoma ovarico hanno un rischio più elevato di sviluppare questa neoplasia.

Nel tumore ovarico, quando la malattia cresce, le cellule tumorali raggiungono ed intaccano la membrana che riveste gli organi e la cavità dell'addome (il peritoneo). Questo avviene perchè le cellule malate possono circolare libere nella cavità addominale trasportate dal liquido peritoneale. Le cellule tumorali presenti nel liquido possono morire oppure sopravvivere nutrendosi di sostanze contenute nel liquido stesso. Queste cellule tendono ad accumularsi in alcuni punti di maggiore riassorbimento del liquido, formando degli agglomerati, che crescono sempre di più, diffondendosi in tutto l'addome, originando la carcinosi.

CARCINOSI PERITONEALE - COME SI CURA

Per molto tempo la **carcinosi peritoneale** è stata considerata una patologia non curabile chirurgicamente e poco sensibile alla chemioterapia. Fino a pochi anni fa era considerato impossibile intervenire con un intervento chirurgico e le prospettive di guarigione erano considerate nulle. Un ulteriore ostacolo alle cure sembrava inoltre dato dalla tendenza che molti farmaci somministrati per via endovenosa tendono a concentrarsi molto poco a livello del peritoneo.

Da circa 20 anni a questa parte però, l'evoluzione delle tecniche e la disponibilità di presidi terapeutici e metodi innovativi in ambito chirurgico e farmacologico hanno consentito di trattare in maniera presumibilmente più efficace anche questo tipo di invasione neoplastica (la carcinosi peritoneale).

Questo approccio prevede la **combinazione tra la chirurgia e la chemioipertermia intraperitoneale**, un intervento complesso che prevede due momenti: prima la rimozione chirurgica del tessuto tumorale, poi un "lavaggio" della cavità addominale con farmaci chemioterapici ad alte concentrazioni per distruggere le cellule tumorali libere.

Intervento chirurgico e chemioipertemia sono due parti distinte ed ugualmente importanti per la buona riuscita del trattamento. Per essere efficaci devono essere eseguiti uno immediatamente dopo l'altro: se trascorre anche solo una settimana infatti, la chemioipertermia risulta inefficace perchè le cellule tumorali libere vengono "intrappolate" in brevissimo tempo nel tessuto cicatriziale dove vengono inglobate, nascoste e protette.

LA PERITONECTOMIA

È l'intervento di eliminazione chirurgica del tumore. Prevede che venga rimosso l'organo colpito. Inoltre, tutti gli agglomerati di cellule tumorali visibili sul peritoneo vengono distrutti con strumenti molto sofisticati (bisturi elettrici ad alta potenza, bisturi, etc.). È un intervento lungo e complesso che può durare anche molte ore.

Il ricovero avviene uno o due giorni prima dell'operazione. La preparazione preoperatoria include un esame obiettivo generale, esami strumentali (TAC torace-addome-pelvi, eventuale PET total body) ed esami ematochimici (marcatori tumorali, etc.).

Nei giorni precedenti l'intervento chirurgico verranno posizionati gli stent ureterali: gli ureteri sono due piccoli tubicini che portano l'urina dai reni alla vescica; lo stent ureterale è uno strumento utilizzato per prevenire o risolvere rapidamente un quadro di ostruzione degli ureteri consentendo il drenaggio dell'urina dal rene direttamente in vescica. Questo strumento ha approssimativamente le dimensioni di uno spaghetto e può essere posizionato per via endoscopica attraverso la vescica. Sebbene gli stent ureterali a lunga permanenza (mesi o anni) si usino di solito per by-passare delle ostruzioni ureterali, quelli a permanenza più breve (settimane o mesi) invece si usano di solito in associazione a procedure chirurgiche sul tratto urinario o in prossimità di esso, per renderlo visibile e per proteggerlo da eventuali lesioni o per mantenerlo aperto in seguito alla riparazione delle stesse. In previsione della peritonectomia lo stent ureterale viene posizionato per questo secondo motivo. Il giorno prima dell'intervento poi, l'intestino viene preparato con un lavaggio intestinale.

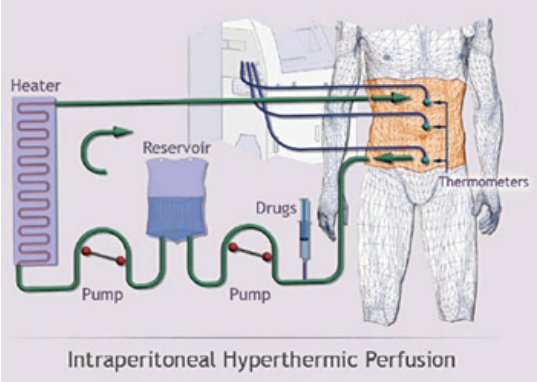
LA CHEMIOIPERTERMIA INTRAPERITONEALE

Una volta asportato il tumore nella sua componente visibile (macroscopica), ciò che presumibilmente rimane (la componente non visibile o microscopica) può essere aggredito con la chemioipertermia intraperitoneale, che ha quindi l'obiettivo di eliminare eventuali cellule tumorali libere nell'addome.

Si tratta di un particolare tipo di chemioterapia che sfrutta l'effetto combinato del calore più quello dei farmaci, che vanno ad agire localmente sulla zona interessata.

La **chemioipertermia intraperitoneale** si è dimostrata particolarmente efficace perché riesce superare quella "barriera" che impedisce ai farmaci chemioterapici di agire nella maniera migliore. Questa tecnica coniuga la possibilità di sfruttare da un lato l'effetto del calore che, oltre possedere di per sé proprietà tumoricide,

favorisce l'ingresso nelle cellule di alcuni farmaci e la loro attività antitumorale. Dall'altro, consente di esporre il tumore ai farmaci antitumorali a dosi centinaia di volte (in qualche caso anche mille volte) superiori a quelle ottenibili quando le stesse sostanze sono somministrate per endovena. Il tutto riducendo al minimo gli effetti indesiderati generali.



La chemioipertermia intraperitoneale in pratica è un vero e proprio "lavaggio" della zona addominale che viene eseguito attraverso l'inserimento di quattro tubi nella parete addominale. Queste quattro cannule sono collegate ad un circuito esterno che funziona come una pompa. Una di queste serve per l'infusione del liquido, le altre, posizionate rispettivamente nella cavità nella porzione più alta, in sede centro addominale e nella pelvi, servono invece per la sua fuoriuscita.
La soluzione circolante viene portata ad una temperatura, di 42-43 gradi grazie ad uno scambiatore di calore. Il liquido rimane in circolo nell'addome per circa un'ora e mezzo, con un flusso di oltre mezzo litro al minuto. In questo modo, tutta la parte addominale viene lavata dalla soluzione farmacologica e si riescono a raggiungere anche le cellule tumorali libere. Una volta terminato il trattamento, il liquido viene aspirato completamente e viene effettuato un ulteriore lavaggio con una soluzione per dialisi peritoneale per circa cinque minuti.
Questo tipo di intervento ha già dimostrato la sua efficacia soprattutto nel combattere il mesotelioma e lo pseudomixoma del peritoneo (rare neoplasie), ma alcuni studi hanno dimostrato che può in alcune situazioni essere efficace anche nel trattamento di tumori del colon, dello stomaco e dell'ovaio. Ulteriori ricerche per valutare gli effetti di questa terapia su questi tipi di cancro sono attualmente in corso: lo studio CHORINE è uno di questi.

Scopo dello studio CHORINE
Molte casistiche hanno mostrato risultati promettenti, ma l'efficacia dell'HIPEC associata alla chirurgia/peritonectomia nell'aumentare la sopravvivenza delle donne affette da tumore dell'ovaio non è ancora stata verificata in uno studio rigoroso.

Poiché si tratta di un intervento invasivo e piuttosto aggressivo che richiede di rimanere in ospedale per circa un mese (una settimana circa in terapia intensiva), esistono dei rischi specifici legati a ciascuna delle due fasi del trattamento: durante l'intervento chirurgico potrebbero infatti verificarsi delle complicanze (in media nel 15% dei casi), tali da rendere necessario il ritorno in sala operatoria.

Allo stesso modo, potrebbero verificarsi delle reazioni al farmaco utilizzato (si

manifestano nel 20% circa dei pazienti).

Tali complicanze rendono ragione del fatto che esiste una piccola ma riconosciuta mortalità perioperatoria connessa alla procedura.

Lo studio CHORINE si propone di valutare la morbi-mortalità connessa alla procedura valutandone altresì l'efficacia nel medio-lungo periodo: se i risultati riportati nelle casistiche fossero confermati dallo studio CHORINE, questo permetterà in futuro di garantire maggiori possibilità di guarigione alle donne affette da tumore dell'ovaio.

Bergamo, 18 luglio 2011

APPENDIX 8

NCI CTC Toxicity scale Version 2.0

COMMON TOXICITY CRITERIA (NCI CTC)

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
			ALLERGY/IMMUNOLOGY		
Allergic reaction/ hypersensitivity (including drug fever)	none	transient rash, drug fever < 38°C (<100.4°F)	urticaria, drug fever ≥ 38°C (≥100.4°F), and/or asymptomatic bronchospasm	symptomatic bronchospasm, requiring parenteral medication(s), with or without urticaria; allergy-related edema/angioedema	anaphylaxis
Note: Isolated urticaria, in the absence of other manifestations of an allergic or hypersensitivity reaction, is graded in the DERMATOLOGY/SKIN category.					
Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip)	none	mild, not requiring treatment	moderate, requiring treatment	-	-
Autoimmune reaction	none	serologic or other evidence of autoimmune reaction but patient is asymptomatic (e.g., vitiligo), all organ function is normal and no treatment is required	evidence of autoimmune reaction involving a non-essential organ or function (e.g., hypothyroidism), requiring treatment other than immunosuppressive drugs	reversible autoimmune reaction involving function of a major organ or other toxicity (e.g., transient colitis or anemia), requiring short-term immunosuppressive treatment	autoimmune reaction causing major grade 4 organ dysfunction; progressive and irreversible reaction; long-term administration of high-dose immuno-suppressive therapy required
Also consider Hypothyroidism, Colitis, Hemoglobin, Hemolysis.					
Serum sickness	none	-	-	present	-
Urticaria is graded in the DERMATOLOGY/SKIN category if it occurs as an isolated symptom. If it occurs with other manifestations of allergic or hypersensitivity reaction, grade as Allergic reaction/hypersensitivity above.					
Vasculitis	none	mild, not requiring treatment	symptomatic, requiring medication	requiring steroids	ischemic changes or requiring amputation
Allergy/Immunology-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
			AUDITORY/HEARING		
Conductive hearing loss is graded as Middle ear/hearing in the AUDITORY/HEARING category.					
Earache is graded in the PAIN category.					
External auditory canal	normal	external otitis with erythema or dry desquamation	external otitis with moist desquamation	external otitis with discharge, mastoiditis	necrosis of the canal soft tissue or bone
Note: Changes associated with radiation to external ear (pinnae) are graded under Radiation dermatitis in the DERMATOLOGY/SKIN category.					
Inner ear/hearing	normal	hearing loss on audiometry only	tinnitus or hearing loss, not requiring hearing aid or treatment	tinnitus or hearing loss, correctable with hearing aid or treatment	severe unilateral or bilateral hearing loss (deafness), not correctable
Middle ear/hearing	normal	serous otitis without subjective decrease in hearing	serous otitis or infection requiring medical intervention; subjective decrease in hearing; rupture of tympanic membrane with discharge	otitis with discharge, mastoiditis or conductive hearing loss	necrosis of the canal soft tissue or bone
Auditory/Hearing-Other (Specify, _____)	normal	mild	moderate	severe	life-threatening or disabling
			BLOOD/BONE MARROW		
Bone marrow cellularity	normal for age	mildly hypocellular or 25% reduction from normal cellularity for age	moderately hypocellular or >25 - ≤ 50% reduction from normal cellularity for age or >2 but <4 weeks to recovery of normal bone marrow cellularity	severely hypocellular or >50 - ≤ 75% reduction in cellularity for age or 4 - 6 weeks to recovery of normal bone marrow cellularity	aplasia or >6 weeks to recovery of normal bone marrow cellularity
Normal ranges: children (≤ 18 years) younger adults (19-59) older adults (≥ 60 years)	 90% cellularity average 60-70% cellularity average 50% cellularity average				

Toxicity	Grade 0	1	2	3	4
Note: Grade Bone marrow cellularity only for changes related to treatment not disease.					
CD4 count	WNL	< LLN - 500/mm^3	200 - < 500/mm^3	50 - < 200/mm^3	< 50/mm^3
Haptoglobin	normal	decreased	-	absent	-
Hemoglobin (Hgb)	WNL	< LLN - 10.0 g/dl < LLN - 100 g/L < LLN - 6.2 mmol/L	8.0 - < 10.0 g/dl 80 - < 100 g/L 4.9 - < 6.2 mmol/L	6.5 - < 8.0 g/dl 65 - 80 g/L 4.0 - < 4.9 mmol/L	< 6.5 g/dl < 65 g/L < 4.0 mmol/L
Note: The following criteria may be used for leukemia studies or bone marrow infiltrative/myelophthisic process if the protocol so specifies.					
For leukemia studies or bone marrow infiltrative/ myelophthisic processes	WNL	10 - <25% decrease from pretreatment	25 - <50% decrease from pretreatment	50 - <75% decrease from pretreatment	≥75% decrease from pretreatment
Hemolysis (e.g., immune hemolytic anemia, drug-related hemolysis, other) Also consider Haptoglobin, Hgb.	none	only laboratory evidence of hemolysis [e.g., direct antiglobulin test (DAT, Coombs') schistocytes]	evidence of red cell destruction and ≥ 2gm decrease in hemoglobin, no transfusion	requiring transfusion and/or medical intervention (e.g., steroids)	catastrophic consequences of hemolysis (e.g., renal failure, hypotension, bronchospasm, emergency splenectomy)
Leukocytes (total WBC)	WNL	< LLN - 3.0 x 10^9 /L < LLN - 3000/mm^3	≥2.0 - < 3.0 x 10^9 /L ≥2000 - < 3000/mm^3	≥1.0 - < 2.0 x 10^9 /L ≥1000 - < 2000/mm^3	< 1.0 x 10^9 /L < 1000/mm^3
For BMT studies:	WNL	≥2.0 - <3.0 X 10^9/L ≥2000 - <3000/mm^3	≥1.0 - <2.0 x 10^9 /L ≥1000 - <2000/mm^3	≥0.5 - <1.0 x 10^9 /L ≥500 - <1000/mm^3	<0.5 x 10^9 /L <500/mm^3
Note: The following criteria using age, race and sex normal values may be used for pediatric studies if the protocol so specifies.		*≥75 - <100% LLN*	*≥50 - <75% LLN*	*≥25 - 50% LLN*	*<25% LLN*
Lymphopenia	WNL	<LLN - 1.0 x 10^9 /L <LLN - 1000/mm^3	≥0.5 - <1.0 x 10^9 /L ≥500 - <1000/mm^3	<0.5 x 10^9 /L <500/mm^3	-
Note: The following criteria using age, race, and sex normal values may be used for pediatric studies if the protocol so specifies.		*≥75-<100%LLN*	*≥50-<75%LLN*	*≥25-<50%LLN*	*<25%LLN*
Neutrophils/granulocytes (ANC/AGC)	WNL	≥1.5 - <2.0 x 10^9 /L ≥1500 - <2000/mm^3	≥1.0 - <1.5 x 10^9 /L ≥1000 - <1500/mm^3	≥0.5 - <1.0 x 10^9 /L ≥500 - <1000/mm^3	< 0.5 x 10^9 /L < 500/mm^3
For BMT:	WNL	≥1.0 - <1.5 x 10^9 /L ≥1000 - <1500/mm^3	≥0.5 - <1.0 x 10^9 /L ≥500 - <1000/mm^3	≥0.1 - <0.5 x 10^9 /L ≥100 - <500/mm^3	<0.1 x 10^9 /L <100/mm^3
Note: The following criteria may be used for leukemia studies or bone marrow infiltrative/myelophthisic process if the protocol so specifies.					
For leukemia studies or bone marrow infiltrative/ myelophthisic process	WNL	10 - <25% decrease from baseline	25 - <50% decrease from baseline	50 - <75% decrease from baseline	≥75% decrease from baseline
Platelets	WNL	< LLN - <75.0 x 10^9 /L < LLN - 75000/mm^3	≥50.0 - < 75.0 x 10^9 /L ≥50000 - < 75000/mm^3	≥10.0 - < 50.0 x 10^9 /L ≥10000 - < 50000/mm^3	< 10.0 x 10^9 /L < 10000/mm^3
For BMT:	WNL	≥50.0 - <75.0 x 10^9 /L ≥50000 - <75000/mm^3	≥20.0 - <50.0 x 10^9 /L ≥20000 - <50000/mm^3	≥10.0 - <20.0 x 10^9 /L ≥10000 - <20000/mm^3	<10.0 x 10^9 /L <10000/mm^3
Note: The following criteria may be used for leukemia studies or bone marrow infiltrative/myelophthisic process if the protocol so specifies.					
For leukemia studies or bone marrow infiltrative/ myelophthisic process	WNL	10 - <25% decrease from baseline	25 - <50% decrease from baseline	50 - <75% decrease from baseline	≥75% decrease from baseline
Transfusion: Platelets	none	-	-	yes	platelet transfusions and other measures required to improve platelet increment; platelet transfusion refractoriness associated with life-threatening bleeding. (e.g., HLA or cross matched platelet transfusions)
For BMT:	none	1 platelet transfusion in 24 hours	2 platelet transfusions in 24 hours	≥3 platelet transfusions in 24 hours	platelet transfusions and other measures required to improve platelet increment; platelet transfusion refractoriness associated with life-threatening bleeding. (e.g., HLA or cross matched platelet transfusions)
Also consider Platelets.					
Transfusion: pRBCs	none	-	-	Yes	-
For BMT:	none	≤2 u pRBC (*≤15cc/kg*) in 24 hours elective or planned	3 u pRBC (*>15 ≤30cc/kg*) in 24 hours elective or planned	≥4 u pRBC (*>30cc/kg*) in 24 hours	hemorrhage or hemolysis associated with life-threatening anemia; medical

Toxicity	Grade 0	1	2	3	4
					intervention required to improve hemoglobin
Also consider Hemoglobin.					
Blood/Bone Marrow-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
CARDIOVASCULAR (ARRHYTHMIA)					
Conduction abnormality/ Atrioventricular heart block	none	asymptomatic, not requiring treatment (e.g., Mobitz type I second-degree AV block, Wenckebach)	symptomatic, but not requiring treatment	symptomatic and requiring treatment (e.g., Mobitz type II second-degree AV block, third-degree AV block)	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Nodal/junctional arrhythmia/dysrhythmia	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Palpitations	none	present	-	-	-
Note: Grade palpitations only in the absence of a documented arrhythmia.					
Prolonged QTc interval (QTc > 0.48 seconds)	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Sinus bradycardia	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Sinus tachycardia	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment of underlying cause	-
Supraventricular arrhythmias (SVT/atrial fibrillation/ flutter)	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Syncope (fainting) is graded in the NEUROLOGY category.					
Vasovagal episode	none	-	present without loss of consciousness	present with loss of consciousness	-
Ventricular arrhythmia (PVCs/bigeminy/trigeminy/ ventricular tachycardia)	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Cardiovascular/ Arrhythmia-Other (Specify, _____)	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic, and requiring treatment of underlying cause	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
CARDIOVASCULAR (GENERAL)					
Acute vascular leak syndrome	absent	-	symptomatic, but not requiring fluid support	respiratory compromise or requiring fluids	life-threatening; requiring pressor support and/or ventilatory support
Cardiac-ischemia/infarction	none	non-specific T-wave flattening or changes	asymptomatic, ST- and T-wave changes suggesting ischemia	angina without evidence of infarction	acute myocardial infarction
Cardiac left ventricular function	normal	asymptomatic decline of resting ejection fraction of ≥ 10% but < 20% of baseline value; shortening fraction ≥ 24% but < 30%	asymptomatic but resting ejection fraction below LLN for laboratory or decline of resting ejection fraction ≥ 20% of baseline value; < 24% shortening fraction	CHF responsive to treatment	severe or refractory CHF or requiring intubation
CNS cerebrovascular ischemia is graded in the NEUROLOGY category.					
Cardiac troponin I (cTnI)	normal	-	-	levels consistent with unstable angina as defined by the manufacturer	levels consistent with myocardial infarction as defined by the manufacturer
Cardiac troponin T (cTnT)	normal	≥ 0.03 - < 0.05 ng/ml	≥ 0.05 - < 0.1 ng/ml	≥ 0.1 - < 0.2 ng/ml	≥ 0.2 ng/ml
Edema	none	asymptomatic, not requiring therapy	symptomatic, requiring therapy	symptomatic edema limiting function and unresponsive to therapy or requiring drug discontinuation	anasarca (severe generalized edema)
Hypertension	none	asymptomatic, transient increase by >20 mmHg (diastolic) or to > 150/100* if previously WNL; not requiring treatment	recurrent or persistent or symptomatic increase by > 20 mmHg (diastolic) or to > 150/100* if previously WNL; not requiring treatment	requiring therapy or more intensive therapy than previously	hypertensive crisis
**Note: For pediatric patients, use age and sex appropriate normal values > 95th percentile ULN.*					
Hypotension	none	changes, but not requiring	requiring brief fluid	requiring therapy and	shock (associated with

Toxicity	Grade 0	1	2	3	4
		therapy (including transient orthostatic hypotension)	replacement or other therapy but not hospitalization; no physiologic consequences	sustained medical attention, but resolves without persisting physiologic consequences	acidemia and impairing vital organ function due to tissue hypoperfusion)
Also consider Syncope (fainting). Note: Angina or MI is graded as Cardiac- ischemia/infarction in the CARDIOVASCULAR (GENERAL) category. *For pediatric patients, systolic BP 65 mmHg or less in infants up to 1 year old and 70 mmHg or less in children older than 1 year of age, use two successive or three measurements in 24 hours.*					
Myocarditis	none	-	-	CHF responsive to treatment	severe or refractory CHF
Operative injury of vein/artery	none	primary suture repair for injury, but not requiring transfusion	primary suture repair for injury, requiring transfusion	vascular occlusion requiring surgery or bypass for injury	myocardial infarction; resection of organ (e.g., bowel, limb)
Pericardial effusion/ pericarditis	none	asymptomatic effusion, not requiring treatment	pericarditis (rub, ECG changes, and/or chest pain)	physiologic consequences resulting from symptoms	tamponade (drainage or pericardial window required)
Peripheral arterial ischemia	none	-	brief episode of ischemia managed non-surgically and without permanent deficit	requiring surgical intervention	life-threatening or with permanent functional deficit (e.g., amputation)
Phlebitis (superficial) Note: Injection site reaction is graded in the DERMATOLOGY/SKIN category. Thrombosis/embolism is graded in the CARDIOVASCULAR (GENERAL) category.	none	-	present	-	-
Syncope (fainting) is graded in the NEUROLOGY category.					
Thrombosis/embolism	none	-	deep vein thrombosis, not requiring anticoagulant	deep vein thrombosis, requiring anticoagulant therapy	embolic event including pulmonary embolism
Vein/artery operative injury is graded as Operative injury of vein/artery in the CARDIOVASCULAR (GENERAL) category.					
Visceral arterial ischemia (non-myocardial)	none	-	brief episode of ischemia managed non-surgically and without permanent deficit	requiring surgical intervention	life-threatening or with permanent functional deficit (e.g., resection of ileum)
Cardiovascular/ General-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
COAGULATION					
Note: See the HEMORRHAGE category for grading the severity of bleeding events.					
DIC (disseminated intravascular coagulation) Also grade Platelets. Note: Must have increased fibrin split products or D-dimer in order to grade as DIC.	absent	-	-	laboratory findings present with no bleeding	laboratory findings and bleeding
Fibrinogen	WNL	≥0.75 - <1.0 x LLN	≥0.5 - <0.75 x LLN	≥0.25 - <0.5 x LLN	<0.25 x LLN
Note: The following criteria may be used for leukemia studies or bone marrow infiltrative/myelophthisic process if the protocol so specifies.					
For leukemia studies:	WNL	<20% decrease from pretreatment value or LLN	≥20 - <40% decrease from pretreatment value or LLN	≥40 - <70% decrease from pretreatment value or LLN	<50 mg%
Partial thromboplastin time (PTT)	WNL	> ULN - ≤ 1.5 x ULN	> 1.5 - ≤ 2 x ULN	>2 x ULN	-
Phelbitis is graded in the CARDIOVASCULAR (GENERAL) category.					
Prothrombin time (PT)	WNL	> ULN - ≤ 1.5 x ULN	> 1.5 - ≤ 2 x ULN	>2 x ULN	-
Thrombosis/embolism is graded in the CARDIOVASCULAR (GENERAL) category.					
Thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura/TTP or hemolytic uremic syndrome/HUS)	absent	-	-	laboratory findings present without clinical consequences	laboratory findings and clinical consequences, (e.g., CNS hemorrhage/ bleeding or thrombosis/ embolism or renal failure) requiring therapeutic intervention
For BMT:	-	evidence of RBC destruction (schistocytosis) without clinical consequences	evidence of RBC destruction with elevated creatinine (≤3 x ULN)	evidence of RBC destruction with creatinine (>3 x ULN) not requiring dialysis	evidence of RBC destruction with renal failure requiring dialysis and/or encephalopathy
Also consider Hemoglobin (Hgb), Platelets, Creatinine. Note: Must have microangiopathic changes on blood smear (e.g., schistocytes, helmet cells, red cell fragments).					
Coagulation-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
CONSTITUTIONAL SYMPTOMS					
Fatigue (lethargy, malaise, asthenia)	none	increased fatigue over baseline, but not altering normal activities	moderate (e.g., decrease in performance status by 1 ECOG level or 20% Karnofsky or *Lansky*) or causing difficulty performing some activities	severe (e.g., decrease in performance status by ≥2 ECOG levels or 40% Karnofsky or *Lansky*) or loss of ability to perform some activities	bedridden or disabling

Toxicity	Grade 0	1	2	3	4
Note: See Appendix III for performance status scales.					
Fever (in the absence of neutropenia, where neutropenia is defined as AGC < 1.0 x 10^9/L) Also consider Allergic reaction/hypersensitivity. Note: The temperature measurements listed above are oral or tympanic.	none	38.0 - 39.0°C (100.4 - 102.2°F)	39.1 - 40.0°C (102.3 - 104.0°F)	> 40.0°C (>104.0°F) for < 24hrs	> 40.0°C (>104.0°F) for > 24hrs
Hot flashes/flushes are graded in the ENDOCRINE category.					
Rigors, chills	none	mild, requiring symptomatic treatment (e.g., blanket) or non-narcotic medication	severe and/or prolonged, requiring narcotic medication	not responsive to narcotic medication	-
Sweating (diaphoresis)	normal	mild and occasional	frequent or drenching	-	-
Weight gain Also consider Ascites, Edema, Pleural effusion.	< 5%	5 - <10%	10 - <20%	≥ 20%	-
Weight gain - veno-occlusive disease (VOD) Note: The following criteria is to be used ONLY for weight gain associated with Veno-Occlusive Disease.	<2%	≥2 - <5%	≥5 - <10%	≥10% or as ascities	≥10% or fluid retention resulting in pulmonary failure
Weight loss Also consider Vomiting, Dehydration, Diarrhea.	< 5%	5 - <10%	10 - <20%	≥20%	-
Constitutional Symptoms-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
DERMATOLOGY/SKIN					
Alopecia	normal	mild hair loss	pronounced hair loss	-	-
Bruising (in absence of grade 3 or 4 thrombocytopenia) Note: Bruising resulting from grade 3 or 4 thrombocytopenia is graded as Petechiae/purpura and Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia in the HEMORRHAGE category, not in the DERMATOLOGY/SKIN category.	none	localized or in dependent area	generalized	-	-
Dermatitis, focal (associated with high-dose chemotherapy and bone marrow transplant)	none	faint erythema or dry desquamation	moderate to brisk erythema or a patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	confluent moist desquamation, ≥1.5 cm diameter, not confined to skin folds; pitting edema	skin necrosis or ulceration of full thickness dermis; may include spontaneous bleeding not induced by minor trauma or abrasion
Dry skin	normal	controlled with emollients	not controlled with emollients	-	-
Erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis)	absent	-	scattered, but not generalized eruption	severe or requiring IV fluids (e.g., generalized rash or painful stomatitis)	life-threatening (e.g., exfoliative or ulcerating dermatitis or requiring enteral or parenteral nutritional support)
Flushing	absent	present	-	-	-
Hand-foot skin reaction	none	skin changes or dermatitis without pain (e.g., erythema, peeling)	skin changes with pain, not interfering with function	skin changes with pain, interfering with function	-
Injection site reaction	none	pain or itching or erythema	pain or swelling, with inflammation or phlebitis	ulceration or necrosis that is severe or prolonged, or requiring surgery	-
Nail changes	normal	discoloration or ridging (koilonychia) or pitting	partial or complete loss of nail(s) or pain in nailbeds	-	-
Petechiae is graded in the HEMORRHAGE category.					
Photosensitivity	none	painless erythema	painful erythema	erythema with desquamation	-
Pigmentation changes (e.g., vitiligo)	none	localized pigmentation changes	generalized pigmentation changes	-	-
Pruritus	none	mild or localized, relieved spontaneously or by local measures	intense or widespread, relieved spontaneously or by systemic measures	intense or widespread and poorly controlled despite treatment	-
Purpura is graded in the HEMORRHAGE category.					
Radiation dermatitis Note: Pain associated with radiation dermatitis is graded separately in the PAIN category as Pain due to radiation.	none	faint erythema or dry desquamation	moderate to brisk erythema or a patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	confluent moist desquamation, ≥1.5 cm diameter, not confined to skin folds; pitting edema	skin necrosis or ulceration of full thickness dermis; may include bleeding not induced by minor trauma or abrasion
Radiation recall reaction (reaction	none	faint erythema or dry desquamation	moderate to brisk erythema or a patchy moist	confluent moist desquamation, ≥1.5 cm	skin necrosis or ulceration of full

Toxicity	Grade 0	1	2	3	4
following chemotherapy in the absence of additional radiation therapy that occurs in a previous radiation port)			desquamation, mostly confined to skin folds and creases; moderate edema	diameter, not confined to skin folds; pitting edema	thickness dermis; may include bleeding not induced by minor trauma or abrasion
Rash/desquamation	none	macular or papular eruption or erythema without associated symptoms	macular or papular eruption or erythema with pruritus or other associated symptoms covering <50% of body surface or localized desquamation or other lesions covering <50% of body surface area	symptomatic generalized erythroderma or macular, papular or vesicular eruption or desquamation covering ≥50% of body surface area	generalized exfoliative dermatitis or ulcerative dermatitis
For BMT:	none	macular or papular eruption or erythema covering <25% of body surface area without associated symptoms	macular or papular eruption or erythema with pruritis or other associated symptoms covering ≥25 - <50% of body surface or localized desquamation or other lesions covering ≥25 - <50% of body surface area	symptomatic generalized erythroderma or symptomatic macular, papular or vesicular eruption, with bullous formation, or desquamation covering ≥50% of body surface area	generalized exfoliative dermatitis or ulcerative dermatitis or bullous formation
Also consider Allergic reaction/hypersensitivity. Note: Erythema multiforme (Stevens-Johnson syndrome) is graded separately as Erythema multiforme.					
Urticaria (hives, welts, wheals)	none	requiring no medication	requiring PO or topical treatment or IV medication or steroids for <24 hours	requiring IV medication or steroids for ≥24 hours	-
Wound- infectious	none	cellulitis	superficial infection	infection requiring IV antibiotics	necrotizing fascitis
Wound- non-infectious	none	incisional separation	incisional hernia	fascial disruption without evisceration	fascial disruption with evisceration
Dermatology/Skin -Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
ENDOCRINE					
Cushingoid appearance (e.g., moon face with or without buffalo hump, centripetal obesity, cutaneous striae) Also consider Hyperglycemia, Hypokalemia.	absent	-	present	-	-
Feminization of male	absent	-	-	present	-
Gynecomastia	none	mild	pronounced or painful	pronounced or painful and requiring surgery	-
Hot flashes/flushes	none	mild or no more than 1 per day	moderate and greater than 1 per day	-	-
Hypothyroidism	absent	asymptomatic,TSH elevated, no therapy given	symptomatic or thyroid replacement treatment given	patient hospitalized for manifestations of hypothyroidism	myxedema coma
Masculinization of female	absent	-	-	present	-
SIADH (syndrome of inappropriate antidiuretic hormone)	absent	-	-	present	-
Endocrine-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
GASTROINTESTINAL					
Amylase is graded in the METABOLIC/LABORATORY category.					
Anorexia	none	loss of appetite	oral intake significantly decreased	requiring IV fluids	requiring feeding tube or parenteral nutrition
Ascites (non-malignant)	none	asymptomatic	symptomatic, requiring diuretics	symptomatic, requiring therapeutic paracentesis	life-threatening physiologic consequences
Colitis	none	-	abdominal pain with mucus and/or blood in stool	abdominal pain, fever, change in bowel habits with ileus or peritoneal signs, and radiographic or biopsy documentation	perforation or requiring surgery or toxic megacolon
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, Melena/GI bleeding, Rectal bleeding/hematochezia, Hypotension.					
Constipation	none	requiring stool softener or dietary modification	requiring laxatives	obstipation requiring manual evacuation or	obstruction or toxic megacolon

Toxicity	0	1	2	3	4
				Grade	
				enema	
Dehydration	none	dry mucous membranes and/or diminished skin turgor	requiring IV fluid replacement (brief)	requiring IV fluid replacement (sustained)	physiologic consequences requiring intensive care; hemodynamic collapse
Also consider Hypotension, Diarrhea, Vomiting, Stomatitis/pharyngitis (oral/pharyngeal mucositis).					
Diarrhea Patients without colostomy:	none	increase of < 4 stools/day over pre-treatment	increase of 4-6 stools/day, or nocturnal stools	increase of ≥7 stools/day or incontinence; or need for parenteral support for dehydration	physiologic consequences requiring intensive care; or hemodynamic collapse
Patients with a colostomy:	none	mild increase in loose, watery colostomy output compared with pretreatment	moderate increase in loose, watery colostomy output compared with pretreatment, but not interfering with normal activity	severe increase in loose, watery colostomy output compared with pretreatment, interfering with normal activity	physiologic consequences, requiring intensive care; or hemodynamic collapse
For BMT	none	>500 - ≤1000ml of diarrhea/day	>1000 - ≤1500ml of diarrhea/day	>1500ml of diarrhea/day	severe abdominal pain with or without ileus
For Pediatric BMT:		*>5 - ≤10 ml/kg of diarrhea/day*	*>10 - ≤15 ml/kg of diarrhea/day*	*>15 ml/kg of diarrhea/day*	-
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, Pain, Dehydration, Hypotension.					
Duodenal ulcer (requires radiographic or endoscopic documentation)	none	-	requiring medical management or non-surgical treatment	uncontrolled by outpatient medical management; requiring hospitalization	perforation or bleeding, requiring emergency surgery
Dyspepsia/heartburn	none	mild	moderate	severe	-
Dysphagia, esophagitis, odynophagia (painful swallowing)	none	mild dysphagia, but can eat regular diet	dysphagia, requiring predominantly pureed, soft, or liquid diet	dysphagia, requiring IV hydration	complete obstruction (cannot swallow saliva) requiring enteral or parenteral nutritional support, or perforation
Note: If toxicity is radiation-related, grade either under Dysphagia- esophageal related to radiation or Dysphagia- pharyngeal related to radiation.					
Dysphagia- esophageal related to radiation	none	mild dysphagia, but can eat regular diet	dysphagia, requiring predominantly liquid, pureed or soft diet	dysphagia requiring feeding tube, IV hydration or hyperalimentation	complete obstruction (cannot swallow saliva); ulceration with bleeding not induced by minor trauma or abrasion or perforation
Also consider Pain due to radiation, Mucositis due to radiation. Note: Fistula is graded separately as Fistula- esophageal.					
Dysphagia - pharyngeal related to radiation	none	mild dysphagia, but can eat regular diet	dysphagia, requiring predominantly pureed, soft, or liquid diet	dysphagia, requiring feeding tube, IV hydration or hyperalimentation	complete obstruction (cannot swallow saliva); ulceration with bleeding not induced by minor trauma or abrasion or perforation
Also consider Pain due to radiation, Mucositis due to radiation. Note: Fistula is graded separately as Fistula- pharyngeal.					
Fistula- esophageal	none	-	-	present	requiring surgery
Fistula- intestinal	none	-	-	present	requiring surgery
Fistula- pharyngeal	none	-	-	present	requiring surgery
Fistula- rectal/anal	none	-	-	present	requiring surgery
Flatulence	none	mild	moderate	-	-
Gastric ulcer (requires radiographic or endoscopic documentation)	none	-	requiring medical management or non-surgical treatment	bleeding without perforation, uncontrolled by outpatient medical management; requiring hospitalization or surgery	perforation or bleeding, requiring emergency surgery
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia.					
Gastritis	none	-	requiring medical management or non-surgical treatment	uncontrolled by out-patient medical management; requiring hospitalization or surgery	life-threatening bleeding, requiring emergency surgery
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia.					
Hematemesis is graded in the HEMORRHAGE category.					
Hematochezia is graded in the HEMORRHAGE category as Rectal bleeding/hematochezia.					
Ileus (or neuroconstipation)	none	-	intermittent, not requiring intervention	requiring non-surgical intervention	requiring surgery
Mouth dryness	normal	mild	moderate	-	-
Mucositis Note: Mucositis not due to radiation is graded in the GASTROINTESTINAL category for specific sites: Colitis, Esophagitis, Gastritis, Stomatitis/pharyngitis (oral/pharyngeal mucositis), and Typhlitis; or the RENAL/GENITOURINARY category for Vaginititis. Radiation-related mucositis is graded as Mucositis due to radiation.					
Mucositis due to radiation	none	erythema of the mucosa	patchy pseudomembranous reaction (patches generally ≥ 1.5 cm in diameter and non-contiguous)	confluent pseudomembranous reaction (contiguous patches generally > 1.5 cm in diameter)	necrosis or deep ulceration; may include bleeding not induced by minor trauma or abrasion
Also consider Pain due to radiation.					

Toxicity	Grade 0	1	2	3	4
Note: Grade radiation mucositis of the larynx here. Dysphagia related to radiation is also graded as either Dysphagia- esophageal related to radiation or Dysphagia- pharyngeal related to radiation, depending on the site of treatment.					
Nausea	none	able to eat	oral intake significantly decreased	no significant intake, requiring IV fluids	-
Pancreatitis	none	-	-	abdominal pain with pancreatic enzyme elevation	complicated by shock (acute circulatory failure)
Also consider Hypotension. Note: Asymptomatic amylase and Amylase are graded in the METABOLIC/LABORATORY category.					
Pharyngitis is graded in the GASTROINTESTINAL category as Stomatitis/pharyngitis (oral/pharyngeal mucositis).					
Proctitis	none	increased stool frequency, occasional blood-streaked stools, or rectal discomfort (including hemorrhoids), not requiring medication	increased stool frequency, bleeding, mucus discharge, or rectal discomfort requiring medication; anal fissure	increased stool frequency/diarrhea, requiring parenteral support; rectal bleeding, requiring transfusion; or persistent mucus discharge, necessitating pads	perforation, bleeding or necrosis or other life-threatening complication requiring surgical intervention (e.g., colostomy)
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, and Pain due to radiation. Note: Fistula is graded separately as Fistula- rectal/anal. Proctitis occurring more than 90 days after the start of radiation therapy is graded in the RTOG/EORTC Late Radiation Morbidity Scoring Scheme. (See Appendix IV)					
Salivary gland changes	none	slightly thickened saliva/may have slightly altered taste (e.g., metallic); additional fluids may be required	thick, ropy, sticky saliva; markedly altered taste; alteration in diet required	-	acute salivary gland necrosis
Sense of smell	normal	slightly altered	markedly altered	-	-
Stomatitis/pharyngitis (oral/pharyngeal mucositis)	none	painless ulcers, erythema, or mild soreness in the absence of lesions	painful erythema, edema, or ulcers, but can eat or swallow	painful erythema, edema, or ulcers requiring IV hydration	severe ulceration or requires parenteral or enteral nutritional support or prophylatic intubation
For BMT:	none	painless ulcers, erythema, or mild soreness in the absence of lesions	painful erythema, edema or ulcers but can swallow	painful erythema, edema, or ulcers preventing swallowing or requiring hydration or parenteral (or enteral) nutritional support	severe ulceration requiring prophylactic intubation or resulting in documented aspiration pneumonia
Note: Radiation-related mucositis is graded as Mucositis due to radiation.					
Taste disturbance (dysgeusia)	normal	slightly altered	markedly altered	-	-
Typhlitis (inflammation of the cecum)	none	-	-	abdominal pain, diarrhea, fever, or radiographic documentation	perforation, bleeding or necrosis or other life-threatening complication requiring surgical intervention (e.g., colostomy)
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, Hypotension, Febrile/neutropenia.					
Vomiting	none	1 episode in 24 hours over pretreatment	2-5 episodes in 24 hours over pretreatment	≥6 episodes in 24 hours over pretreatment; or need for IV fluids	Requiring parenteral nutrition; or physiologic consequences requiring intensive care; hemodynamic collapse
Also consider Dehydration.					
Weight gain is graded in the CONSTITUTIONAL SYMPTOMS category.					
Weight loss is graded in the CONSTITUTIONAL SYMPTOMS category.					
Gastrointestinal-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
HEMORRHAGE					
Note: Transfusion in this section refers to pRBC infusion. For any bleeding with grade 3 or 4 platelets (< 50,000), always grade Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia. Also consider platelets, transfusion-pRBCS, and transfusion-platelets in addition to the grade that incorporates the site or type of bleeding. If the site or type of hemorrhage/bleeding is listed, also use the grading that incorporates the site of bleeding: CNS hemorrhage/bleeding, Hematuria, Hematemesis, Hemoptysis, Hemorrhage/bleeding with surgery, Melena/lower GI bleeding, Petechiae/purpura (Hemorrhage/bleeding into skin), Rectal bleeding/hematochezia, Vaginal bleeding. If the platelet count is ≥50,000 and the site or type of bleeding is listed, grade the specific site. If the site or type is not listed and the platelet count is ≥50,000, grade Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia and specify the site or type in the OTHER category.					
Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia	none	mild without transfusion		requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Also consider Platelets, Hemoglobin, Transfusion-platelet, Transfusion-pRBCs. Note: This toxicity must be graded for any bleeding with grade 3 or 4 thrombocytopenia. Also grade the site or type of hemorrhage/bleeding. If the site is not listed, grade as Other in the HEMORRHAGE category.					
Hemorrhage/bleeding without grade 3 or 4	none	mild without transfusion		requiring transfusion	catastrophic bleeding requiring major non-elective intervention

Toxicity	Grade 0	1	2	3	4
thrombocytopenia Also consider Platelets, Hemoglobin, Transfusion-platelet, Transfusion-pRBCs. Note: Bleeding in the absence of grade 3 or 4 thrombocytopenia is graded here only if the specific site or type of bleeding is not listed elsewhere in the HEMORRHAGE category. Also grade as Other in the HEMORRHAGE category.					
CNS hemorrhage/bleeding	none	-	-	bleeding noted on CT or other scan with no clinical consequences	hemorrhagic stroke or hemorrhagic vascular event (CVA) with neurologic signs and symptoms
Epistaxis	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Hematemesis	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Hematuria (in the absence of vaginal bleeding)	none	microscopic only	intermittent gross bleeding, no clots	persistent gross bleeding or clots; may require catheterization or instrumentation, or transfusion	open surgery or necrosis or deep bladder ulceration
Hemoptysis	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Hemorrhage/bleeding associated with surgery Note: Expected blood loss at the time of surgery is not graded as a toxicity.	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Melena/GI bleeding	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Petechiae/purpura (hemorrhage/bleeding into skin or mucosa)	none	rare petechiae of skin	petechiae or purpura in dependent areas of skin	generalized petechiae or purpura of skin or petechiae of any mucosal site	-
Rectal bleeding/ hematochezia	none	mild without transfusion or medication	persistent, requiring medication (e.g., steroid suppositories) and/or break from radiation treatment	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Vaginal bleeding	none	spotting, requiring < 2 pads per day	requiring ≥ 2 pads per day, but not requiring transfusion	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Hemorrhage-Other (Specify site, _____)	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
HEPATIC					
Alkaline phosphatase	WNL	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Bilirubin	WNL	> ULN - 1.5 x ULN	> 1.5 - 3.0 x ULN	> 3.0 - 10.0 x ULN	> 10.0 x ULN
Bilirubin- graft versus host disease (GVHD) Note: The following criteria are used only for bilirubin associated with graft versus host disease.	normal	≥2 - <3 mg/100 ml	≥3 - <6 mg/100 ml	≥6 - <15 mg/100 ml	≥15 mg/100 ml
GGT (γ - Glutamyl transpeptidase)	WNL	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Hepatic enlargement Note: Grade Hepatic enlargement only for changes related to VOD or other treatment related toxicity.	absent	-	-	present	-
Hypoalbuminemia	WNL	<LLN - 3 g/dl	≥2 - <3 g/dl	<2 g/dl	-
Liver dysfunction/failure (clinical) Note: Documented viral hepatitis is graded in the INFECTION category.	normal	-	-	asterixis	encephalopathy or coma
Portal vein flow	normal	-	decreased portal vein flow	reversal/retrograde portal vein flow	-
SGOT (AST) (serum glutamic oxaloacetic transaminase)	WNL	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
SGPT (ALT) (serum glutamic pyruvic transaminase)	WNL	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Hepatic-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
INFECTION/FEBRILE NEUTROPENIA					
Catheter-related infection	none	mild, no active treatment	moderate, localized infection, requiring local or oral treatment	severe, systemic infection, requiring IV antibiotic or antifungal	life-threatening sepsis (e.g., septic shock)

Toxicity	Grade 0	1	2	3	4
				treatment or hospitalization	
Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection) (ANC < 1.0 x 10^9/L, fever ≥38.5°C)	none	-	-	Present	Life-threatening sepsis (e.g., septic shock)
Note: Hypothermia instead of fever may be associated with neutropenia and is graded here.					
Infection (documented clinically or microbiologically) with grade 3 or 4 neutropenia (ANC < 1.0 x 10^9/L)	none	-	-	present	life-threatening sepsis (e.g., septic shock)
Note: Hypothermia instead of fever may be associated with neutropenia and is graded here. In the absence of documented infection with grade 3 or 4 neutropenia, grade as Febrile neutropenia.					
Infection with unknown ANC	none	-	-	present	life-threatening sepsis (e.g., septic shock)
Note: This toxicity criterion is used in the rare case when ANC is unknown.					
Infection without neutropenia	none	mild, no active treatment	moderate, localized infection, requiring local or oral treatment	severe, systemic infection, requiring IV antibiotic or antifungal treatment, or hospitalization	life-threatening sepsis (e.g., septic shock)
Infection/Febrile Neutropenia-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
Wound-infectious is graded in the DERMATOLOGY/SKIN category.					
LYMPHATICS					
Lymphatics	normal	mild lymphedema	moderate lymphedema requiring compression; lymphocyst	severe lymphedema limiting function; lymphocyst requiring surgery	severe lymphedema limiting function with ulceration
Lymphatics-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
METABOLIC/LABORATORY					
Acidosis (metabolic or respiratory)	normal	pH < normal, but ≥7.3	-	pH < 7.3	pH < 7.3 with life-threatening physiologic consequences
Alkalosis (metabolic or respiratory)	normal	pH > normal, but ≤7.5	-	pH > 7.5	pH > 7.5 with life-threatening physiologic consequences
Amylase	WNL	> ULN - 1.5 x ULN	> 1.5 - 2.0 x ULN	> 2.0 - 5.0 x ULN	>5.0 x ULN
Bicarbonate	WNL	< LLN - 16 mEq/dl	11 - 15 mEq/dl	8 - 10 mEq/dl	< 8 mEq/dl
CPK (creatine phosphokinase)	WNL	> ULN - 2.5 x ULN	> 2.5 - 5 x ULN	> 5 - 10 x ULN	> 10 x ULN
Hypercalcemia	WNL	> ULN - 11.5 mg/dl > ULN - 2.9 mmol/L	>11.5 - 12.5 mg/dl > 2.9 - 3.1 mmol/L	>12.5 - 13.5 mg/dl > 3.1 - 3.4 mmol/L	> 13.5 mg/dl > 3.4 mmol/L
Hypercholesterolemia	WNL	> ULN - 300 mg/dl > ULN - 7.75 mmol/L	> 300 - 400 mg/dl > 7.75 - 10.34 mmol/L	> 400 - 500 mg/dl >10.34 - 12.92 mmol/L	> 500 mg/dl > 12.92 mmol/L
Hyperglycemia	WNL	> ULN - 160 mg/dl > ULN - 8.9 mmol/L	> 160 - 250 mg/dl > 8.9 - 13.9 mmol/L	> 250 - 500 mg/dl > 13.9 - 27.8 mmol/L	> 500 mg/dl > 27.8 mmol/L or ketoacidosis
Hyperkalemia	WNL	> ULN - 5.5 mmol/L	> 5.5 - 6.0 mmol/L	> 6.0 - 7.0 mmol/L	> 7.0 mmol/L
Hypermagnesemia	WNL	> ULN - 3.0 mg/dl > ULN - 1.23 mmol/L	-	> 3.0 - 8.0 mg/dl > 1.23 - 3.30 mmol/L	> 8.0 mg/dl > 3.30 mmol/L
Hypernatremia	WNL	> ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L	>160 mmol/L
Hypertriglyceridemia	WNL	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 10 x ULN	> 10 x ULN
Hyperuricemia Also consider Tumor lysis syndrome, Renal failure, Creatinine, Potassium.	WNL	> ULN - ≤ 10 mg/dl ≤ 0.59 mmol/L without physiologic consequences	-	> ULN - ≤ 10 mg/dl ≤ 0.59 mmol/L with physiologic consequences	> 10 mg/dl > 0.59 mmol/L
Hypocalcemia	WNL	<LLN - 8.0 mg/dl <LLN - 2.0 mmol/L	7.0 - < 8.0 mg/dl 1.75 - < 2.0 mmol/L	6.0 - < 7.0 mg/dl 1.5 - < 1.75 mmol/L	<6.0 mg/dl < 1.5 mmol/L
Hypoglycemia	WNL	<LLN - 55 mg/dl <LLN - 3.0 mmol/L	40 - < 55 mg/dl 2.2 - < 3.0 mmol/L	30 - < 40 mg/dl 1.7 - < 2.2 mmol/L	< 30 mg/dl < 1.7 mmol/L
Hypokalemia	WNL	<LLN - 3.0 mmol/L	-	2.5 - <3.0 mmol/L	<2.5 mmol/L
Hypomagnesemia	WNL	<LLN - 1.2 mg/dl	0.9 - <1.2 mg/dl	0.7 - < 0.9 mg/dl	< 0.7 mg/dl

Toxicity	Grade 0	1	2	3	4
		<LLN - 0.5 mmol/L	0.4 - < 0.5 mmol/L	0.3 - < 0.4 mmol/L	< 0.3 mmol/L
Hyponatremia	WNL	<LLN - 130 mmol/L	-	120 - <130 mmol/L	<120 mmol/L
Hypophosphatemia	WNL	<LLN -2.5 mg/dl <LLN - 0.8 mmol/L	≥2.0 - <2.5 mg/dl ≥0.6 - <0.8 mmol/L	≥1.0 - <2.0 mg/dl ≥0.3 - <0.6 mmol/L	< 1.0 mg/dl <0.3 mmol/L
Hypothyroidism is graded in the ENDOCRINE category.					
Lipase	WNL	> ULN - 1.5 x ULN	> 1.5 - 2.0 x ULN	> 2.0 - 5.0 x ULN	> 5.0 x ULN
Metabolic/Laboratory-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
MUSCULOSKELETAL					
Arthralgia is graded in the PAIN category.					
Arthritis	none	mild pain with inflammation, erythema or joint swelling but not interfering with function	moderate pain with inflammation, erythema, or joint swelling interfering with function, but not interfering with activities of daily living	severe pain with inflammation, erythema, or joint swelling and interfering with activities of daily living	disabling
Muscle weakness (not due to neuropathy)	normal	asymptomatic with weakness on physical exam	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	bedridden or disabling
Myalgia is graded in the PAIN category.					
Myositis (inflammation/damage of muscle) Also consider CPK. Note: Myositis implies muscle damage (i.e., elevated CPK).	none	mild pain, not interfering with function	pain interfering with function, but not interfering with activities of daily living	pain interfering with function and interfering with activities of daily living	bedridden or disabling
Osteonecrosis (avascular necrosis)	none	asymptomatic and detected by imaging only	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	symptomatic; or disabling
Musculoskeletal-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
NEUROLOGY					
Aphasia, receptive and/or expressive, is graded under Speech impairment in the NEUROLOGY category.					
Arachnoiditis/meningismus/ radiculitis Also consider Headache, Vomiting, Fever.	absent	mild pain not interfering with function	moderate pain interfering with function, but not interfering with activities of daily living	severe pain interfering with activities of daily living	unable to function or perform activities of daily living; bedridden; paraplegia
Ataxia (incoordination)	normal	asymptomatic but abnormal on physical exam, and not interfering with function	mild symptoms interfering with function, but not interfering with activities of daily living	moderate symptoms interfering with activities of daily living	bedridden or disabling
CNS cerebrovascular ischemia	none	-	-	transient ischemic event or attack (TIA)	permanent event (e.g., cerebral vascular accident)
CNS hemorrhage/bleeding is graded in the HEMORRHAGE category.					
Cognitive disturbance/ learning problems	*none*	*cognitive disability; not interfering with work/school performance; preservation of intelligence*	*cognitive disability; interfering with work/school performance; decline of 1 SD (Standard Deviation) or loss of developmental milestones*	*cognitive disability; resulting in significant impairment of work/school performance; cognitive decline > 2 SD*	*inability to work/frank mental retardation*
Confusion	normal	confusion or disorientation or attention deficit of brief duration; resolves spontaneously with no sequelae	confusion or disorientation or attention deficit interfering with function, but not interfering with activities of daily living	confusion or delirium interfering with activities of daily living	harmful to others or self; requiring hospitalization
Cranial neuropathy is graded in the NEUROLOGY category as Neuropathy-cranial.					
Delusions	normal	-	-	present	toxic psychosis
Depressed level of consciousness Note: Syncope (fainting) is graded in the NEUROLOGY category.	normal	somnolence or sedation not interfering with function	somnolence or sedation interfering with function, but not interfering with activities of daily living	obtundation or stupor; difficult to arouse; interfering with activities of daily living	coma
Dizziness/lightheadedness	none	not interfering with function	interfering with function, but not interfering with activities of daily living	interfering with activities of daily living	bedridden or disabling
Dysphasia, receptive and/or expressive, is graded under Speech impairment in the NEUROLOGY category.					
Extrapyramidal/ involuntary movement/ restlessness	none	mild involuntary movements not interfering with function	moderate involuntary movements interfering with function, but not interfering with activities of daily living	severe involuntary movements or torticollis interfering with activities of daily living	bedridden or disabling
Hallucinations	normal	-	-	present	toxic psychosis
Headache is graded in the PAIN category.					

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Insomnia	normal	occasional difficulty sleeping not interfering with function	difficulty sleeping interfering with function, but not interfering with activities of daily living	frequent difficulty sleeping, interfering with activities of daily living	-
Note: This toxicity is graded when insomnia is related to treatment. If pain or other symptoms interfere with sleep do NOT grade as insomnia.					
Irritability *(children <3 years of age)*	*normal*	*mild; easily consolable*	*moderate; requiring increased attention*	*severe; inconsolable*	-
Leukoencephalopathy associated radiological findings	*none*	*mild increase in SAS (subarachnoid space) and/or mild ventriculomegaly; and/or small (+/- multiple) focal T2 hyperintensities, involving periventricular white matter or < 1/3 of susceptible areas of cerebrum*	*moderate increase in SAS; and/or moderate ventriculomegaly; and/or focal T2 hyperintensities extending into centrum ovale; or involving 1/3 to 2/3 of susceptible areas of cerebrum*	*severe increase in SAS; severe ventriculomegaly; near total white matter T2 hyperintensities or diffuse low attenuation (CT); focal white matter necrosis (cystic)*	*severe increase in SAS; severe ventriculomegaly; diffuse low attenuation with calcification (CT); diffuse white matter necrosis (MRI)*
Memory loss	normal	memory loss not interfering with function	memory loss interfering with function, but not interfering with activities of daily living	memory loss interfering with activities of daily living	amnesia
Mood alteration-anxiety agitation	normal	mild mood alteration not interfering with function	moderate mood alteration interfering with function, but not interfering with activities of daily living	severe mood alteration interfering with activities of daily living	suicidal ideation or danger to self
Mood alteration-depression	normal	mild mood alteration not interfering with function	moderate mood alteration interfering with function, but not interfering with activities of daily living	severe mood alteration interfering with activities of daily living	suicidal ideation or danger to self
Mood alteration-euphoria	normal	mild mood alteration not interfering with function	moderate mood alteration interfering with function, but not interfering with activities of daily living	severe mood alteration interfering with activities of daily living	danger to self
Neuropathic pain is graded in the PAIN category.					
Neuropathy-cranial	absent	-	present, not interfering with activities of daily living	present, interfering with activities of daily living	life-threatening, disabling
Neuropathy-motor	normal	subjective weakness but no objective findings	mild objective weakness interfering with function, but not interfering with activities of daily living	objective weakness interfering with activities of daily living	paralysis
Neuropathy-sensory	normal	loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function	objective sensory loss or paresthesia (including tingling), interfering with function, but not interfering with activities of daily living	sensory loss or paresthesia interfering with activities of daily living	permanent sensory loss that interferes with function
Nystagmus Also consider Vision-double vision.	absent	present	-	-	-
Personality/behavioral	normal	change, but not disruptive to patient or family	disruptive to patient or family	disruptive to patient and family; requiring mental health intervention	harmful to others or self; requiring hospitalization
Pyramidal tract dysfunction (e.g., ↑tone, hyperreflexia, positive Babinski, ↓ fine motor coordination)	normal	asymptomatic with abnormality on physical examination	symptomatic or interfering with function but not interfering with activities of daily living	interfering with activities of daily living	bedridden or disabling; paralysis
Seizure(s)	none	-	seizure(s) self-limited and consciousness is preserved	seizure(s) in which consciousness is altered	seizures of any type which are prolonged, repetitive, or difficult to control (e.g., status epilepticus, intractable epilepsy)
Speech impairment (e.g., dysphasia or aphasia)	normal	-	awareness of receptive or expressive dysphasia, not impairing ability to communicate	receptive or expressive dysphasia, impairing ability to communicate	inability to communicate
Syncope (fainting) Also consider CARDIOVASCULAR (ARRHYTHMIA), Vasovagal episode, CNS cerebrovascular ischemia.	absent	-	-	present	-
Tremor	none	mild and brief or intermittent but not interfering with function	moderate tremor interfering with function, but not interfering with activities of daily living	severe tremor interfering with activities of daily living	-
Vertigo	none	not interfering with function	interfering with function, but not interfering with activities of daily living	interfering with activities of daily living	bedridden or disabling
Neurology-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
OCULAR/VISUAL					
Cataract	none	asymptomatic	symptomatic, partial visual	symptomatic, visual loss	-

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
			loss	requiring treatment or interfering with function	
Conjunctivitis	none	abnormal ophthalmologic changes, but asymptomatic or symptomatic without visual impairment (i.e., pain and irritation)	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Dry eye	normal	mild, not requiring treatment	moderate or requiring artificial tears	-	-
Glaucoma	none	increase in intraocular pressure but no visual loss	increase in intraocular pressure with retinal changes	visual impairment	unilateral or bilateral loss of vision (blindness)
Keratitis (corneal inflammation/ corneal ulceration)	none	abnormal ophthalmologic changes but asymptomatic or symptomatic without visual impairment (i.e., pain and irritation)	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	unilateral or bilateral loss of vision (blindness)
Tearing (watery eyes)	none	mild: not interfering with function	moderate: interfering with function, but not interfering with activities of daily living	interfering with activities of daily living	-
Vision- blurred vision	normal	-	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Vision- double vision (diplopia)	normal	-	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Vision- flashing lights/floaters	normal	mild, not interfering with function	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Vision- night blindness (nyctalopia)	normal	abnormal electro-retinography but asymptomatic	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Vision- photophobia	normal	-	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Ocular/Visual- Other (Specify, _____)	normal	mild	moderate	severe	unilateral or bilateral loss of vision (blindness)
			PAIN		
Abdominal pain or cramping	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Arthralgia (joint pain)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Arthritis (joint pain with clinical signs of inflammation) is graded in the MUSCULOSKELETAL category.					
Bone pain	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Chest pain (non-cardiac and non-pleuritic)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Dysmenorrhea	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Dyspareunia	none	mild pain not interfering with function	moderate pain interfering with sexual activity	severe pain preventing sexual activity	-
Dysuria is graded in the RENAL/GENITOURINARY category.					
Earache (otalgia)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Headache	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Hepatic pain	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Myalgia (muscle pain)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Neuropathic pain (e.g., jaw pain, neurologic pain, phantom limb pain, post-infectious neuralgia, or painful neuropathies)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Pain due to radiation	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Pelvic pain	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Pleuritic pain	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Rectal or perirectal pain (proctalgia)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Tumor pain (onset or exacerbation of tumor pain due to treatment)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Tumor flair is graded in the SYNDROME category.					
Pain-Other (Specify, _____)	none	mild	moderate	severe	disabling
			PULMONARY		
Adult Respiratory Distress Syndrome (ARDS)	absent	-	-	-	present
Apnea	none	-	-	present	requiring intubation
Carbon monoxide diffusion capacity (DL_{CO})	≥ 90% of pretreatment or normal value	≥75 - <90% of pretreatment or normal value	≥50 - <75% of pretreatment or normal value	≥25 - <50% of pretreatment or normal value	< 25% of pretreatment or normal value
Cough	absent	mild, relieved by non-prescription medication	requiring narcotic antitussive	severe cough or coughing spasms, poorly controlled or unresponsive to treatment	-
Dyspnea (shortness of breath)	normal	-	dyspnea on exertion	dyspnea at normal level of activity	dyspnea at rest or requiring ventilator support
FEV_1	≥ 90% of pretreatment or normal value	≥75 - <90% of pretreatment or normal value	≥50 - <75% of pretreatment or normal value	≥25 - <50% of pretreatment or normal value	< 25% of pretreatment or normal value
Hiccoughs (hiccups, singultus)	none	mild, not requiring treatment	moderate, requiring treatment	severe, prolonged, and refractory to treatment	-
Hypoxia	normal	-	decreased O_2 saturation with exercise	decreased O_2 saturation at rest, requiring supplemental oxygen	decreased O_2 saturation, requiring pressure support (CPAP) or assisted ventilation
Pleural effusion (non-malignant)	none	asymptomatic and not requiring treatment	symptomatic, requiring diuretics	symptomatic, requiring O_2 or therapeutic thoracentesis	life-threatening (e.g., requiring intubation)
Pleuritic pain is graded in the PAIN category.					
Pneumonitis/pulmonary infiltrates	none	radiographic changes but asymptomatic or symptoms not requiring steroids	radiographic changes and requiring steroids or diuretics	radiographic changes and requiring oxygen	radiographic changes and requiring assisted ventilation
Pneumothorax	none	no intervention required	chest tube required	sclerosis or surgery required	life-threatening
Pulmonary embolism is graded as Thrombosis/embolism in the CARDIOVASCULAR (GENERAL) category.					
Pulmonary fibrosis	none	radiographic changes, but asymptomatic or symptoms not requiring steroids	requiring steroids or diuretics	requiring oxygen	requiring assisted ventilation
Note: Radiation-related pulmonary fibrosis is graded in the RTOG/EORTC Late Radiation Morbidity Scoring Scheme- Lung. (See Appendix IV)					
Voice changes/stridor/larynx (e.g., hoarseness, loss of	normal	mild or intermittent hoarseness	persistent hoarseness, but able to vocalize; may have mild to moderate edema	whispered speech, not able to vocalize; may have marked edema	marked dyspnea/stridor requiring tracheostomy or intubation

Toxicity	Grade 0	1	2	3	4
voice, laryngitis) Note: Cough from radiation is graded as cough in the PULMONARY category. Radiation-related hemoptysis from larynx/pharynx is graded as Grade 4 Mucositis due to radiation in the GASTROINTESTINAL category. Radiation-related hemoptysis from the thoracic cavity is graded as Grade 4 Hemoptysis in the HEMORRHAGE category.					
Pulmonary-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
RENAL/GENITOURINARY					
Bladder spasms	absent	mild symptoms, not requiring intervention	symptoms requiring antispasmotic	severe symptoms requiring narcotic	-
Creatinine *Note: Adjust to age-appropriate levels for pediatric patients.*	WNL	> ULN - 1.5 x ULN	> 1.5 - 3.0 x ULN	> 3.0 - 6.0 x ULN	> 6.0 x ULN
Dysuria (painful urination)	none	mild symptoms requiring no intervention	symptoms relieved with therapy	symptoms not relieved despite therapy	-
Fistula or GU fistula (e.g., vaginal, vesicovaginal)	none	-	-	requiring intervention	requiring surgery
Hemoglobinuria	-	present	-	-	-
Hematuria (in the absence of vaginal bleeding) is graded in the HEMORRHAGE category.					
Incontinence	none	with coughing, sneezing, etc.	spontaneous, some control	no control (in the absence of fistula)	-
Operative injury to bladder and/or ureter	none	-	injury of bladder with primary repair	sepsis, fistula, or obstruction requiring secondary surgery; loss of one kidney; injury requiring anastomosis or re-implantation	septic obstruction of both kidneys or vesicovaginal fistula requiring diversion
Proteinuria Note: If there is an inconsistency between absolute value and uristix reading, use the absolute value for grading.	normal or < 0.15 g/24 hours	1+ or 0.15 - 1.0 g/24 hours	2+ to 3+ or 1.0 - 3.5 g/24 hours	4+ or > 3.5 g/24 hours	nephrotic syndrome
Renal failure	none	-	-	requiring dialysis, but reversible	requiring dialysis and irreversible
Ureteral obstruction	none	unilateral, not requiring surgery	-	bilateral, not requiring surgery	stent, nephrostomy tube, or surgery
Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis) Also consider Acidosis, Bicarbonate, Hypocalcemia, Hypophosphatemia.	none	asymptomatic, not requiring treatment	mild, reversible and manageable with oral replacement	reversible but requiring IV replacement	irreversible, requiring continued replacement
Urinary frequency/urgency	normal	increase in frequency or nocturia up to 2 x normal	increase > 2 x normal but < hourly	hourly or more with urgency, or requiring catheter	-
Urinary retention	normal	hesitancy or dribbling, but no significant residual urine; retention occurring during the immediate postoperative period	hesitancy requiring medication or occasional in/out catheterization (<4 x per week), or operative bladder atony requiring indwelling catheter beyond immediate postoperative period but for < 6 weeks	requiring frequent in/out catheterization (≥ 4 x per week) or urological intervention (e.g., TURP, suprapubic tube, urethrotomy)	bladder rupture
Urine color change (not related to other dietary or physiologic cause e.g., bilirubin, concentrated urine, hematuria)	normal	asymptomatic, change in urine color	-	-	-
Vaginal bleeding is graded in the HEMORRHAGE category.					
Vaginitis (not due to infection)	none	mild, not requiring treatment	moderate, relieved with treatment	severe, not relieved with treatment, or ulceration not requiring surgery	ulceration requiring surgery
Renal/Genitourinary-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
SECONDARY MALIGNANCY					
Secondary Malignancy-Other (Specify type, _____) excludes metastatic tumors	none	-	-	-	present
SEXUAL/REPRODUCTIVE FUNCTION					
Dyspareunia is graded in the PAIN category.					
Dysmenorrhea is graded in the PAIN category.					
Erectile impotence	normal	mild (erections impaired but satisfactory)	moderate (erections impaired, unsatisfactory for	no erections	-

Toxicity	Grade 0	1	2	3	4
			intercourse)		
Female sterility	normal	-	-	sterile	-
Femininization of male is graded in the ENDOCRINE category.					
Irregular menses (change from baseline)	normal	occasionally irregular or lengthened interval, but continuing menstrual cycles	very irregular, but continuing menstrual cycles	persistent amenorrhea	-
Libido	normal	decrease in interest	severe loss of interest	-	-
Male infertility	-	-	Oligospermia (low sperm count)	Azoospermia (no sperm)	-
Masculinization of female is graded in the ENDOCRINE category.					
Vaginal dryness	normal	mild	requiring treatment and/or interfering with sexual function, dyspareunia	-	-
Sexual/Reproductive Function-Other (Specify, _____)	none	mild	moderate	severe	disabling
SYNDROMES (not included in previous categories)					
Acute vascular leak syndrome is graded in the CARDIOVASCULAR (GENERAL) category.					
ARDS (Adult Respiratory Distress Syndrome) is graded in the PULMONARY category.					
Autoimmune reactions are graded in the ALLERGY/IMMUNOLOGY category.					
DIC (disseminated intravascular coagulation) is graded in the COAGULATION category.					
Fanconi's syndrome is graded as Urinary electrolyte wasting in the RENAL/GENITOURINARY category.					
Renal tubular acidosis is graded as Urinary electrolyte wasting in the RENAL/GENITOURINARY category.					
Stevens-Johnson syndrome (erythema multiforme) is graded in the DERMATOLOGY/SKIN category.					
SIADH (syndrome of inappropriate antidiuretic hormone) is graded in the ENDOCRINE category.					
Thrombotic microangiopathy (e.g., thromboitic thrombocytopenic purpura/TTP or hemolytic uremic syndrom/HUS) is graded in the COAGULATION category.					
Tumor flare Also consider Hypercalcemia. Note: Tumor flare is characterized by a constellation of symptoms and signs in direct relation to initiation of therapy (e.g., anti-estrogens/androgens or additional hormones). The symptoms/signs include tumor pain, inflammation of visible tumor, hypercalcemia, diffuse bone pain, and other electrolyte disturbances.	none	mild pain not interfering with function	moderate pain; pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain; pain or analgesics interfering with function and interfering with activities of daily living	Disabling
Tumor lysis syndrome Also consider Hyperkalemia, Creatinine.	absent	-	-	present	-
Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis) is graded under the RENAL/GENITOURINARY category.					
Syndromes-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling

APPENDIX 9

SHORT FORM-36 (SF36) SURVEY

Please answer the following questions about your health. Select **ONLY ONE ANSWER** for each question

1. In general, would you say your health is:

    1. Excellent
    2. Very Good
    3. Good
    4. Fair
    5. Poor

2. Compared to one year ago, how would you rate your health in general now?

    1. Much better now than one year ago
    2. Somewhat better now than one year ago

3. About the same as one year ago
4. Somewhat worse now than one year ago
5. Much worse than one year ago

3. Does your health now limit you in this activity? If so, how much? Vigorous activities, such as
running, lifting heavy objects, participating in
strenuous sports.

1. Yes, limited a lot
2. Yes, limited a little
3. No, not limited at all

The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

4. Does your health now limit you in this activity? If so, how much? Moderate activities, such as
moving a table, pushing a vacuum cleaner,
bowling or playing golf.

1. Yes, limited a lot
2. Yes, limited a little
3. No, not limited at all

5. Does your health now limit you in this activity? If so, how much? Lifting or carrying groceries.

1. Yes, limited a lot
2. Yes, limited a little
3. No, not limited at all

6. Does your health now limit you in this activity? If so, how much? Climbing several flights of stairs.

1. Yes, limited a lot
2. Yes, limited a little
3. No, not limited at all

7. Does your health now limit you in this activity? If so, how much? Climbing one flight of stairs.

1. Yes, limited a lot
2. Yes, limited a little
3. No, not limited at all

8. Does your health now limit you in this activity? If so, how much? Bending, kneeling, or stooping.

1. Yes, limited a lot
2. Yes, limited a little
3. No, not limited at all

9. Does your health now limit you in this activity? If so, how much? Walking more than a mile.

1. Yes, limited a lot
2. Yes, limited a little
3. No, not limited at all

10. Does your health now limit you in this activity? If so, how much? Walking several blocks.

1. Yes, limited a lot
2. Yes, limited a little
3. No, not limited at all

11. Does your health now limit you in this activity? If so, how much? Walking one block.

1. Yes, limited a lot
2. Yes, limited a little
3. No, not limited at all

12. Does your health now limit you in this activity? If so, how much? Bathing or dressing yourself.

1. Yes, limited a lot
2. Yes, limited a little
3. No, not limited at all

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your PHYSICAL HEALTH?

13. During the past 4 weeks, have you had the following problem with your work or other regular daily activities as a result of your physical health? Cut down the amount of time you spent on work or other activities.

1. Yes
2. No

14. During the past 4 weeks, have you had the following problem with your work or other regular daily activities as a result of your physical health? Accomplished less than you would like.

1. Yes
2. No

15. During the past 4 weeks, have you had the following problem with your work or other regular daily activities as a result of your physical health? Were limited in the kind of work or other activities.

1. Yes
2. No

16. During the past 4 weeks, have you had the following problem with your work or other regular daily activities as a result of your physical health? Had difficulty performing the work or other activities (for example, it took extra effort).

1. Yes
2. No

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of

any EMOTIONAL PROBLEMS (such as feeling depressed or anxious)?

17. During the past 4 weeks, have you had the following problem with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)? Cut down the amount of time you spent on work or other activities.

1. Yes
2. No

18. During the past 4 weeks, have you had the following problem with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)? Accomplished less than you would like.

1. Yes
2. No

19. During the past 4 weeks, have you had the following problem with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)? Didn't do work or other activities as carefully as usual.

1. Yes
2. No

20. During the past 4 weeks, to what extent has your physical health OR emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

1. Not at all
2. Slightly
3. Moderately
4. Quite a bit
5. Extremely

21. How much bodily pain have you had during the past 4 weeks?

1. None
2. Very mild
3. Mild
4. Moderate
5. Severe
6. Very severe

22. During the past 4 weeks how much did pain interfere with your normal work (including both work outside the home and housework)?

1. Not at all
2. A little bit
3. Moderately
4. Quite a bit
5. Extremely

These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling.

23. How much of the time during the past 4 weeks: Did you feel full of pep?

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. None of the time

24. How much of the time during the past 4 weeks: Have you been a very nervous person?

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. None of the time

25. How much of the time during the past 4 weeks: Have you felt so down in the dumps that nothing could cheer you up?

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. None of the time

26. How much of the time during the past 4 weeks: Have you felt calm and peaceful?

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. None of the time

27. How much of the time during the past 4 weeks: Did you have a lot of energy?

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. None of the time

28. How much of the time during the past 4 weeks: Have you felt downhearted and blue?

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. None of the time

29. How much of the time during the past 4 weeks: Did you feel worn out?

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. None of the time

30. How much of the time during the past 4 weeks: Have you been a happy person?

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. None of the time

31. How much of the time during the past 4 weeks: Did you feel tired?

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. None of the time

32. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

1. All of the time
2. Most of the time
3. Some of the time
4. A little of the time
5. None of the time

33. How true or false is the following statement? I seem to get sick a little easier than other people.

1. Definitely true

2. Mostly true
3. Don't know
4. Mostly false
5. Definitely false

34. How true or false is the following statement? I am as healthy as anybody I know.
    1. Definitely true
    2. Mostly true
    3. Don't know
    4. Mostly false
    5. Definitely false

35. How true or false is the following statement? I expect my health to get worse.
    1. Definitely true
    2. Mostly true
    3. Don't know
    4. Mostly false
    5. Definitely false

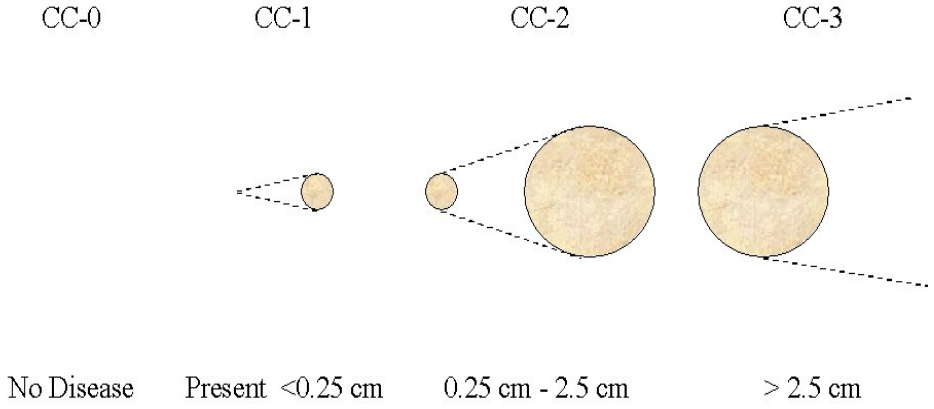
36. How true or false is the following statement? My health is excellent.
    1. Definitely true
    2. Mostly true
    3. Don't know
    4. Mostly false
    5. Definitely false

APPENDIX 10

PERITONECTOMY PROCEDURES

	Total	Partial
1.greater omentectomy, right parietal peritonectomy and right colon resection		
2.left upper quadrant peritonectomy, splenectomy and left parietal peritonectomy		
3.right upper quadrant peritonectomy and Glissonian's capsule resection		
4.lesser omentectomy, colecystectomy, stripping of omental bursa and antrectomy		
5.pelvic peritonectomy with sigmoid colon resection with or without hysterectomy and bilateral salpingo-oophorectomy		
6.other intestinal resection and/or abdominal mass resection.		
7.bowel anastomosis		

Sugarbaker's criteria on the completeness of cytoreduction



APPENDIX 11

PATIENTS' EVALUATION PLAN

Analysis/ Evaluation	End of Surgery	3 hours	6 hours	1st day	2nd day	3rd day	5th day	7th day	10th day	15th day	30th day
Blood Cell Count	*	*	*	*	*	*	*	*	*	*	*
Leukocytes formula	*			*	*	*	*	*	*	*	*
PT/PTT/Fibrinogen	*		*	*	*	*	*	*			
Urea/Creatinine	*	*	*	*	*	*	*	*	*	*	*
Na/K/Ca	*	*	*	*	*	*	*	*	*	*	*
Serum Protein/Albumine	*			*	*	*	*	*	*	*	*
GOT/GPT/Bilirubin	*			*	*	*	*	*	*	*	*
Alkalyne Phosphatase GGT				*	*	*	*	*	*	*	*
Serum Lypase/Amylase				*		*	*	*			
PCR				*	*	*	*	*	*	*	*
CPK/LDH	*			*	*	*	*	*	*	*	*
Ca 125 / Ca 19.9	*			*			*		*	*	*
Blood Gas Analysis	*	*	*	*	*	*					
Serum Lactate			*	*	*	*	*				
Fever/Chills	*	*	*	*	*	*	*	*	*	*	*
Chest/Abdominal Pain	*	*	*	*	*	*	*	*	*	*	*
Headache/Dizziness			*	*	*	*	*	*	*	*	
Nausea/Vomiting			*	*	*	*	*	*	*	*	
Dyspnea	*	*	*	*	*	*	*	*	*	*	*
Dysuria						*	*	*	*	*	*
Stools/Diarrhea/Flatus				*	*	*	*	*	*	*	*
Dysphagia						*	*	*	*	*	*
Paresthesia/Weakness Neuropatic pain				*	*	*	*	*	*	*	*
Memory loss				*	*	*	*	*	*	*	*
Anxiety/Agitation				*	*	*	*	*	*	*	*

	3 months	6 months	1 year	18 months	2 years	3 years	5 years
Clinical Examination	*	*	*	*	*	*	*
Ca 125	*	*	*	*	*	*	*
Chest-Abdominal CT scan			*		*	*	*
SF-36 QOL evaluation		*	*				

APPENDIX 12

ANALYSIS PLAN FOR THE WHOLE STUDY

Time 0	24 months	49 months	54 months	60 months
BEGINNING OF STUDY	END OF RECRUITMENT	STATISTICAL ANALYSIS	WRITING OF THE REPORT	EVENTUAL PUBLICATION

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