EDMOCS

PROTOCOL

Early Dehiscence Markers in Ovarian Cancer Surgery

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Vall d'Hebron Barcelona Campus Hospitalari	**EDMOCS** **Protocol**	Date:18/11/2016
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PROJECT TITLE: **Procalcitonin and C-reactive Protein as Early Anastomotic Dehiscence Markers in Ovarian Cancer Surgery**

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ACRONYM: **EDMOCS**

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DATE OF PROTOCOL: **18/11/2016**

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Contents

Summary

Acronym	EDMOCS
ID ClinicalTrials.gov.	
Full Title	**Procalcitonin and C- reactive Protein as Early Anastomotic Dehiscence Markers in Ovarian Cancer Surgery**
Primary Objective	To determine the usefulness of procalcitonin and C-reactive protein levels as early markers of anastomotic suture failure after surgery for advanced ovarian cancer in patients undergoing colorectal and/or bowel resection.
Design	Multicentre. Observational. Prospective
Sample size	The estimated sample size is 70 patients. Based on the data available in the literature, an anastomotic suture dehiscence rate in patients who underwent surgery for advanced ovarian cancer with rectosigmoid resection is estimated to be **7%.** Assuming an AUC > 0.80 in the ROC curve analysis for both C-reactive protein and procalcitonin, with a power of 95%, 70 patients will need to be included.
Inclusion criteria	**Pre-operative** a) Patients with a suspected diagnosis of stage III-IV ovarian cancer, by examination, CA 125 marker and thoracic-abdominal CT scan, who are candidates for primary cytoreductive, interval or recurrence surgery. b) ≥ 18 years of age. c) Accepts and signs the informed consent.

	Intraoperative 1. Colorectal resection with mechanical or manual anastomosis. 2. Mechanical or manual small bowel resection. 3. Colorectal resection with protective ileostomy.
Exclusion criteria	- The patient does not require bowel and/or colorectal resection. - There is infection at the time of surgery. - Emergency surgery.
Primary objective	To determine the usefulness of serum C-reactive protein (CRP) and procalcitonin (PCT) determination in the early diagnosis of intestinal anastomotic suture failure in patients with advanced ovarian cancer.
Secondary objectives	To determine optimal post-surgical reference values for CRP and PCT for early diagnosis of anastomotic suture failure in the population of patients with advanced ovarian cancer.
Other objectives	Correlation between pre- and post-surgical CRP and PCT levels with respect to clinical variables of interest (age, BMI, smoking habits, need for surgery). Correlation of pre- and post-surgical CRP and PCT levels with respect to anatomopathological variables of interest (FIGO stage, grade, lymph node involvement, histological type). To determine the best day to measure PCT and CRP values for early detection of anastomotic suture failure. Correlation between CRP and PCT levels with anastomotic failure and peritoneal carcinomatosis index (PCI). To establish whether there are differences in the incidence of AF and other major complications, as well as in hospital stay between participating centres that apply multimodal rehabilitation programmes and those that do not.
Other variables analysed	Incidence rate of complications after surgery for advanced ovarian cancer with rectosigmoid resection. Risk factors for anastomotic suture failure and their distribution in the study population (age, need for surgery, nutritional status, BMI, smoking habits, stage, histology, post-surgical residual tumour, surgical time, bleeding, need for blood transfusions, etc.). To compare baseline CRP and PCT values in patients with primary surgery and interval surgery in advanced ovarian cancer.

Relevance	Several studies have demonstrated the usefulness of markers such as CRP and PCT in the diagnosis of anastomotic suture failure in colorectal surgery, allowing active and early management and potentially reducing mortality and morbidity, as well as costs associated with this highly feared complication. Using these markers also allows a more selective and targeted use of imaging tests in the post-operative period. Finally, the information provided by these tests allows a full application of multimodal rehabilitation protocols, including avoiding the use of drains and ostomies as far as possible and early discharge of the patient. This study aims to establish whether these benefits are applicable to patients with advanced epithelial ovarian cancer and what interpretation should be made of CRP and PCT values in this patient population.

Statistical analysis	Based on the literature and the results at our centre, our statistical calculation was based on the following assumptions: a suture failure incidence of 7% and a difference of at least 0.1 in the area under the ROC curve of CRP and PCT on day 3 and day 5. Using statistical analysis software, a box-plot calculation and Kruskall Wallis test will be performed to compare the distribution of biomarkers between different groups. To compare the reliability of biomarkers as predictors of anastomotic failure, the respective ROC curves and Areas Under the Curve (AUC) will be assessed. A 95% confidence interval (CI) will be used to calculate specificity (Sp), sensitivity (Se), positive predictive value (PPV) and negative predictive value (NPV). In the univariate analysis, differences between numerical variables will be analysed with the t-Student test.
Follow-up	All intraoperative and post-operative complications shall be reported and classified using a Clavien-Dindo grading system (Appendix 4). Complications occurring during the surgical procedure will be classified as intraoperative, while those occurring within 30 days after surgery will be considered early post-operative. After discharge, patients will be monitored by post-surgical visits one week after surgery and 30 days after surgery, after which they will follow the usual controls according to the protocols of each centre.

Background and state of the art

Ovarian cancer is one of the most prevalent gynaecological types of neoplasms, with the worst prognosis. In 2014, 3,276 new cases were diagnosed in Spain, making it the fifth most common cancer in women. In 2012 it was the seventh most common cancer in women in the world (239,000 new cases)[1]. Its prognosis is unfavourable overall, and the age-standardised 5-year survival rate in Spain for patients diagnosed during the period 2000-2007 was 36.8%, similar to that of Europe as a whole (37.6%)[2].

Cytoreductive surgery followed by platinum-based chemotherapy is the mainstay of treatment for patients with advanced disease. Achieving optimal complete cytoreduction, i.e. the absence of macroscopic residual tumour after cytoreductive surgery, is universally considered the most important prognostic factor[3].

Given the proximity of the rectosigmoid portion of the colon to the female genital tract, the former is frequently affected in cases of advanced ovarian cancer. Similarly, when peritoneal dissemination occurs, tumour implants can compromise the serosa or the small bowel mesum, causing intestinal obstruction. For this reason, intestinal resection is often required during the process of cytoreduction. Although in patients at particular risk of anastomotic suture failure, the Hartmann's procedure (rectosigmoid colon resection, distal stump closure and proximal unloading colostomy) may be considered preferable, low anterior resection with primary colorectal anastomosis (LARA) has proven to be the treatment of choice, with acceptable morbidity and mortality rates in advanced ovarian cancer (AOC)[4-5].

Failure of anastomotic healing results in anastomotic leakage (AL), of varying degrees and outcomes. Mortality ranges from 5% to 18% and even up to 22%[6]. Some patients with asymptomatic AL will progress favourably with conservative treatment, but clinically symptomatic patients will require radiological drainage or surgical re-intervention and possibly need a stoma, which may be temporary or permanent, with relevant functional consequences. In addition, these patients will often require admission to an intensive care unit and prolonged hospital stay and a high healthcare cost[7]. Finally, another important aspect to consider is the

negative prognostic impact that complications derived from anastomotic failure have on the evolution of ovarian cancer, delaying the initiation of chemotherapy and, therefore, increasing the risk of progression and recurrence.

The incidence of AL at colorectal level varies depending on the published series. In colorectal cancer surgery, where more data are available, the incidence is 4% in colon resection and 10% in rectal resections[8]. In ovarian cancer patients, despite concomitant surgical procedures involving the entire abdominal cavity (resection of multiple organs/viscera) being performed, and with longer surgical times and greater blood loss than in colorectal surgery, the anastomotic failure rate described in most series is 7% [9].

Definition of Anastomotic Suture Failure

A review of the medical literature shows that the definition of anastomotic leakage varies widely between sources, making it difficult to compare data on the incidence, diagnosis and outcome of this complication.

In order to standardise concepts, in 1991 the United Kingdom Surgical Infection Study Group (SISG) proposed a standard definition of AL as the leakage of luminal contents from the surgical junction between two hollow viscera. This content may emerge through wounds or an intra-abdominal drain, or may collect near the anastomosis causing fever, abscess, septicaemia, metabolic disorders, and/or multi-organ failure. Despite this SISG proposal, this standard definition for AL has remained largely unused.

In 2001, Bruce et al[10] reviewed the AL definition criteria and proposed a classification according to the AL clinical expression:

- **"Radiological" anastomotic leakage**: a leak detected only on routine imaging studies, with no associated clinical findings, and which does not require active management.

- **"Minor clinical" anastomotic leakage:** a radiologically-confirmed leak with intestinal or purulent discharge through the wound or drains, fever greater than 38^{o}C, leukocytosis > 10,000/L or abscess and requiring no change in management but prolonging the patient's hospital stay (ASA I-II).

- **"Major clinical" anastomotic leakage:** a radiologically-confirmed leak presenting the same clinical signs and symptoms as "minor clinical", but whose degree of anastomotic dehiscence and its clinical consequences require change in management and intervention (ASA III-IV).

On the other hand, Rahbari et al[11] published a consensus document on the definition and grade of AL proposing a subdivision of AL according to its clinical management:

A) AL doesn't require active therapeutic intervention. It is connected to the term used as "radiological leakage", is not associated with clinical symptoms or alteration of analytical parameters.

B) AL requires active therapeutic intervention without re-laparotomy. Laboratory findings usually include leukocytosis and increased C-reactive protein (CRP).

C) AL requires re-laparotomy. Patients may present with signs of peritonism on examination and laboratory parameters consistent with infection.

For the purposes of this study, Bruce et al's definition of AL will be used.

Anastomotic suture failure risk factors

AL risk factors can be classified as pre-operative (patient-specific) and intraoperative, including resection-specific factors.

Patient-specific preoperative factors include obesity, smoking, drinking, diverticulosis, steroid use, pre-operative nutritional status, pre-operative radiation and chemotherapy, and ASA status III-IV [11, 12].

Malnutrition, described as recent weight loss of more than 5 kg and albumin levels below 35 g/L, is one of the most important risk factors for the development of AL [13]. In this context, the intensified or multimodal rehabilitation approach, also called Fast Track, in which preoperative nutritional adequacy plays a key role in reducing AL rates, is of particular interest.

Intraoperative factors associated with an increased risk of AL are procedure duration greater than 2-4 hours, perioperative transfusion, intraoperative sepsis, tissue ischaemia at the anastomotic site and shorter distance from the anastomotic site to the perianal skin[14]. A protective stoma has not been shown to reduce the incidence of AL, but it may reduce the morbidity and mortality associated with AL[15], so some authors recommend the performance of a protective stoma in patients with multiple risk factors for AL.

It is also worth noting that in intraperitoneal anastomoses, unlike ultra-low colorectal anastomoses, the use of drainage has not shown any beneficial effect in AL prophylaxis[16]. Similarly, mechanical bowel preparation has not been shown to decrease the risk of AL and there are no differences in AL rates between manual and mechanical anastomosis[17]. Finally, the surgeon factor is an independent prognostic variable that should be taken into account.

Anastomotic leakage markers. C-reactive protein and procalcitonin.

The body's response to infection occurs through the activation of complex immune mechanisms and the appearance of numerous inflammatory mediators, and it has been suggested that some of these mediators could be used as markers for the presence and severity of infection.

The identification of a biological marker that can predict an infectious complication, particularly AL, before obvious clinical signs develop would have significant advantages in patient management. On the one hand, it would allow early identification of those patients with a high probability of presenting a major complication, bringing forward the performance of diagnostic tests such as abdominal CT, as well as the relevant therapeutic measures; and on the other hand, it would allow identification of those patients with a low risk of presenting a major complication, thus promoting an accelerated post-surgical recovery and early discharge, within the centre's own multimodal rehabilitation programmes.

C-reactive protein

C-reactive protein (CRP) is a biological marker that increases in levels in response to inflammation. At the physiological level, it is involved in innate immunity by activating the complement system and phagocytosis by macrophages. At the onset of the inflammatory process, CRP increases its plasma concentration within the first 6 hours and reaches a peak within 24-72 hours, after which it decreases rapidly as the inflammatory process resolves itself[18]. CRP is, however, a non-specific marker that can be increased by any alteration – not only infectious processes - that provokes an inflammatory response. Other factors that can increase CRP levels are obesity, smoking, osteoarthritis, older age, burns, emotional changes and menstrual cycle alterations[19] .

Regarding surgery, an increase in CRP after surgery has been described in all patients, which declines between the 2nd and 3rd post-operative day in patients with no post-operative complications but increases in patients with infectious complications. The meta-analysis by Nunes (2011)[20] found an 85% sensitivity for the detection of complications using CRP and a mean specificity of 86% with an area under the ROC curve of 0.906. The meta-analysis concludes a high value CRP in the diagnosis and prognosis of

post-surgical infection. However, the article did not specifically refer to intra-abdominal complications, mention AL as a major complication, nor did it consider the influence of active neoplasia on CRP values.

In recent years, the usefulness of CRP for early detection of postoperative infectious complications in rectal surgery and, more specifically, as an early indicator of AL has been suggested. Matthiessen et al [21] and Woeste et al [22] concluded that early higher CRP concentration, and maintaining it, after colorectal surgery is an indicator of AL, and that monitoring it after surgery makes possible an early diagnosis of AL. Almeida et al[23] provide a cut-off point for CRP of 140 mg/L on post-operative day 3 with a sensitivity of 78% and a specificity of 86%.

However, the translation of these results into clinical practice in epithelial ovarian cancer means that it might be difficult to define baseline values prior to surgery in a group of patients who may have elevated baseline CRP values. Several studies have shown that cancer patients have markedly higher levels of circulating CRP in the blood, even years before diagnosis[24, 25].

In the specific case of ovarian epithelial cancer, the proinflammatory environment has been classically considered a fundamental part of the carcinogenic process. Rupture of the ovarian surface epithelium would induce a local inflammatory reaction leading to chronic cell damage, proliferation and increased potential for aberrant DNA repair, inactivation of tumour suppressor genes and thus increased local mutagenesis [26]. In parallel, chronic diseases of the lower genital tract in women, such as endometriosis, polycystic ovarian syndrome or pelvic inflammatory disease, have been identified as possible risk factors for the development of ovarian cancer[27].

Some recent studies have established a relationship between CRP levels at the time of diagnosis of ovarian neoplasia and the severity of the disease. In a recent article published by Lu et al[28] , a significant difference was found in CRP values according to stage at diagnosis, histological grade and presence of adenopathic disease, with mean pre-surgical values above 30mg/l in advanced stages (III-IV) (Table 1).

Correlation of serum CRP concentration with the clinicopathological parameters of patients with epithelial ovarian cancer.

Clinicopathological parameter	n	CRP level, mg/l	P-value[a], ANOVA	CRP-positive rate[b], n (%)	P-value[a], ANOVA
Age, years					
>50	63	22.24±36.39	0.283	35 (56)	0.081
≤50	44	29.27±23.93		31 (54)	
FIGO stage					
I	29	4.61±3.06	<0.001	4 (14)	<0.001
II	14	10.81±4.48		10 (71)	
III	44	35.48±36.98		35 (91)	
IV	20	51.04±33.23		17 (80)	
Histological grading					
G1	28	12.03±14.21	0.005	11 (39)	0.165
G2	44	26.75±29.70		30 (68)	
G3	35	38.66±41.58		25 (71)	
Type					
Pathological serous cystadenocarcinoma	43	29.93±35.93	0.089	28 (65)	0.118
Mucinous cystadenocarcinoma	38	13.24±10.93		22 (58)	
Other types of epithelial carcinoma	26	32.19±34.18		16 (62)	
Ascites					
With	42	36.01±34.92	0.014	36 (86)	0.026
Without	65	20.36±29.63		30 (46)	
Tumor resection					
Residual tumor diameter <2 cm	69	21.14±27.43	0.006	39 (57)	0.004
Residual tumor diameter ≥2 cm	38	40.04±39.98		27 (71)	
Lymph node metastasis					
Positive	21	30.79±36.99	0.002	17 (81)	0.004
Negative	44	10.14±15.31		15 (34)	

[a]Fisher's exact probability method using a two-way ANOVA.
[b]CRP >8 mg/l. CRP, C-reactive protein; ANOVA, analysis of variance; FIGO, International Federation of Gynecologists and Obstetricians.

Table 1. Lu Y, Huang S, Li P, Chen B, Liu W, Chen Z, Yin F. Prognostic evaluation of preoperative serum C-reactive protein concentration in patients with epithelial ovarian cancer. Expl Ther Med. 2015 May; 9(5): 2003-2007.

Procalcitonin

PCT is normally synthesised in small amounts in the C cells of the thyroid gland and in neuroendocrine cells of the lung. Its plasma concentration in healthy patients is very low (0.01-0.05 ng/ml). However, its blood levels shoot up in response to pro-inflammatory stimuli such as cytokines and, in particular, bacterial products such as endotoxins. Its action mechanism is not fully understood, but it is known to play an important role in the sepsis pathogenesis, as it shows chemotactic properties for leukocytes and modulates nitric oxide production by endothelial cells.

In recent years, procalcitonin has been used in intensive care units to diagnose and monitor patients with sepsis[29]. Regarding the usefulness of PCT in surgical management, Takakura et al[30] concluded that PCT is the most reliable marker for diagnosing sepsis after colorectal cancer surgery.

Oberhofer et at[31] published a similar study with 79 patients, which showed predictive values similar for CRP on day 3 post-surgery day and for PCT on day 2 post-surgery (AUC 0.746 and 0.750 respectively), the best cut-off values being 99.0 mg/L for CRP and 1.34 mg/L for PCT. Garcia-Granero et al[32], after a study with 250 patients, reported the best accuracy for AL diagnosis of PCT with an AUC on day 5 post-surgery of 0.86 (100% sensitivity, 72% specificity and 100% NPV) with a cut-off value of 0.31 ng/ml.

In 2015, Witkiewicz's group[33] included 55 patients with bowel resection with measurements of CRP and PCT pre-surgery and post-surgery at 8 hours, on day 1 and day 3. Both proteins increased during the post-operative process. On day 3, the mean CRP value was 114 mg/L in patients without AL and 321 mg/L in patients diagnosed with AL (p=0.0001). On the other hand, the mean PCT value was 0.56 ng/mL in patients without AL and 10.4 ng/mL in patients diagnosed with AL (p=0.017). The analysis of

ROC and AUC curves gave a cut-off point for CRP of 245.64 mg/L (Sens 100%, Sp 98%) and for PCT of 3.83 mg/L (Sens 75%, Sp 100%). With these results, it was suggested that the measurement of both markers on day 3 post-surgery were included to identify those patients at low risk of AL, so that they could be safely discharged using the ERAS protocol.

Similarly, in the recently published PREDICS [34] study, which assessed the usefulness of PCT in the early diagnosis of AL after colorectal surgery, low PCT values showed a good NPV for AL, allowing early discharge. It also indicated that the association of PTC with CRP as AL markers on day 5 post-surgery would improve the AL diagnosis rate. However, there is no consensus on the appropriate cut-off point for PCT and CRP to predict AL in colorectal surgery, and there is also controversy regarding the appropriateness of performing the measurement on day 3 or 5. In the PREDICS study, the cut-off points established were 2.7 ng/ml for PCT and 16.9 mg/ml for CRP on day three and of 2.3 ng/ml and 12.5 mg/ml on day 5 post-surgery, with an NPV greater than 95% in all cases.

Despite growing evidence of the usefulness of these markers for the early diagnosis of major post-surgical complications in patients undergoing bowel resection, there is no study to date that assesses their use in patients undergoing surgery for advanced ovarian cancer.

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Hypothesis/Rationale for the Study

Anastomotic suture failure is a rare but potentially fatal complication of cytoreductive surgery for advanced ovarian cancer. Although there are risk factors related to this complication that may lead to a more exhaustive follow-up of certain patients, the available data show that the appearance of clinical signs of suspicion is late, so that diagnosis is often delayed with a consequent increase in morbidity and mortality and hospital stay. In contrast, post-operative assessment of some biological markers is a potentially useful tool for the early detection of AL in these patients.

So far there is evidence on a higher and persistently higher CRP and PCT in patients with AL after colorectal cancer surgery, but its usefulness in advanced ovarian cancer has not been evaluated.

HYPOTHESIS

Determining CRP and PCT at post-surgical follow-up may serve as an early marker of anastomotic suture failure in patients undergoing cytoreduction for advanced ovarian cancer.

Objectives

Primary objective

- To define the usefulness of serum C-reactive protein (CRP) and procalcitonin (PCT) determination in the early diagnosis of colorectal and intestinal suture failure in patients undergoing cytoreductive surgery for advanced ovarian cancer.

Secondary objective

- To define optimal post-surgical reference values for CRP and PCT for the early diagnosis of anastomotic suture failure in the population of patients with advanced ovarian cancer.

Other objectives

- Correlation between pre- and post-surgical CRP and PCT levels with respect to clinical variables of interest (age, BMI, smoking habits, need for surgery).
- Correlation of pre- and post-surgical CRP and PCT levels with respect to anatomopathological variables of interest (FIGO stage, grade, lymph node involvement, histological type).
- To establish the best day to measure PCT and CRP values for early detection of anastomotic suture failure.
- Correlation between CRP and PCT levels with anastomotic failure and peritoneal carcinomatosis index (PCI).
- To establish whether there are differences in the incidence of AL and other major complications, as well as in hospital stay in participating centres between those that apply multimodal rehabilitation programmes and those that do not.

METHODOLOGY

Requirements for the participation of the centres

- Hospitals with gynaecological oncology units.
- ≥15 Stage III-IV ovarian cancers/year.
- Standard protocol or Fast Track/ERAS protocol.
- Study approval by the Hospital Ethics Committee.

Inclusion criteria

Pre-surgery

a) Patients diagnosed with advanced ovarian cancer (III-IV), undergoing primary cytoreductive surgery, interval surgery or secondary surgery.

b) ≥ 18 years.

c) Accepts and signs informed consent.

Exclusion criteria

- There is infection at the time of surgery.
- No bowel resection.
- Urgent surgery (first intestinal occlusion).

Description of the study

Pre-surgery

Patients will be assessed for inclusion in the study at the surgical scheduling visit. At that time, the patient will be given the information sheet, will sign the informed consent form and the pre-surgery form will be filled in with the required data (Form 1).

Patients who are eligible to participate in the study will have their CRP and PCT, as well as markers of baseline nutritional status included in Table 2, and tumour markers (Ca 125; Ca 19.9; CEA; HE4; AFP and BHCG in <35a) taken as part of the pre-surgery assessment.

Complete blood count (CBC) and coagulation	**CRP**
Liver Biochemistry	Cholesterol
Creatinine	Triglycerides
Glucose	Prealbumin
Urea	Albumin
Ionogram	Pancreatic alpha-amylase
Proteins	24h urine (creatinine, urea and proteinuria)

Table 2. Markers of baseline nutritional status.

In those centres where there is an adequate care structure for the application of an intensive recovery programme (ERAS/Fast Track), pre-, intra- and post-surgery management will be carried out in accordance with the guidelines and protocols accredited and defined by the GERM group (http://www.grupogerm.es/protocolos-zaragoza-2016/) / Hospital Vall d'Hebron (See Appendix 3).

Centres without a multimodal rehabilitation programme will be required to provide documentation of the protocols in place.

Intraoperative

The patient will undergo the prescribed surgery according to the state of her illness and the centre protocol.

Patients with any of the following criteria will be excluded from the study:

- Not requiring intestinal resection.
- With signs of peritonitis or active infection at the time of surgery.
- Emergency surgery.

Excluded patients will remain in the database and the reason for exclusion will be recorded on Form 2.

For patients remaining in the study, immediate post-surgery surgical data will be collected according to Form 3.

Post-surgery period

- Standard post-surgery care, according to the Unit protocols.

Post-surgery follow-up will specifically collect the variables listed in Form 4 within the context of the study:

- Daily recording of clinical data and vital signs from the first day post-surgery until discharge. Three measurements per day shall be recorded.
- Post-surgery laboratory tests on days 1, 3, 5, 7 and 10 (if the patient has not been discharged earlier) including: CBC, biochemistry (Na+, K+, Cl-, glucose, urea and creatinine) and coagulation tests.
- Post-surgery analytical determination on days 1, 2, 3, 4, 5 and 6 including C-Reactive Protein and Procalcitonin.

The method used to determine PCT will be sandwich immunoassay (BRAHMS PCT reagent) with Advia Centaur (Siem) equipment.

The method used to determine the CRP shall be by immunoturbidimetry with Olympus AU5400 (Beckman Coulter) equipment.

Assessment of the operated patient for the presence of one or more criteria for sepsis:

- Temperature (over 38.5°C)
- Hypothermia (< 36°C)
- Heart rate > 90 beats / min.

- Tachypnoea > 20 breaths / min.
- Altered mental state
- Significant oedema (positive water balance)
- Hyperglycaemia (plasma glycaemia > 120 mg/dl)
- Leukocytosis (> 12,000 µL-1)
- Leukopenia (< 4000 µL-1)
- Normal white blood cell count with more than 10% immature forms.

- If sepsis criteria are met, investigation of the possible septic focus should be undertaken:
  - Wound infection (examination and sample for microbiology)
  - Lung infection (X-ray/CT)
  - Urinary tract infection (sediment/culture)
  - Abdominal or pelvic infection to rule out suture failure (abdomino-pelvic CT scan with contrast/enema with water-soluble contrast). Rectal examination with rectoscopy if necessary.
  - Others according to clinical data.

In case of suspected anastomotic failure, a CT enema with water-soluble contrast will be performed. The anastomotic leak will be classified as "minor" (Clavien Dindo 1-2, conservative treatment only) or "major" (Clavien Dindo 3-4, radiological or surgical drainage). Treatment of anastomotic leakage will depend on the participating centre's Colorectal Surgery protocols.

Complications

All intraoperative and early postoperative complications (< 30d) shall be reported using the Clavien-Dindo classification (see Appendix 4).

Definition of complications:

a) Wound infection: clear inflammatory signs at the wound margin or purulent drainage through the wound.

b) Pulmonary infection: diagnosed as pulmonary infiltration on conventional radiology or chest CT, accompanied by clinical symptoms, physical or laboratory signs.

c) Urinary tract infection (sediment/culture): positive urine sediment result accompanied by clinical or laboratory signs or symptoms.

d) Abdominal or pelvic infection:

- "Minor" clinical leakage: detected radiologically, which do not require aggressive measures (reintervention and/or percutaneous drainage), despite prolonging the hospital stay (Grades I-II of the Clavien-Dindo classification).
- "Major" clinical leakage when reintervention or percutaneous drainage is required (Clavien-Dindo Grades III-IV-V).

Discharge criteria

These are the guideline criteria included in our discharge protocol:

- Passing gas and/or stool.
- Oral painkillers are sufficient for pain management.
- Independence for daily activities (walking, feeding, washing, etc.).
- Having eaten three or more solid meals (basal diet).
- Patient agrees to discharge.
- In patients with a stoma: controlled debit.

POST-OPERATIVE FOLLOW-UP

Follow-up will consist of a visit one week after hospital discharge with a complete physical examination and analytical determination, and a final assessment 30 days post-surgery, when the case closure report (Form 6) will be completed.

Once all the information has been completed, it will be forwarded to the coordinating centre for processing.

Withdrawal from the research project

Patients will be informed that they may voluntarily choose to withdraw from the study at any time, for any reason, and that it will not affect their medical care. However, in such cases, the researcher will make an appropriate effort to determine the reason for voluntary withdrawal from the study and to document the reason for withdrawal in the medical record, if known.

The last known disease status of these patients will be reported with the study results according to the closure form and all attempts to locate patients lost to follow-up will also be documented.

Patients will be informed that if they withdraw from the study, they must remain under the care of an appropriately experienced physician until such time as the physician deems necessary. Causes for discontinuation of a patient's participation in the study include:

- Completion of the study
- Voluntary withdrawal
- Relocation of the patient to another geographical area
- Lost at follow-up

- Other

If a patient moves to another geographical area requiring a change of doctor, reasonable attempts will be made to locate and seek the cooperation of this doctor in order to complete the follow-up.

Types and number of procedures DERIVED from the study

This is a study to define the usefulness of determining pre- and post-surgical procalcitonin and CRP in the early diagnosis of anastomotic suture failure in patients operated on for advanced ovarian cancer. The management of these patients will be carried out according to the protocols established by each participating centre. The extraordinary procedures devised in the study are exclusively focused on the performance of the indicated analytical determinations, so their application does not entail any greater risk for the patients.

WORK PLAN

Trial approval by the coordinating centre ethics committee (February 2017)

Admission of collaborating sites (February-April 2017)

Recruitment start date: 1 March 2017

Recruitment end date: March 2018

Partial results date: May 2018

End of data analysis: June 2018

The study will be conducted in the operating theatre, hospital ward and outpatient gynaecological oncology department of the participating centres, using the usual facilities.

SUMMARY OF CHECKS

Pre-surgery visit (Form 1)

Surgery (Forms 2 and 3)

Post Surgical Hospital Monitoring (Form 4)

Outpatient Monitoring (Form 5)

Case Closure (Form 6)

MINIMUM REQUIREMENTS FOR PARTICIPATION IN THE STUDY

a) No. of advanced ovarian cases/year.

b) Adequate administrative support.

c) Protocol acceptance.

d) Approved by the local ethics committee.

REGULATORY CONSIDERATIONS

All participating institutions shall conduct the EDMOCS study in accordance with the Good Clinical Practice (GCP) Guidelines and IHC (International Harmonisation Conference) Standards. (http://en.vhir.org/portal1/article_menu_comites.asp?s=institut&contenttypeid=317&contentid=1330&sub=354)

STATISTICAL ANALYSIS

Continuous variables will be expressed as means and standard deviations, while categorical variables will be expressed as number of patients and percentage.

For the univariate analysis, differences between continuous variables will be performed with the Student t-test. When a non-parametric analysis is required, the Mann-Whitney U test and the Kruskal-Wallis test will be used. A value of $p<0.05$ will be considered statistically significant.

To analyse the reliability of the different clinical variables (heart and respiratory rate, temperature) and analytical variables (PCT, CRP, leukocytes, neutrophils, platelets) as possible diagnostic tests for the early detection of AL, the ROC curves will be analysed and the area under the curve (AUC) will be calculated for each of these variables. Assuming an AUC > 0.80 in the ROC curve analysis for both C-reactive protein and procalcitonin, with a power of 95%, it has been calculated that 70 patients will need to be included.

DATA MANAGEMENT

Each centre will be responsible for completing the forms submitted for each of the patients included in the study. After including a patient, the coordinating centre will be notified in order to assign a unique identification number. Once the follow-up period for each of the patients has been completed, or when a patient is excluded, all the information associated with the patient coded with her identification number will be sent to the coordinating centre where it will be merged into a single database.

FUNDING

The EDMOCS study is a non-commercial study that does not receive any external funding by the industry. Participating centres will not receive any financial compensation for their participation in the study.

AMENDMENTS TO PROTOCOL

Any amendments to the protocol must be approved by the coordinating committee. Any amendment deemed appropriate must be approved by the ethics committees of all participating centres and no patient may be included in the amended protocol until such approval is obtained from all centres.

PUBLICATION STANDARDS (in accordance with ENGOT standards)

General

A) The order and number of authors will be calculated according to the number of patients per institution/group where the institution/group leading the project will have the top positions.

B) Each institution/group is free and independent to include the author's name according to their number and position of co-authorship.

Number of co-authors per group:

A) An institution/group will be granted a co-author position if it has recruited/presented at least 5% of the total number of patients/cases. Each additional 5% = 1 additional co-author.

B) Institutions recruiting less than 5% of patients may co-author secondary publications.

Additional publications of sub-projects or sub-groups/institutional data

A) Each participating institution/group can receive a dataset of the patients recruited by said institution/study group after the final analysis, if desired.

B) Independent analyses performed by a participating centre/group on its own patients included in the study must not include primary or secondary endpoints and the coordinating centre must be informed about any such project.

C) All sub-publications or meta-analyses can only be published after the main study has been published.

D) Any additional population-wide subgroup analyses (using data from other institutions) conducted by a participating institution/group should be evaluated and agreed upon by the entire working group.

E) The order and number of co-authors in sub-publications will follow the same rules as for the main publication.

LIST OF APPENDICES

APPENDIX 1. Abbreviations

AL	Anastomotic Leakage
AUC	Area Under the Curve
CRP	C-Reactive Protein
NPV	Negative Predictive Value
PCT	Procalcitonin
PPV	Positive Predictive Value
ROC	Receiver Operating Characteristic

APPENDIX 2. Surgical and pathological staging of ovarian, fallopian tube and peritoneal cancer (2014 FIGO Staging)

Stage I. The tumour is limited to the ovaries or fallopian tubes.

IA Tumour limited to one ovary (intact capsules) or fallopian tube, absence of tumour on ovarian or fallopian tube surface; absence of malignant cells in ascites or peritoneal washings.

IB Tumour limited to both ovaries (intact capsules) or both fallopian tubes, absence of tumour on ovarian or tubal surfaces; absence of malignant cells in ascites or peritoneal washings.

IC Tumour limited to one or both ovaries or fallopian tubes with any of the following lesions:

- **IC1**-Operative rupture.
- **IC2-** Pre-surgery ruptured capsule, or ovarian or tubal surface tumour.
- **IC3-** Presence of malignant cells in ascites or peritoneal washings.

Stage II. The tumour is in one or both ovaries or fallopian tubes with pelvic extension (below the promontory) or is a primary tumour of the peritoneum.

IIA Extension and/or implants in the uterus and/or fallopian tubes and/or ovaries.

IIB Extension to other intraperitoneal pelvic tissues.

Stage III. The tumour involves one or both ovaries or fallopian tubes, or it is primary peritoneal cancer with extra-pelvic peritoneal dissemination, and/or cytologically or histologically confirmed retroperitoneal lymph node metastases.

IIIA Microscopic peritoneal metastasis outside the pelvis (above the promontory) (no gross tumour) with or without metastasis to retroperitoneal lymph nodes.

IIIA1: Only cytologically or histologically confirmed retroperitoneal (pelvic and/or para-aortic) lymph node metastases.

IIIA1 (i) Metastases less than or equal to 10 mm in greatest diameter.

IIIA1 (ii) Metastases larger than 10 mm in greatest diameter.

IIIA2 Microscopic extra-pelvic metastases with or without retroperitoneal lymph node involvement.

IIIB Gross peritoneal metastases outside the pelvis equal to or less than 2cm in size with or without metastases to retroperitoneal lymph nodes.

IIIC Macroscopic peritoneal metastases outside the pelvis greater than 2 cm in size with or without metastases to retroperitoneal lymph nodes. Extension to the hepatic and splenic capsule is classified as stage IIIC.

Stage IV. Tumour involves one or both ovaries with distant metastases (excluding peritoneal metastases).

IVA Pleural effusion with positive cytology for malignant cells.

IVB Parenchymal metastases and metastases to extra-abdominal organs (including inguinal lymph nodes and those located outside the abdominal cavity) Liver parenchymal metastases is the same as IVB stage.

APPENDIX 3. Fast-Track Protocol Hospital Vall d'Hebron

PERIOD	GYNAECOLOGICAL CANCER SURGERY PROTOCOL
Before admission	-Comprehensive written and oral **information** to the patient **-ANAESTHETIC-SURGICAL RISK ASSESSMENT. Nutritional, cardiological, anaemia and comorbidity optimisation.** Cardiologist evaluation if active cardiac pathology of recent onset or decompensated disease Nutritional assessment: -Nutritional Screening Test (MUST). Nutritional supplementation if appropriate -Assessment of Diabetes Mellitus: ▪ glycaemia and HbA1c ▪ If diabetes poorly controlled or previously undiagnosed, refer to Primary Care and/or Endocrinology ▪ Assessment of anaemia (pre-surgery anaemia management algorithm). -Stop smoking and alcohol consumption (ideally ONE month prior to surgery). -Assess inclusion in tri-modal pre-habilitation programme (optimum 4 weeks, minimum 2 weeks). -**Sign Informed Consents** -**Refer to the Stomatherapy Clinic if ileostomy/Colostomy**
	Immediately Pre-surgery *(if possible, schedule admission on the same day of surgery)* -Low-residue, low-fat diet 4 days prior to surgery -Continue with previous nutritional treatment if undernourished -Fast: 6 hours for solids and 2 hours for clear liquids - Carbohydrate drink supplement: 12.5% maltodextrin 200ml 2h before surgery (if diabetic patient, administered together with anti-diabetic medication). -Start thromboembolic prophylaxis according to hospital protocol.

Perioperative	-**NO abterograde bowel preparation** -Cassen enema the night before -Full bath -Shaving with electric razor if necessary -Colostomy marking if anticipated -Fitting of compression stockings or intermittent pneumatic compression stockings -Prophylactic administration of antibiotics 30-60 min before surgical incision. In prolonged procedures repeat doses according to the drugs' half-life. -Careful administration of short half-life sedatives
	Intraoperative **-Routine monitoring**: -ECG, Non-Invasive Blood Pressure (NIBP), Pulse Oximetry (%Sat O2), FiO2, Capnography, Temperature, Intraoperative glycaemia, Anaesthetic Depth (BIS), Neuromuscular Block (optional) -Consider deep muscle relaxation. Consider the use of **aminosteroid relaxants.** as first choice (if Sugammadex is available). **-Bladder catheterisation** **-Invasive monitoring**: -No invasive blood pressure routinely (potentially in patients with severe cardiorespiratory impairment). -No central venous catheter routinely **-Anaesthetic induction and maintenance** with short-acting agents **-Oxygenation FiO2 >50%** **-Fluid therapy:** Haemodynamic optimisation by **goal-directed fluid therapy** with validated devices is recommended. If these are not available, ideal weight-based fluid therapy in continuous perfusion balanced solution (3-5ml/kg/h for laparoscopy; 5-7ml/kg/h for laparotomy) is recommended. -**No nasogastric tube routinely** **-Active heating** with thermal blanket and fluid heater **-Prophylaxis of postoperative nausea and vomiting according to the Apfel scale (according to Annex FADN)** -Lower thoracic or upper lumbar **epidural analgesia** for all patients undergoing open surgery. Patients contraindicated for epidural may benefit from **bilateral TAP** and/or **infiltrate trocars with local anaesthetic.** **-Intravenous analgesic adjuvants:** - NSAIDs during surgery - Ketamine (if treated with major opioids) -**Avoid blood glucose levels > 180 mg/dl** in patients at risk of developing insulin resistance (obese, elderly, long surgical duration). -Laparotomies with low transverse incisions where possible -**Avoid drains** except in cases where there is a risk of pelvic collections.
	Immediate post-surgery period (Resuscitation Unit-Hospitalisation ward) -Active temperature maintenance -Maintenance of FiO2 0.5 2 hours after the end of the surgery. -Pain assessment: VAS (aim 0-3 pain level) -Painkillers according to intervention (based on epidural). -Minimal administration of morphine. NSAIDs as adjuvant therapy. -Restrictive fluid therapy -Start of oral tolerance 6 hours after surgery -Beginning of mobilisation 6 hours after surgery -Thromboprophylaxis -Respiratory physiotherapy -Strict blood glucose control maintaining levels < 110 mg/dl in non-diabetics, and between 110-150 mg/dl in diabetics.
1st day post-surgery	-Nutritional supplements in selected cases -Liquid/semi-liquid diet according to tolerance -Respiratory physiotherapy -Assess removal of drains, if present

	-Pain assessment: VAS (aim 0-3 pain level). Intravenous painkillers (do not remove epidural catheter until pain controlled with intravenous painkillers). Avoid administration of morphine. -Active mobilisation (bed/chair/start of ambulation) -If oral tolerance is correct, withdrawal of intravenous fluids. -Assessment of bladder catheter removal -PONV prophylaxis. -Anti-ulcer prophylaxis -Thromboembolic prophylaxis -Strict blood glucose control - maintaining levels between 110-150 mg/dl for diabetics. - Colostomy care -start stoma management education if appropriate
2nd day post-surgery	-Consider bladder catheter removal (if present) -Semi-soft/soft diet -Respiratory physiotherapy -Active mobilisation (ambulation) -Intravenous painkillers. Assess oral painkillers -Withdrawal of intravenous fluids (if not already withdrawn) -Prophylaxis of thromboembolism -PONV prophylaxis. -Strict blood glucose control -Anti-ulcer prophylaxis - Colostomy care and start stoma management education, if appropriate
3rd day Post-surgery (and remaining hospitalisation)	-Specific diet for colostomy patients -Oral painkillers -Respiratory physiotherapy -Removal of the venous line -Active mobilisation (ambulation) -Prophylaxis of thromboembolism -Home discharge from the 3rd day onwards -Strict blood glucose control -Colostomy care and start stoma management education, if applicable **ASSESS DISCHARGE CRITERIA** Assessment of possible discharge if the following criteria are met: -No surgical complications -No fever -Pain controlled with oral painkillers -Full ambulation -Correct oral tolerance
AT DISCHARGE	-Personalised, comprehensible and comprehensive information -Dietary recommendations for patients with ileostomies -Maintenance of thromboprophylaxis 28 days after surgery -Telephone checks after discharge - Follow-up at discharge/continuity of care: 1, 3 and 6 months post-discharge - Follow-up in Stomatherapy Consultation if necessary. *Home support-Coordination with Primary Care

APPENDIX 4 Clavien-Dindo Classification of post-surgery complications

Grade	Definition
I	Any deviation from the normal postoperative course that does not require pharmacological, endoscopic, surgical or interventional radiology treatment. Pharmacological treatments such as anti-emetics, antipyretics, analgesics, electrolyte solutions and physiotherapy are allowed. Includes superficial surgical site infections treatable at the patient's bedside.
II	Pharmacological treatment with drugs other than the above is required. Includes transfusion of blood products and total parenteral nutrition.
III	Requires surgical, endoscopic or radiological treatment. IIIa Without general anaesthetic IIIb With general anaesthetic
IV	Life-threatening complication requiring treatment in an intermediate or intensive care unit. IVa Single organ dysfunction (includes use of dialysis) IVb Multiple organ dysfunction
V	Patient's death
"d" suffix	If the patient suffers a complication at discharge, a "d" (for disability) suffix is added to the respective grade. This indicates the need for follow-up for a correct assessment of the complication.

APPENDIX 5. ECOG Scale

ECOG 0	The patient is completely asymptomatic and is able to work and to perform normal daily activities.
ECOG 1	The patient presents with symptoms that prevent her from performing strenuous work, although she's able to carry out normal daily activities and do light work. The patient only stays in bed to sleep at night.
ECOG 2	The patient is not able to work, her symptoms force her to stay in bed for several hours a day, in addition to those at night, but not more than 50% of the day. The individual satisfies most of her personal needs alone.
ECOG 3	The patient's symptoms require her to be bedridden for more than half a day. She needs help with most daily activities such as getting dressed.
ECOG 4	The patient remains bedridden 100% of the day and needs help with all daily activities, such as body hygiene, moving around in bed and even feeding.
ECOG 5	Deceased.

APPENDIX 6. Participation application for new centres

MEMBERSHIP FORM FOR NEW CENTRES

In relation to the study entitled:

PROCALCITONIN AND C-REACTIVE PROTEIN AS EARLY MARKERS OF ANASTOMOTIC LEAKAGE IN ADVANCED GYNAECOLOGICAL CANCER.

Name of Collaborating Centre:

Doctor in charge:

Contact telephone:

E-mail:

THE UNDERSIGNED DECLARE,

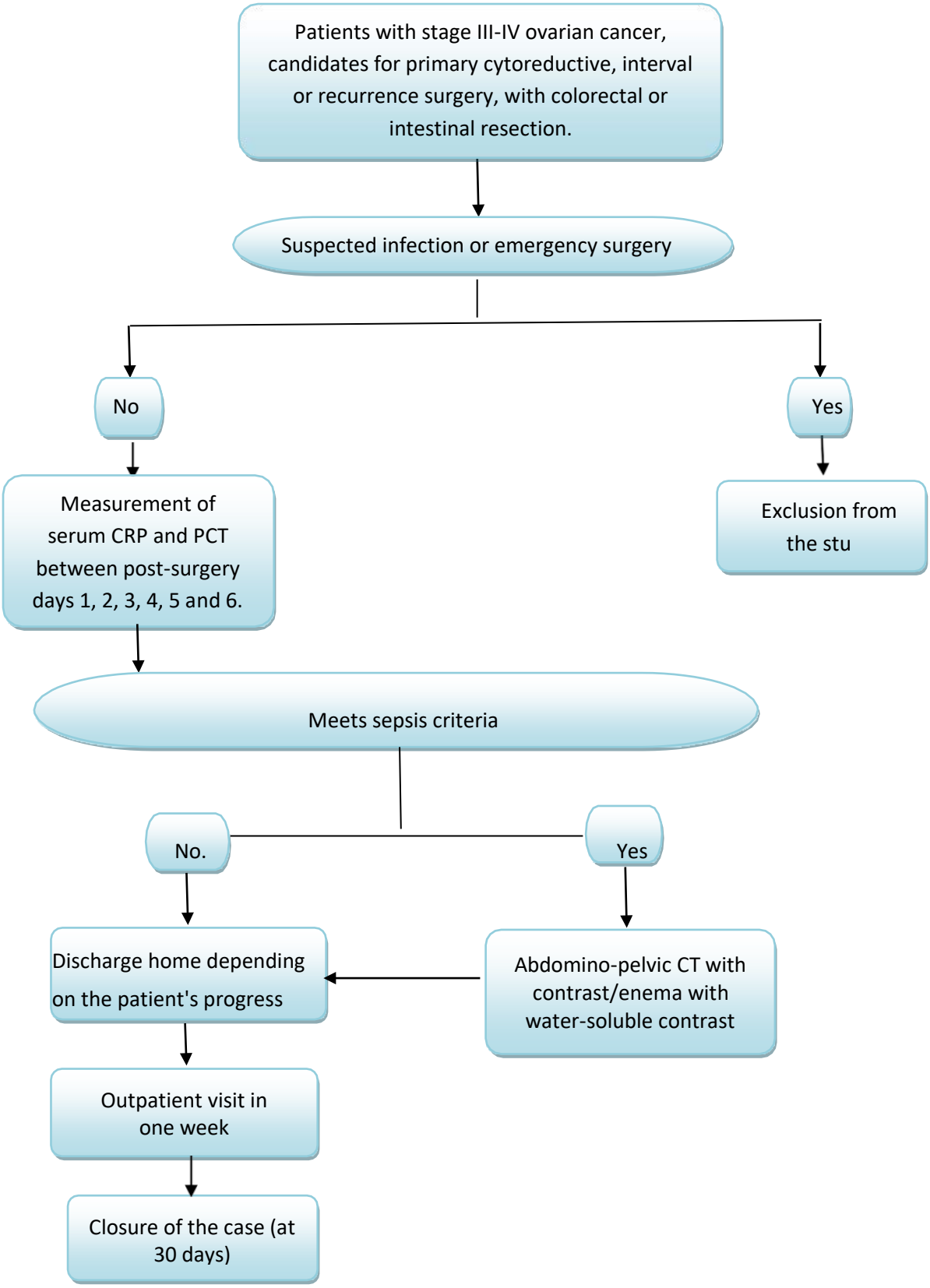
1. That they are aware of and agree with the aforementioned protocol, and agree to participate as collaborating researchers in this study.

2. That they meet the minimum conditions necessary to collaborate in the study and that the Centre's Ethics Committee approves their participation in the project.

3. That they undertake to collect and deliver the forms of those patients who are recruited for this study.

Researcher's signature:
Name:
Date:

APPENDIX 7. EDMOCS Flowchart



APPENDIX 8. EDMOCS Study Guide

Pre-surgery

If a patient has suspected diagnosis of stage III-IV ovarian cancer, by examination, CA 125 marker and Thoracic-abdominal CT scan, who is due to undergo primary cytoreductive, interval or recurrence surgery, the patient will be offered to participate in the EDMOCS study at the outpatient clinic. The patient will be given an information sheet and be asked to sign the informed consent form.

A pre-surgery blood test including measurement of C-Reactive Protein and Procalcitonin will be performed.

During surgery

Patients will be included in the study if they present one of these three situations:

1. Performance of colorectal resection with mechanical or manual anastomosis.
2. Mechanical or manual small bowel resection.
3. Colorectal resection with ileostomy/protective colostomy.

Patients with suspected infection or who receive emergency surgery or Hartmann's surgery will be excluded from the study.

Post-surgery hospital monitoring

- Usual postoperative care, according to the Unit's protocols.
- Daily recording of clinical data and vital signs from the first day post-surgery until discharge. Three measurements per day shall be recorded.
- Post-surgery laboratory tests on days 1, 3, 5, 7 and 10 (unless the patient has been discharged earlier) including: CBC, biochemistry (Na+, K+, Cl-, glucose, urea and creatinine) and coagulation tests.
- Post-surgery analytical determination on days 1, 2, 3, 4, 5 and 6 including: C-Reactive Protein and Procalcitonin.

- Assessment of the operated patient for the presence of one or more criteria for sepsis:
    - Temperature (over 38.5ºC)
    - Hypothermia (< 36ºC)
    - Heart rate > 90 beats / min.
    - Tachypnoea > 20 breaths / min.
    - Altered mental state
    - Significant oedema (positive water balance)
    - Hyperglycaemia (plasma glycaemia > 120 mg/dl)
    - Leukocytosis (> 12,000 µL-1)
    - Leukopenia (< 4000 µL-1)
    - Normal white blood cell count with more than 10% immature forms.
- If sepsis criteria are met, investigation of the possible septic focus should be undertaken:
    - Wound infection (examination and sample for microbiology)
    - Lung infection (X-ray/CT)
    - Urinary tract infection (sediment/culture)
    - Abdominal or pelvic infection. Rule out suture failure (abdomino-pelvic CT scan with contrast/enema with water-soluble contrast). Rectal examination with rectoscopy if necessary.

Discharge criteria will be considered (as per the protocols of each participating centre):

- No post-surgery complications of any kind
- Passing gas and/or stools
- Oral painkillers are enough to manage pain
- Independence for daily activities (walking, feeding, washing, etc.)
- Have taken three or more solid meals (basal diet).
- Agree to discharge.
- In patients with a stoma, controlled debit

Outpatient clinical follow-up one week after discharge and closure of the episode 30 days after surgery.

APPENDIX 9. Patient Identification Register

REGISTRATION FORM FOR PATIENTS INCLUDED IN THE EDMOCS STUDY

(Procalcitonin and C-reactive Protein as Early Anastomotic Dehiscence Markers in Ovarian Cancer Surgery.)

Study Code:
Community Code:
Centre Code:
Researching Doctor:

CRD Number	NHC	Date of 1st visit	Surgery date	Date of visit postop.	Closing date form
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Researcher's signature: _____

Patient Recruitment Start Date: _____

APPENDIX 10. Patient Information Sheet

Research project entitled

PROCALCITONIN AND C-REACTIVE PROTEIN AS EARLY MARKERS OF ANASTOMOTIC LEAKAGE IN ADVANCED OVARIAN CANCER.

Principal Investigator Dr *Sánchez Iglesias, JL; Pérez Benavente, A; Morales Comas, C; Carbonell Socias, M; Gil Moreno, A.*

Gynaecological Oncology Service

Objectives:

We are asking for your participation in this research project with the main objective of evaluating procedures that may help in the treatment of *advanced ovarian cancer*.

Benefits:

There may be no direct benefit from your participation in this study. However, the evaluation of new strategies related to the treatment of *ovarian cancer* may contribute to improving your prognosis in the future.

Study procedures. Risks and complications.

You have been diagnosed with the disease described above and therefore surgery is indicated as part of the standard treatment in order to improve the prognosis of your disease. In some patients, part of the small or large intestine, if affected, must be removed and the ends of the healthy intestine must be sutured together during surgery. In a small percentage of cases, the intestinal suture may fail, which is a serious complication.

C-reactive protein and procalcitonin are two proteins used in the study of severe infections, which have been identified as early detection markers for intestinal suture failure in colorectal surgery, due to their increase in the early days following surgery. The benefits in their management in advanced ovarian cancer have not yet been demonstrated.

Thus, in the first six days after surgery, daily analyses will be carried out where both proteins will be analysed. For the rest, the care offered will be the usual post-surgery care for advanced ovarian cancer, as established in our unit's protocol.

The results of the aforementioned markers will not be a reason to initiate complementary studies, as their usefulness has not been demonstrated at the present time. If the clinical criteria for intestinal suture failure are met, they will be investigated with the usual imaging techniques.

Should any complications arise, they will be treated by the surgeon who has followed and treated your condition, as would be the case in normal practice.

Protection of personal data:

In accordance with [Spanish] Law 15/1999 on Personal Data Protection, the personal data obtained will be those necessary to fulfil the purposes of the study. Your name will not appear in any of the study reports, and your identity will not be revealed to any person except for the purposes of the study, and in the case of a medical emergency or legal requirement. Any personally identifiable information will be kept securely encrypted by the principal investigator (Dr Sánchez Iglesias), or by an institution designated by him. Access to such information will be restricted to study personnel designated for this purpose or to other authorised personnel who will be obliged to maintain the confidentiality of the information.

In accordance with current law, you have the right to access your personal data and, if justified, the right to correct and delete it. If you so wish, you should request this from the doctor attending you in this study.

In accordance with current legislation, you have the right to be informed of any data relevant to your health that are obtained in the course of the study. This information will be communicated to you if you wish; if you prefer not to be informed, your decision will be respected.

If you require more information about this study, please contact the researcher in charge, Dr Morales / Sánchez / Carbonell / Pérez Benavente / Gil, of the Gynaecology Oncology Service. Tel. +34 934893066. E-mail addresses: c.morales@vhebron.net, jlsanchez@vhebron.net.

Your participation in the study is completely voluntary, and if you choose not to participate you will receive all the medical care you need and your relationship with the medical team caring for you will not be affected.

APPENDIX 11. Informed Consent Form

Informed Consent Form

TITLE OF THE STUDY:

PROCALCITONIN AND C-REACTIVE PROTEIN AS EARLY MARKERS OF ANASTOMOTIC LEAKAGE IN ADVANCED OVARIAN CANCER.

Principal Investigator

Gynaecological Oncology Service

I (name and surname(s))

.....

- have read the information sheet provided to me.
- was able to ask questions about the study.
- have received sufficient information about the study.
- have spoken to:

.....

(name of researcher)

I understand that my participation is voluntary.

I understand that I can withdraw from the study:

1. Whenever I want
2. Without having to provide an explanation.
3. Without it affecting my medical care.

- I freely agree to participate in the study and consent to the access and use of my data under the conditions detailed in the information sheet.
- I agree to the use of the extracted samples ONLY for the purpose of this project, with subsequent destruction at the end of the project.

Patient's signature: **Researcher's signature:**

Name: **Name**:

Date: **Date**:

APPENDIX 12. Study Forms

Hospital: Patient ID number:

PROCALCITONIN AND C-REACTIVE PROTEIN AS EARLY MARKERS OF ANASTOMOTIC LEAKAGE IN ADVANCED OVARIAN CANCER

Please return this form to:

Gynaecology Oncology Unit (Planta 4ª) Edificio Materno-Infantil. Hospital Vall d'Hebron, Passeig de la Vall d'Hebron, 119-129, 08035 Barcelona.

Tel: +34 93 4893066

E-mails: c.morales@vhebron.net, jlsanchez@vhebron.net

Instructions

1. Please do not include any identifying information about the patient (name, address, medical record number, etc.) on the form.
2. Please fill in the fields according to the information requested. If you need to add additional information, please use the specific space at the end of the form.
3. Fill in data requiring dates in DD/MM/YY format and hours in a 24-hour format, e.g. 18.37.
4. If you are unable to fill in some of the information, please use the final section of the form.
5. If you have any queries completing this form, please contact our Unit (c.morales@vhebron.net, jlsanchez@vhebron.net).

Form 1. Pre-surgery information

1. Year of birth .....

2. Patient's age at diagnosis .....

3. BMI at first visit .....

4. Smoker: Yes (No. of cigarettes/day .....)
   No
   Used to smoke

5. Previous co-morbidities (select according to attached code) .....

0. No comorbidities, 1. HTA, 2. Heart disease, 3. Kidney disease, 4. Diabetes, 5. Psychiatric pathology, 6. Haematological disorder, 7. Endocrine pathology (except diabetes), 8. Inflammatory disease, e.g. Crohn's disease, 9. Epilepsy 10. Autoimmune disease. 11. Previous neoplasms. 12. HIV. 13. Liver disease. 98. Other (specify after code).

6. ECOG ....

7. Charlson Index ....

8. Initial nutritional parameters

Haemoglobin.....	Protein.....
Haematocrit.....	Cholesterol.....
AST/ALT ..... /.....	Triglycerides.....
Creatinine.....	Prealbumin.....
Glucose.....	Albumin.....
Urea.....	Pancreatic alpha-amylase.....
Sodium/Potassium...../	24h urine (creatinine, urea and high levels of protein) ...../ ..... / .....

9. Pre-surgery FIGO stage .....

10. Peritoneal carcinomatosis index ....

11. Tumour markers

CA125 ..... HE4 .....

CA19.9 ..... AFP .....

CEA ..... BHCG ....

12. Inflammatory markers C-

Reactive Protein .....

Procalcitonin .....

13. Surgery for this patient will be:

1. Primary cytoreduction
2. Interval cytoreduction
3. Relapse
4. Palliative

Form 2. Exclusion criteria

1. Infection before surgery Yes/ No
   Fever Yes / No
   Compatible symptomatology Yes / No
   CBC (leukocytosis) Yes /No

2. Urgent surgery (e.g. intestinal occlusion) Yes /No

If YES was selected in any of the above items, the patient will be excluded from the study.

Form 3. Surgery details

1. Surgery date ..../..../....

2. Bowel preparation: 1. Antegrade 2. Enema 3. Enema +antegrade

3. Type of bowel resection:
    1. Recto-sigma
    2. Right ileo-colic
    3. Right hemicolectomy
    4. Right hemicolectomy extended to transverse
    5. Left hemicolectomy
    6. Transversectomy
    7. Small bowel resection

4. Type of suture used in the anastomosis

    .....

5. Use of drainage Yes / No

6. Surgical cytoreduction:
    1. Complete
    2. Optimal (larger implant < 1 cm)
    3. Sub-optimal (larger implant size =/> 1 cm)

7. Estimated surgery time (minutes) .....

8. Estimated blood loss (ml) .....

9. Incidents observed during surgery:

Form 4. Post-surgery hospital management

1. Patient included in Fast-track protocol 1. Yes 2. No 2.

2. Parenteral nutrition 1. Yes. 2. No

3. Patient's vital signs (note down 3 times a day)

Day	BP, HR, TºC, Sat 02	BP, HR, TºC, Sat 02	BP, HR, TºC, Sat 02
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			

4. Analytical data (CBC, Na+, K+, Cl-, glucose, urea and creatinine, CRP and PCT)

Day 1 .....

Day 2 .....

Day 3 .....

Day 4 .....

Day 5 .....

Day 6 .....

Day 7 .....

Day 10 .....

5.Surgical complications (according to the Dindo-Clavien classification):

1. No
2. I
3. II

4. IIIa / IIIb
5. IVa / IVb
6. V

If yes, please indicate the day of appearance .....

6. Need for blood transfusion 1. Yes 2. No

If yes, no. of red blood cell concentrates ..... and day of transfusion .....

7. Diagnosis of postoperative infections 1. Yes. 2. No

Please specify according to code .....

0. Intra-abdominal infection, 1. Surgical wound infection, 2. UTI/PNA, 3. Respiratory infection, 4. Central or peripheral tract infection, 5. Other (specify).

8. Performance of postoperative abdominal CT scan 1. Yes 2. No

Reason for performance (use codes) .....

0.Clinical suspicion of suture dehiscence, 1. Suspected bleeding, 2. Suspected infection other than intra-abdominal, 3. Other (specify reason)

9. Abdominal CT scan result (radiological diagnosis of anastomotic suture dehiscence)

1 Yes 2 No

10. Reintervention due to suspected suture dehiscence 1. Yes. 2. No

11. Treatment of anastomotic leakage 1. Drainage. 2. New surgery
In case of surgery, technique used: 1. Hartmann 2. Ileostomy + suture AL 3.Other

12. New surgery for other reasons 1. Yes 2. No

1. Abscess
1. Haemoperitoneum
1. Pancreatic fistula
1. Other

13. Number of total days in hospital .....

Form 5. Outpatient Monitoring

1. Date of post-operative visit ..../ ..../ .....
2. Did the patient need to visit A & E? Yes /No
3. Has she been readmitted to hospital? Yes /No Please

   indicate reason .....

   1. Pain management. 2. Suspected infection with conservative treatment, 3. Suspected infection that required surgery, 4. Transfusion, 5. Other (specify)

4. FIGO stage by Anatomical disease.....

5. Histological Type .....

Form 6. Case Closure (at 30 days post-surgery)

1. Date of post-operative visit ..../ ..../ .....
2. Did the patient need to visit A & E? Yes /No

3. Has she been readmitted to hospital? Yes /No Indicate

   reason .....

   1. Pain management. 2. Suspected infection with conservative treatment, 3. Suspected infection that required surgery, 4. Transfusion, 5. Other (specify)

4. Diagnosis of anastomotic suture dehiscence Yes / No

5. Patient's death Yes / No

   Date ..../ ...../ ......

   Reason for death .....

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