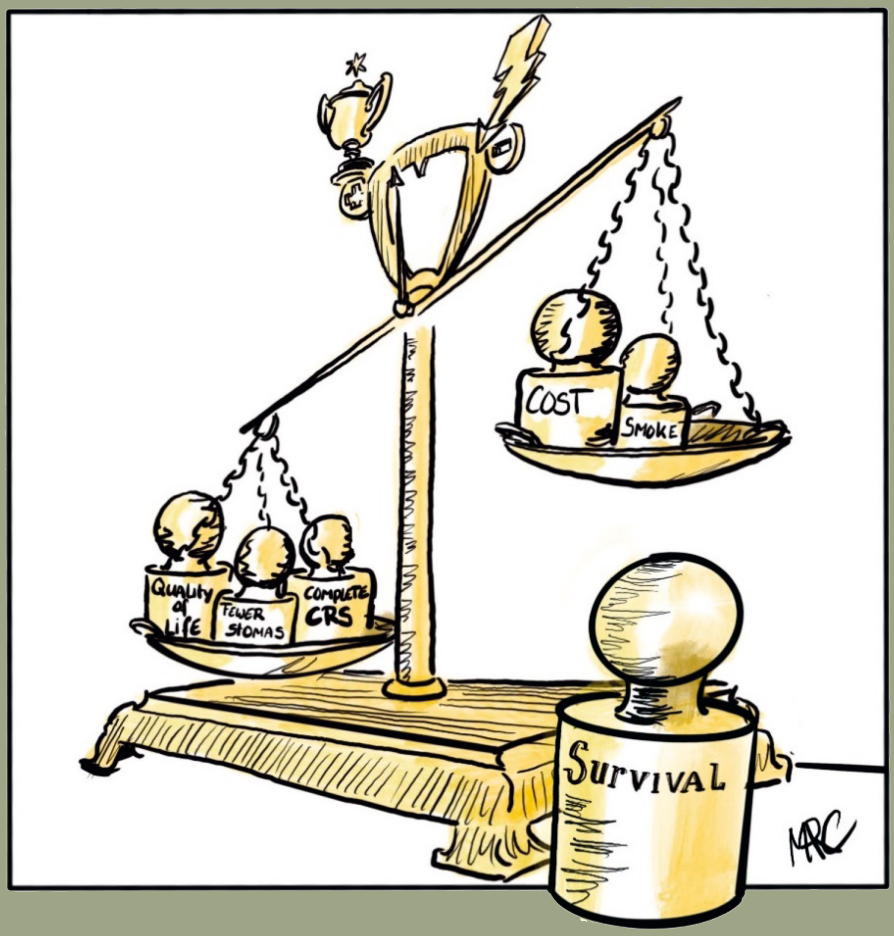
Cytoreductive Surgery for Ovarian Cancer

Improvement of surgical outcome with the PlasmaJet Surgical device



Gatske M. Nieuwenhuyzen-de Boer

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Cytoreductieve chirurgie voor ovariumcarcinoom

Verbetering van de uitkomst van de operatie door de inzet van de PlasmaJet

Proefschrift

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‘And whatever you do, whether in word or deed,
do it all in the name of the Lord Jesus,
giving thanks to God the Father through Him’

(Collosians 3:17)

Voor alle vrouwen met ovariumcarcinoom

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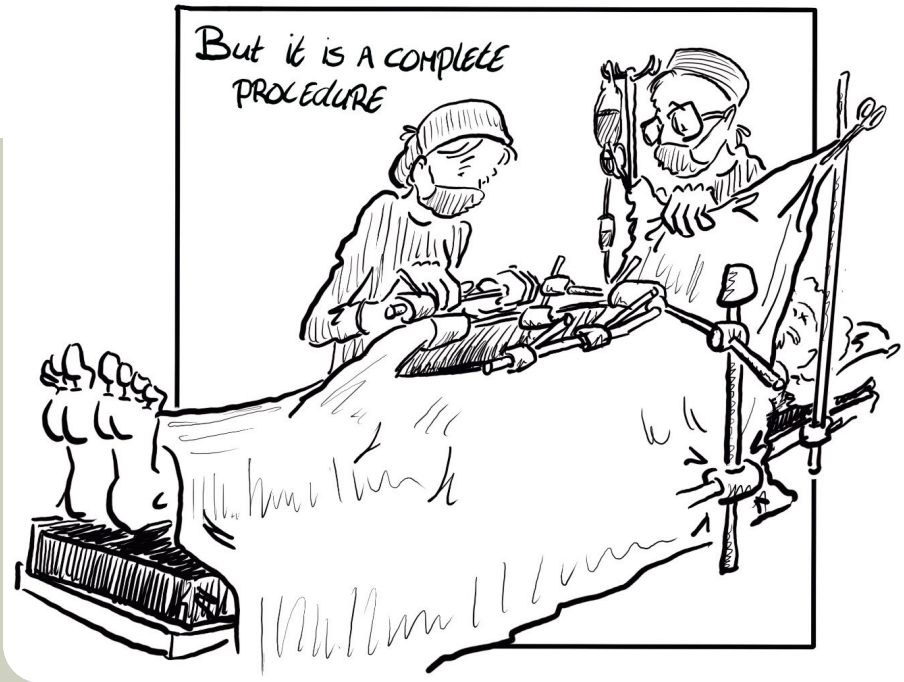
General introduction and outline of the thesis



Introduction

The first laparotomy in a human being was a gynecologic procedure. The oophorectomy described in literature took place on Christmas Day in 1809. The pioneer in abdominal surgery, Ephraim McDowell, removed a large benign tumor(1,2). Legend has it that a surly crowd gathered outside during this surgery and waited to hang him on his patient's certain death(3). But the patient did not die.

Figure 1 The first oophorectomy, 1809

In 1901, the first laparoscopy was again a gynecologic procedure. It was performed by Dimitri Von Ott, who inspected the abdominal cavity of a pregnant women(4). Among general surgeons, laparoscopy only gained increasing interest after 1987, when the French gynecologist Mouret performed the first acknowledged laparoscopic cholecystectomy by means of four trocars(5).

History seems to repeat itself with respect to the use of plasma-based devices during surgical procedures(6,7). In the early 1990s, plasma-based devices were first used in the management of ovarian cancer, because of the improved control of thermal depth of injury compared to monopolar electrocoagulation(8). In 2004, the PlasmaJet

device received its first approval and since then it has been used mainly during gynecological surgeries(9,10).

The basis of this thesis comes from a lesson in the past. Within gynecology, new treatments such as the Essure -a contraceptive with a permanent implant for women- were implemented without extensive preliminary research. Devices have withdrawn from the market due to long-term complications(11-14). It emphasizes that a new device or new techniques must be scientifically researched before they are implemented. This thesis focuses on the safety and efficacy of using a new surgical device, the PlasmaJet Surgical device during cytoreductive surgery (CRS) for ovarian cancer.

General background on ovarian cancer

Ovarian cancer is one of the three most common gynecologic cancers and has the worst prognosis(15). The most important reasons of the high mortality rate are the asymptomatic tumor growth and the lack of screening tools(16). As a result, about 75% of the patients with a serous epithelial cancer are diagnosed at an advanced stage of disease(17). For women diagnosed with an advanced stage disease, the five-year survival is 30 to 40%(18,19).

Ovarian cancer can be staged with two classification systems, the tumor-node-metastasis (TNM) system and the system of the International Federation of Gynecology and Obstetrics (FIGO)(21). Advanced stage ovarian cancer is defined as T2b-T4 or FIGO stage IIB-IV. FIGO stage IIB means that metastases are present in other tissue within the pelvis, while FIGO stage III means that metastases are present in the entire abdominal cavity, and FIGO stage IV means that metastases are even found outside the abdominal cavity.

Standard treatment of advanced stage epithelial ovarian cancer (EOC) consists of CRS and chemotherapy, followed by maintenance therapy with a poly adenosine diphosphate-ribose polymerase (PARP) inhibitor in selected patients(22,23). In patients with FIGO stage III ovarian cancer, guidelines recommend hyperthermic intraperitoneal chemotherapy (HIPEC) just after an interval CRS, as it improves recurrence-free and overall survival(24).

Over the past few decades, surgery for ovarian cancer has evolved considerably, with increasing implementation of higher radicality(25). Several studies demonstrated

a survival advantage among patients after optimal cytoreduction (< 1 cm residual disease) compared to patients who received suboptimal cytoreduction (>1cm residual disease)(26,27). Now, the focus has shifted from optimal CRS to complete CRS (no residual disease). Achieving maximum tumor clearance is the only independent parameter for longer recurrence-free and overall survival (OS)(28,29).

Factors influencing surgical outcome

While surgical outcome is an important parameter in primary treatment, improving surgical outcome and achieving a higher rate of complete CRS hinges on several factors, which can be subdivided into individual patient factors, tumor factors and organization or surgery factors (Figure 2).

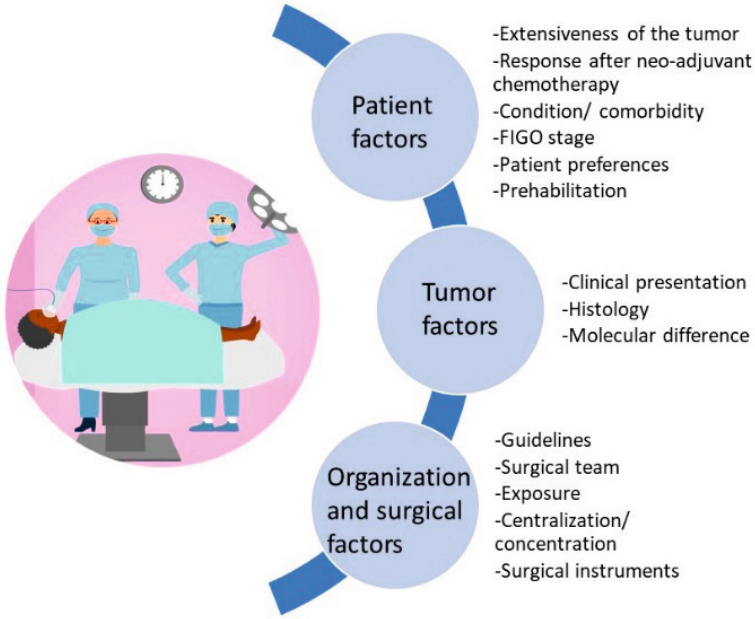


Figure 2 Factors influencing surgical outcome

Patient factors

First of all, it is important to observe the patient herself to determine whether she will benefit from a CRS. Obvious factors of importance are the extensiveness of the tumor on CT scan and the possibility to perform primary CRS. In case of extensive tumor, neo-adjuvant chemotherapy is usually started and a response evaluation will be assessed after three courses for radiological (CT scan) or biochemical response (Cancer Antigen 125). The possibility to perform CRS depends on the patient's condition and comorbidities.

Furthermore, the surgical outcome may depend on the FIGO stage of the disease. Prior to surgery, the patient and the doctor can discuss and decide not to construct a stoma because of a FIGO stage IV disease. Due to such a preoperative decision, complete CRS will not be achieved in case of extensive involvement of the bowel during surgery because in that case, a stoma cannot be avoided.

A new strategy to optimize health care efficiency is prehabilitation(30). In some studies, prehabilitation has led to an improvement of the patient's condition. In case of a better preoperative condition of the patient, it is possible to perform more extensive surgery, which increases the chances of achieving a complete CRS.

Tumor factors

Ovarian cancer has a distinctive biology and behavior at the clinical, cellular and molecular level(31). Clinically, ovarian cancer often presents as a cystic mass in the pelvis. Unlike cancer in many other sites, cancer in the ovary has no anatomical barrier to prevent widespread metastasis into the abdominal cavity. Usually, small clusters of cancer cells are shed by the ovary and settle on the peritoneal surface and diaphragm. Metastasis can occur through lymphatic vessels or blood vessels. Often, fluid leaks from the disrupted tumor vessels (ascites). Findings from recent studies provide additional evidence that the most common type of ovarian cancer, high-grade epithelial cancer, may originate in the fallopian tubes(32,33).

At the cellular and molecular level, ovarian cancer is remarkably heterogeneous. The normal ovary is a complex tissue with several components. Although ovarian cancers can develop from germ cells or stromal cells, more than 90% of ovarian cancers have epithelial histology. Considerable heterogeneity has been observed in the cellular grades, proliferation indexes and histotypes of ovarian cancers.

At the molecular level, altered patterns of gene expression in different histotypes correlate with characteristic patterns of gene expression in the normal ovary. Histotypes are also correlated with the abnormal re-expression of genes that are normally expressed only during gynecological organogenesis.

Depending on these factors and on the response to neoadjuvant chemotherapy, the presence of tumor varies from patient to patient. This variation greatly affects the surgical outcome.

Organization and surgical factors

A third type of factors that influence surgical outcome are the organization and surgical factors. The European Society of Gynecologic Oncology (ESGO) has developed quality indicators for surgery of advanced ovarian cancer to monitor and improve clinical practice in Europe and beyond(22). These guidelines provide advice for perioperative management. Improved practice adherence to the guidelines for diagnosis and treatment will improve surgical outcomes.

Surgical outcome can also be influenced by the composition of the surgical team. This includes the team members' experience as well as the availability of other medical disciplines. Vernooij et al. showed that the outcome of ovarian cancer treatment was better when treatment was provided by a gynecologic oncologist rather than by a general gynecologist(34). Besides, scientific research has shown that higher volume (>20 procedures per year) leads to a better surgical outcome(35,36).

Finally, it is possible that surgical outcome is also influenced by the instruments available during surgery. Little is known about this aspect, which is the focus of the present thesis. We aim to establish whether the use of the PlasmaJet surgical device contributes to surgical outcome. If the use of this new device increases the percentage of complete cytoreductive surgery, the implementation of this device might potentially contribute to increasing disease-free and overall survival.

PlasmaJet Surgical device

The surgical tool investigated in this thesis is a thermal plasma energy device, named the PlasmaJet® Surgical device (Plasma Surgical, Inc., Roswell, GA, USA). The device consists of a cathode, intermediate electrodes and an anode. An electrical

current is discharged across the device elements inside an electrode channel where argon gas is heated to generate plasma (Figure 3). Plasma is an energetic state of matter consisting of ions and free electrons. This state is typically created by electric discharges in a plasma medium and can be used for direct tissue effect. Plasma-based devices have been clinically evaluated in gynecology for coagulating, for ablating and, to a lesser extent, for cutting tissues.

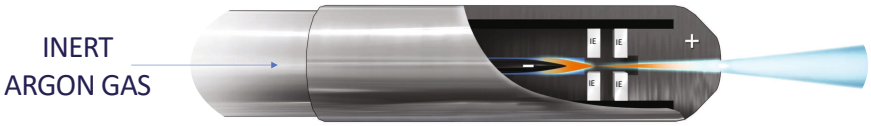


Figure 3 PlasmaJet device: argon gas is heated to generate plasma. (-) Cathode; (+) Anode; (IE) Intermediate Electrodes.

Patients with advanced stage ovarian cancer frequently present with peritoneal carcinomatosis, with diaphragmatic involvement observed in about 40% of cases(37). Other preferred locations of multiple tumor lesions can be the peritoneum, the mesentery and the bowel. Due to the use of an electrically neutral device, there is no muscle contraction during removal of the diaphragm or peritoneum. Also, superficial tumor lesions which can be present throughout the abdomen can be removed due to the vaporizing effect of plasma. Finally, while there may be various adhesions due to extensive tumor deposits, finding the correct tissue planes can be simplified by the ablation effect of plasma.

The mean thermal tissue depth during CRS using the PlasmaJet for ovarian cancer is unknown. The thermal effects of the PlasmaJet device have only been assessed in uterine leiomyomas and sigmoid bowel serous carcinomas samples or ex vivo in ovarian cancer patients(38). In those studies, increasing the power and exposure time resulted in more tissue vaporization (0.2-3.5 mm), whereas the depth of the eschar remained relatively constant (<1 mm). In case series published on this subject, no additional complications were described(10).

Aims and outline of the thesis

The general aim of this thesis was to improve the knowledge on a surgical factor for improving surgical outcome for patients with advanced stage ovarian cancer,

i.e. the introduction of a new surgical device, the PlasmaJet. Besides, we aim to determine the relevance of tumor marker CA-125 and the CT scan for predicting surgical outcome.

Part I: The effectiveness and safety of the PlasmaJet during cytoreductive surgery

Part 1 of this thesis aimed to improve the knowledge on the adjuvant use of the PlasmaJet Surgical device during cytoreductive surgery for advanced stage ovarian cancer. **Chapter 2** presents a systematic review about the effectiveness and safety of the PlasmaJet Surgical device in gynecological procedures.

Due to the lack of a randomized controlled trial on this topic, a study design was composed and submitted to the medical ethics committee of the Erasmus MC. **Chapter 3** presents the study protocol for a multicenter randomized controlled trial, the PlaComOv study.

The PlaComOv study is a multicenter, single-blinded, randomized, controlled superiority trial. The acronym 'PlaComOv' refers to the research question: 'Will the use of the PLAsmaJet® device improve the rate of COMplete cytoreductive surgery for advanced-stage OVarian cancer?'

Patients with suspected advanced stage EOC, fallopian tube or peritoneal carcinoma FIGO stage IIIB-IV were eligible for inclusion if they were fit enough to undergo CRS and chemotherapy. The surgical procedure was either primary CRS or interval CRS. Actual inclusion in the study was decided upon if advanced stage EOC (FIGO stage IIIB-IV) was diagnosed during surgery.

Patients were recruited from four gynecological oncology centers and nine centers specialized in ovarian cancer surgery in the Netherlands. They were randomized into an intervention group and a control group. All participating hospitals have experience in CRS, and during all surgeries, one of the surgeons was a gyneco-oncologist from one of the oncology centers.

Each cytoreductive surgery was attended by someone with experience with the PlasmaJet. Besides, all the participating surgeons were required to attend a course in which they were trained to perform operations with the PlasmaJet. The theoretical knowledge of the PlasmaJet was discussed in detail, followed by practice operations on laboratory animals.

When introducing a new technology, several aspects are important. The chapters 4 to 7 describe the aspects of safety, effectiveness, cost and the effect on quality of life.

Chapter 4 presents the outcomes of the PlaComOv study, the results regarding the safety and the effectiveness of the PlasmaJet Surgical device during CRS. This chapter describes the rates of complete CRS in patients operated with the standard

use of electrocoagulation (control group) compared to the rates in patients operated with the adjuvant use of PlasmaJet (intervention group).

Chapter 5 deals with the depth of thermal tissue damage and compares the in-vivo thermal tissue depth effects of neutral argon plasma with those of electrocoagulation during cytoreductive surgery.

Chapter 6 presents the outcomes of a cost study on the additional costs for CRS with the use of the PlasmaJet. All costs from diagnosis until six weeks after the last cycle of chemotherapy are analyzed for patients with advanced stage ovarian cancer.

Chapter 7 describes the influence of the use of the PlasmaJet on quality of life in the single blinded PlaComOv study. The results were compared to quality of life of patients who underwent surgery without the use of the PlasmaJet.

Part II: The predictive value of CA-125 and CT scan on surgical outcome

Part 2 of this thesis aimed to improve knowledge on how to appropriately select patients who will benefit from CRS with the primary goal to achieve complete CRS.

In chapters 8 and 9, we analyzed the predictive value of the Cancer Antigen 125 (CA-125) level and the results of the CT scan for surgical outcome. **Chapter 8** presents an overview of the literature of the prognostic value of the CA-125 level on the surgical outcome. In this chapter, the CA-125 level of patients in the PlaComOV study and the CA-125 decrease after neo-adjuvant chemotherapy are correlated to surgical outcome. **Chapter 9** describes the outcomes of a systematic review of studies on the CT features that predict the inability to achieve a complete CRS.

Chapter 10 describes the treatment and survival of patients included in the PlaComOv study in whom surgery was abandoned due to unresectability after abdominal exploration. In this chapter we focus on the awareness for this “forgotten group” of patients. For patients with unresectable disease, we advocate an international registry of their treatment and follow-up to provide a treatment recommendation in clinical guidelines.

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2

Effectiveness and Safety of the PlasmaJet® Device in Advanced Stage Ovarian Cancer: a systematic review

G.M. Nieuwenhuyzen-de Boer; J. van der Kooy; H.J. van Beekhuizen

Journal of Ovarian Research 2019, Volume 12, Article number 71

Abstract

Background

About 80% of all women affected by ovarian cancer present with advanced stage disease at the time of diagnosis. Achieving complete cytoreduction is complicated when many small tumor spots are found. Yet, complete cytoreduction is the most important determinant of survival. Application of a thermal plasma energy device to standard surgical instruments may help achieve complete cytoreduction. The 'PlasmaJet® Device' (Plasma Surgical, Inc., Roswell, GA, USA) is an electrically neutral device which emits a high–energy jet of argon plasma for direct tissue effects.

The primary outcome was the proportion of complete cytoreductions. The secondary outcomes were: complication rate, proportion of colostomies applied, histological findings, disease-free survival and overall survival.

Methods

We performed a literature review to investigate whether the use of the 'PlasmaJet® Device' in surgery of advanced stage ovarian carcinoma (FIGO IIIB-IV) is effective and safe.

Results

Five case series or reports were found, including a total of 77 patients with FIGO stage IIIC-IV ovarian cancer in whom the PlasmaJet® device was used for primary or interval debulking. Complete cytoreduction was obtained in 79% of the patients. Apart from one pneumothorax after extensive surgery, but no harm or additional complications related to the use of the PlasmaJet® Device were reported. Data on disease-free survival or overall survival were not reported.

Conclusions

These findings suggest that the PlasmaJet® Device is an efficient and safe innovative surgical device for debulking surgery with encouraging results. We have proposed an RCT in which we will compare feasibility, safety and effectiveness aspects of the use of the PlasmaJet® versus conventional electrosurgery in advanced stage epithelial ovarian cancer (FIGO IIIB-IV).

Introduction

Ovarian cancer is the fifth leading cause of cancer-related death among women and is the deadliest of gynecologic cancers worldwide(1). Eighty percent of all women affected by ovarian cancer present with advanced stage disease at the time of diagnosis. The standard treatment for advanced stage ovarian carcinoma is cytoreductive surgery combined with chemotherapy.

Complete cytoreductive surgery (CCS) is the most important determinant of prognosis and survival in advanced stage ovarian carcinoma(2, 3). The success rate of the operation varies with factors such as patient selection and morbidity, tumor location and surgeon's expertise(4). Novel surgical and chemotherapeutic treatments introduced over the past decade have not led to significant improvement in survival.

Achieving complete cytoreduction is complicated when many small tumor spots are found on the intestines and the diaphragm. Conventional electrosurgery then often does not result in complete removal of these spots. A number of published case series suggest that application of the 'PlasmaJet® Device' (Plasma Surgical, Inc., Roswell, GA, USA) during cytoreductive surgery results in higher rates of complete cytoreduction and lesser need of a colostomy. The device uses neutral argon plasma to vaporize small tumor nodules with minimal collateral damage(5, 6). This technique seems to be effective in tumor ablation; especially to remove peritoneal carcinomatosis on the abdominal peritoneum, in the diaphragmatic region, intestinal mesentery and bowel serosa.

Methods

We performed a literature review to investigate the effectiveness and safety of the use of the PlasmaJet® device in surgery of advanced stage ovarian carcinoma (FIGO IIIB-IV) based on CT scan. We aimed to compare the outcomes of surgery with the additional use of the PlasmaJet® device with the outcomes of conventional surgery (using electrosurgery, scalpel, and scissors).

Primary outcome: percentage complete cytoreductive surgery.

Secondary outcomes: complication rate, proportion of colostomies applied, histological findings, disease-free survival and overall survival.

The following databases were searched: https://www.embase.com, https://www.controlled-trials.com, https://www.clinicaltrials.gov, and https://www.york.ac.uk/inst/crd/ at December 2018. The search strategy was as follows:

((neutral NEAR/6 argon NEAR/6 plasma) OR (jet NEAR/6 plasma NEAR/6 (coagulat* OR remov*)) OR PlasmaJet):ab,ti.

The titles and abstracts of citations retrieved from the search were screened on relevance by two authors (GN, BK) independently. Study inclusion criteria were as follows: 1) Primary epithelial ovarian, fallopian tube or peritoneal carcinoma, 2) FIGO stage IIB to IV, 3) patients treated with cytoreductive surgery, 4) residual disease categorized as complete (no macroscopic residual disease), optimal (largest diameter 0,1–1 cm) and suboptimal (largest diameter > 1 cm) and 5) complication rate reported.

Results

The search retrieved 84 citations. After screening of titles and abstracts six articles remained. After reading of full texts by all authors, three case series and two case reports were included (Table 1). Randomized controlled trials on this topic were not found. Cordeiro et al.(7) included 51 patients with FIGO stage IIIC-IV ovarian cancer in whom the PlasmaJet® device was used for primary/interval debulking. Complete debulking was achieved in 40 (78%) patients. A pleural drain was needed in eight (16%) patients in whom the PlasmaJet® was used for diaphragmatic stripping. No other post-operative complications were found. The authors did not provide data on colostomies. Panuccio et al.(8) included 19 patients undergoing primary/interval or secondary debulking for ovarian cancer FIGO stage IIIC-IV. Complete debulking was achieved in all 19 patients. A pneumothorax occurred in one patient (5%). Bowel or urological fistulas did not occur. Renaud et al. (9) described six patients who underwent surgery with the PlasmaJet® device. Complete debulking was achieved in one patient. The authors claim that in none of these patients optimal debulking could have been reached without the use of the device. Two case studies by Seror and Butler-Manuel described the use of PlasmaJet® without any complications(10, 11).

Table 1 Studies using PlasmaJet for cytoreductive surgery in case of advanced stage ovarian cancer (FIGO IIIC-IV)

Author	Number	Debulking	Complete debulking	Colostomy	Complications related to PlasmaJet
CORDEIRO VIDAL G [7]	51	Primary (41%) and interval (59%)	78%	No data	Pleural drain after diafragmatic stripping (n=8)
PANUCCIO E [8]	19	Primary and interval	100%		Pneumothorax (n=1) Bloodtransfusion (n=5)
RENAUD MC [9]	6		20%	none	
SEROR J [10]	1	Primary	Yes	no	None
BUTLER-MANUEL S [11]	1	Interval	Yes	no	Superficial wound defect

Discussion

The aggregated evidence from the five included studies shows that complete cytoreduction was obtained in 79% of the patients in whom the PlasmaJet® device was used during surgery. Apart from one pneumothorax after extensive surgery, no other harm or complications possibly related to the use of the PlasmaJet® device were described.

Histological examination of lateral thermal spread and the collateral tissue destruction caused by the use of the PlasmaJet® device has been performed for different power settings and exposure times. The lateral thermal spread increased with increased power, while the depth of eschar penetration remained relatively the same(4). In a study in pig, the use of the PlasmaJet® device was compared to laparoscopic bipolar coagulation and surgical resection of the peritoneum. Histological analysis 14 days after surgery showed that all areas were equally destroyed; adhesions were only seen in bipolar coagulation(4). Sonoda et al., investigating the thermal damage of PlasmaJet® histologically, similarly concluded that minimal lateral damage and depth of vaporization had occurred(6).

The use of the PlasmaJet® device in the removal of rectal endometriosis showed promising results with no major complications preventing colorectal resection. A randomized controlled trial in sixty women undergoing corrective abdominoplasty performed with either conventional monopolar electrosurgery or the use of the PlasmaJet® showed significantly fewer postoperative complications (mainly wound infections), one day earlier discharge, and better cosmetic outcomes with the use of the PlasmaJet® device(12).

Conclusions

To our knowledge, this is the first systematic review on the use of the PlasmaJet® Device in surgery of advanced ovarian carcinoma. The available data suggest that the device comes with several features that are well suited for debulking surgery. Application of the device is efficient in precise tissue dissection with minimal collateral damage, especially when many small tumor spots are found on the intestines and the diaphragm.

We have proposed an RCT named PlaComOv-study in which we will compare feasibility, safety and effectiveness aspects of the use of the PlasmaJet® with those of conventional electrosurgery in advanced stage epithelial ovarian cancer (FIGO IIIB-IV)(13). We hypothesize that the probability of achieving complete cytoreduction is significantly higher in the group of patients randomized to surgery with the use of the PlasmaJet® device. Secondary outcome include 30-days morbidity, ability to avoid bowel surgery and stoma formation, quality of life and cost-effectiveness.

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3

Evaluation of Effectiveness of the PlasmaJet Surgical Device in the Treatment of Advanced Stage Ovarian Cancer (PlaComOv-study): Study protocol of a randomized controlled trial in the Netherlands

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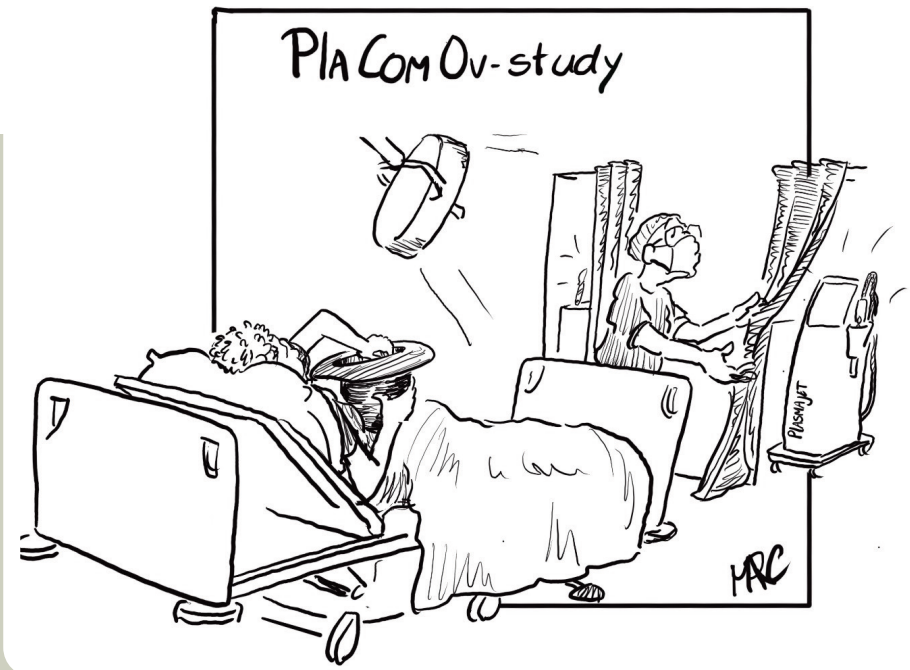

Abstract

Background

The most important goal for survival benefit of advanced stage ovarian cancer is to surgically remove all visible tumour, because complete cytoreductive surgery (CCS) has been shown to be associated with prolonged survival. In a remarkable number of women, CCS is very challenging. Especially in women with many small metastases on the peritoneum and intestinal surface, conventional CCS with electrosurgery is not able to be "complete" in removing safely all visible tumour.

In this randomized controlled trail (RCT) we investigate whether the use of the PlasmaJet Surgical Device increases the rate of CCS, and whether this indeed leads to a longer progression free and overall survival.

The main research question is: does the use of the PlasmaJet Surgical Device in surgery for advanced stage ovarian cancer result in an increased number of complete cytoreductive surgeries when compared with conventional surgical techniques. Secondary study objectives are: 30-day morbidity, duration of surgery, blood loss, length of hospitalisation, Quality of Life, disease-free survival, overall survival, percentage colostomy, cost-effectiveness.

Methods

The study design is a multicentre single-blinded superiority RCT in two university and nine non-university hospitals in The Netherlands. Three hundred and thirty women undergoing cytoreductive surgery for advanced stage ovarian carcinoma (FIGO Stage IIIB-IV) will be randomized into two arms: use of the PlasmaJet (intervention group) versus the use of standard surgical instruments combined with electrocoagulation (control group). The primary outcome is the rate of complete cytoreductive surgery in both groups.

Secondary study objectives are: 30-day morbidity, duration of surgery, blood loss, length of hospitalisation, Quality of Life, disease-free survival, overall survival, percentage colostomy, cost-effectiveness. Quality of life will be evaluated using validated questionnaires at baseline, at 1 and 6 months after surgery and at 1, 2, 3 and 4 years after surgery.

Conclusions

We hypothesize the additional value of the use of the PlasmaJet in CCS for advanced stage epithelial ovarian cancer. More knowledge about efficacy, side effects, recurrence rates, cost effectiveness and pathology findings after using the PlasmaJet Device is advocated. This RCT may aid in this void.

Introduction

Ovarian cancer is the seventh most common cancer in women worldwide with 239.000 new cases diagnosed in 2012. In The Netherlands 1325 patients were affected by ovarian cancer in 2016; of these 80% were diagnosed with advanced stage disease, for which surgical cytoreduction combined with chemotherapy is indicated(1-3). During the last decade, surgical and chemotherapeutic treatment has not led to significant improvement in survival. In surgical treatment it is important that all visible tumour is removed (complete cytoreductive surgery, CCS) because the progression-free survival (PFS) and overall survival (OS) after complete cytoreduction is significantly longer than after optimal cytoreductive surgery, where tumour volume of up to $1cm^2$ remains in the abdomen(4-10). In some cases it is impossible to achieve complete cytoreduction with conventional surgery due to the presence of many small tumour foci scattered on the intestines. Electrosurgery is unsuitable for tissues such as the intestine because of lateral thermal spread and depth of tissue destruction(11).

The PlasmaJet Surgery Device is an advanced energy system delivering pure plasma to the tissues. Plasma is a highly energized phase of gas which is short-lived and quickly dissipates at the targeted site of application, allowing controlled use(12,13). PlasmaJet is able to vaporize small tumour spots on intestine, mesentery, peritoneal surface, liver and spleen and is able to dissect peritoneum from the underlying tissue without muscle impulses and with less tissue damage than with conventional electrosurgery(11). In the case series published on this subject application of the PlasmaJet during cytoreduction resulted in higher rates of CCS (79%) and fewer colostomies without any additional complications(14-20).

In this study, we will compare the success rate of CCS with the use of conventional surgery including electrocoagulation (control) with the addition of PlasmaJet Device (intervention) in a single blinded multicentre randomized controlled trial (RCT) to evaluate the effectiveness of the PlasmaJet when applied in the surgical treatment of women with advanced-stage ovarian cancer(21).

Methods/design

Setting and study population

This study is called the PlaComOv-study. It is an acronym for 'Will the use of the PLAsmajet device improve the rate of COMplete cytoreductive surgery for advanced stage OVarian cancer'.

In this study, 330 patients with a FIGO IIIB-IV epithelial ovarian cancer, carcinoma of the fallopian tube or extra-ovarian epithelial ovarian cancer(peritoneal cancer) in whom the surgical goal is to achieve complete cytoreduction will be included. Patients should to be fit for CCS and chemotherapy.

Patients from the following Dutch hospitals may be included: Albert Schweitzer (Dordrecht), Bravis (Bergen op Zoom), Catharina Cancer Institute (Eindhoven), Erasmus MC (Rotterdam), Franciscus Gasthuis and Vlietland (Rotterdam), Groene Hart Hospital (Gouda), Haags Medisch Centrum (Den Haag), Haga Hospital (Den Haag), Leids University MC (Leiden), Medisch Spectrum Twente (Enschede), Reinier de Graaf Groep (Delft).

All surgeons are trained and certified in the use of PlasmaJet during the preparation of the study.

This study will compare the complete cytoreductive surgery rate when using electrocoagulation only (standard) with that achieved with additional use of the PlasmaJet Surgical Device (intervention). We expect that use of the PlasmaJet during surgery will result in a higher rate of complete cytoreduction and fewer colostomies(14-20).

Standard therapy is primary cytoreductive (upfront) surgery followed by chemotherapy, or neoadjuvant chemotherapy followed by interval cytoreductive surgery. Standard chemotherapy comprises of 6 cycles of carboplatin and paclitaxel, with a duration of 21 days for each cycle(1). In upfront cytoreductive surgery, all 6 cycles of chemotherapy are given after surgery. In interval cytoreductive surgery, 3 cycles of chemotherapy are administered prior to surgery and 3 cycles thereafter. Patients from both the upfront and interval cytoreductive groups may be included.

The standard of care is to reach complete cytoreduction in all women who are fit to undergo extensive surgery. This radical surgery may involve bowel surgery sometimes including colostomy. Electrocoagulation (Diathermy, LigaSure), scalpel and scissors

are used during conventional surgery to remove visible tumour and to dissect tumour tissue from peritoneal surfaces. The disadvantage of electrocoagulation is the lateral thermal spread and the depth of tissue destruction, which render it unsuitable for use on the intestines. Electrocoagulation (Diathermy, LigaSure), scalpel, scissors and PlasmaJet are used when indicated during surgery in the intervention arm.

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- patients with epithelial ovarian, tuba or peritoneal carcinoma FIGO IIIB-IV who are fit enough to undergo radical cytoreductive surgery as discussed in the Tumorboard. Patients can either be scheduled for primary cytoreduction or for interval cytoreduction after neoadjuvant chemotherapy
- patients should understand the patient information form and sign informed consent
- pre-operative CT scan meets criteria for resectability

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- patients who are not willing to participate or not able to give their informed consent (language barrier) and patients who are not willing to undergo extensive surgery
- patients who are unfit to undergo extensive surgery (assessed by gynaecologist and anaesthesiologist and discussed in Tumorboard)
- patients who are not fit enough to get the standard complete chemotherapy (six cycles carboplatin paclitaxel) (assessed by medical oncologist and discussed in Tumorboard)
- patients with a non-epithelial, borderline ovarian tumour or an ovarian metastasis of another primary tumour
- patients with recurrence of ovarian cancer.

Primary outcome

The primary study objective is to determine the rate of complete cytoreductive surgery in each group.

Secondary outcomes

- Complication rate (30 day-morbidity)
- Duration of surgery and hospital stay
- Blood loss during surgery and number of blood transfusions
- Number of partial bowel resections and colostomies
- Progression free survival(22)
- Overall survival(22)
- Quality of life (questionnaires filled in prior to surgery, at 1 and 6 months and at 1, 2, 3 and 4 years after surgery
- Accuracy of presurgical structured reporting of CT scans (according to a structured checklist). This will be compared with surgical findings (as recorded by a Gynaecological Oncologist immediately after surgery) and histological findings(23-28).
- Histology: depth of tissue destruction(29-32)
- Cost effectiveness analysis(33-37): Costs per (complete) cytoreduction and costs per gained life year QALY
- Total number of chemotherapy courses during overall survival
- Comparison of completeness of surgery between both study groups according to an independent review of the operation field by photos

A histology review will be carried out in a subpopulation of 30 patients from the PlasmaJet group (15 primary cytoreductive surgery, 15 interval cytoreductive surgery). We will study at specific spots of macroscopic tumour during surgery. One spot will be vaporized with PlasmaJet Device and analysed at the presence of residual tumour. Another spot will be the control sample.

Our hypothesis is that vaporization by the PlasmaJet Device will result in less tissue damage than electrocoagulation and that we shall not find vital tumour cells in tissue treated with PlasmaJet.

Intervention group

In the intervention group, the PlasmaJet Device will be used if necessary as an additional device during cytoreductive surgery.

PlasmaJet Surgical Device uses neutral argon plasma to vaporize small tumour nodules with minimal collateral damage(11-14). This device helps to achieve complete cytoreductive surgery in patients with advanced stage ovarian cancer, most particularly by ablating small tumour foci on the abdominal peritoneum, diaphragm, intestinal mesentery and bowel serosa.

Control group

In the control group, standard surgical instruments combined with electrocoagulation will be used during cytoreductive surgery.

Assignment of intervention

The study will be explained verbally to the patient by the gynaecologist, and patients will receive written information in accordance with Good Clinical Practice guidelines. Those wishing to participate will sign an informed consent form and will be randomized preoperatively. It is not always possible to assess the presence and stage of ovarian cancer preoperative, and in some cases it is unknown whether enlarged ovaries are malignant. In these cases, women can be randomized preoperatively and the gynaecologist will decide during the surgery whether the patient is eligible to be included in the study, depending on the result of frozen section and tumour stage.

Computer randomization will be used to allocate patients to the intervention or control group. Randomization will be carried out in blocks of varying size prior to surgery. Inclusions will be stratified depending on high or low suspicion of peritoneal carcinomatosis (based on the pre-operative CT scan), primary and interval cytoreductive surgery, and the use of OVHIPEC during surgery or not(38-40).

The RCT is single blinded: the patient does not know to which arm she has been assigned.

Data collection

Coded data are stored both on paper and in an electronic database. Collected data are stored in a digital case report form (CRF). Raw data is available only to the principal and coordinating investigator.

Patient characteristics will be stored in 'Open Clinica' and analysed in SPSS.

A CRF will be completed preoperatively, postoperatively-discharge and at 1½, 6, 12, 24 and 48 months postoperatively (Figure 1).

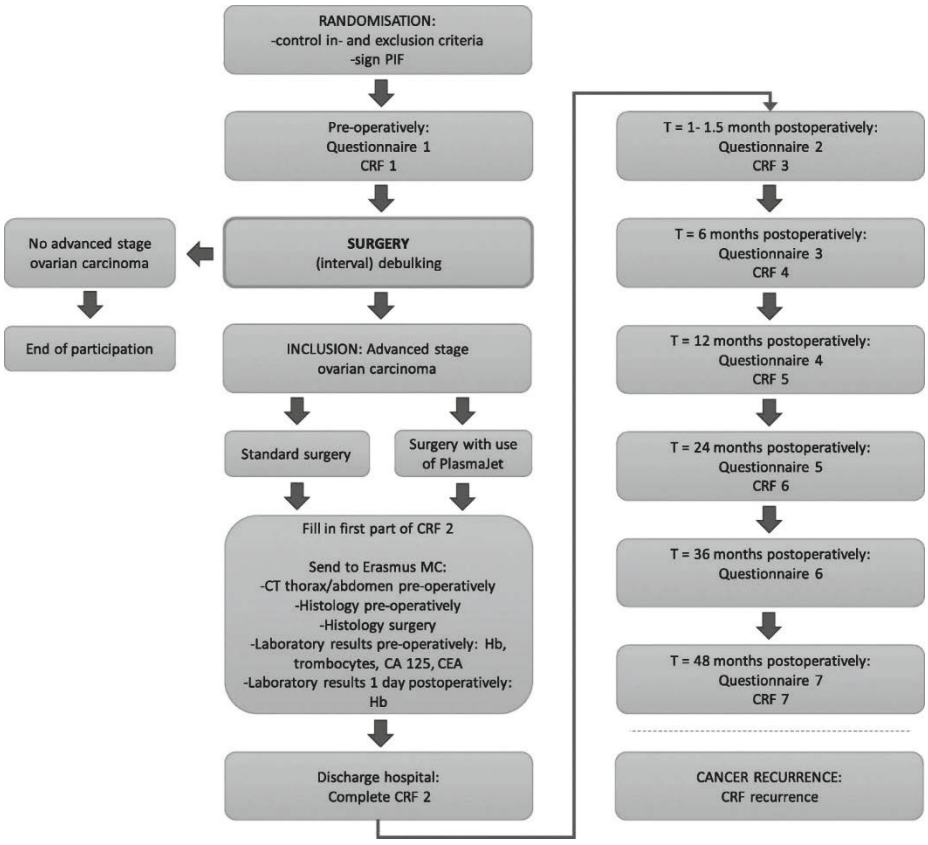

Figure 1 Flowchart of the study design

Prior to surgery and at 1½, 6, 12, 24, 36 and 48 months postoperatively, a quality of life questionnaire will be completed (EORTC, QLQ-30 and EQ-5D) (Figure 1). The following data are recorded:

-Preoperatively:

Patient characteristics, presence of germline mutations such as BRCA1 or 2, investigations carried out to make the diagnosis, outcome of structural reported CT scan, chemotherapy, quality of life.

-(Post)operatively:

Adverse effects of chemotherapy, operative parameters, tumour location, effectiveness of PlasmaJet during surgery, outcome of surgery, postoperative hospitalization, hospital discharge.

-4–6 weeks follow-up:

Complications postoperatively, re-hospitalization, histology outcome, planned chemotherapy, quality of life.

-6 months follow-up:

Complications of chemotherapy, re-hospitalization, indication of recurrence of malignancy, quality of life.

-1,2,3 and 4 years follow-up:

Indication of recurrence of malignancy, new lines of chemotherapy administered, quality of life.

Statistical considerations

Sample size calculations are based on our primary outcome measure. To demonstrate the additional value of the PlasmaJet, we assume an absolute increase of 15% in complete cytoreductive surgery in the PlasmaJet group (77% versus 62%). With a total type I error (alpha) of 5%, and a Type II error (beta) of 20%, 147 patients should be enrolled in each research arm.

Assuming a 12% loss of follow-up, a total of 330 patients should be recruited.

Statistical analysis

The primary outcome measure, percentage complete surgery, will be calculated for each arm of the study together with a confidence interval based on the Wilson method. They will be compared using a chi-squared test with continuity correction. We will also calculate the risk difference. This will be presented with a 95% confidence interval (calculated using Newcombe's method).

The study will be analysed according to the intention to treat principle. An exploratory subgroup analysis will be performed in a subset of patients with more than 50 lesions in the abdomen (peritoneal carcinomatosis), as complete cytoreductive surgery is not feasible for this group of patients. No multiplicity correction will be performed for these subgroup analyses.

Continuous secondary outcomes (duration of surgery, duration of hospital stay, blood loss) will be calculated using t-tests and the discrete variables (complication rate, bowel surgery, colostomies, number of chemotherapy courses) using chi-square tests using continuity correction.

All outcomes will be analysed using regression techniques. Progression-free and overall survival will be studied using the Kaplan-Meier method. Additionally Cox regression will be performed to study the influence of peritoneal carcinomatosis, complete, optimal or suboptimal cytoreduction. A p-value $p < 0.05$ will be considered significant.

Multiple imputation using chained equations will be used for missing co-values.

The other study parameters will be analysed as follows:

1. Progression free survival (after 5 and 10 years) (Kaplan-Meier method)
2. Overall survival (after 5 and 10 years) (Kaplan-Meier method)
3. Cost per life year gained
4. Number of chemotherapy courses (chi-square tests using continuity correction)

No interim analysis for futility and effectiveness will be performed. A safety committee has been installed to monitor harm. The committee will receive data on safety and harm after each group of 50 consecutive patients and may advise stopping the trial for safety reasons after each analysis.

Ethics and dissemination

The study has been approved by the Medical Ethical Committee of Erasmus Medical Centre Rotterdam. The study will be performed according to the standards outlined in the Declaration of Helsinki. Ethics committee approval has been granted.

Patients will receive verbal and written information from their gynaecologist during the intake for surgery. Randomization happens after signing of the Informed Consent.

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons. At this moment there are no specific criteria for withdrawal. After withdrawal the patient will be replaced since this is an intention to treat trial.

A monitoring plan is installed to ensure patients' safety and the quality of this trial. Adverse events are recorded and reported by the sponsor through a local protocol. Study results will be offered for publication in international medical journals and on the website of the patient association for women with gynaecological cancer.

Discussion

This study will contribute to the understanding of surgical treatment in patients with high stage ovarian cancer and will answer questions on implementation of the PlasmaJet Surgical Device. The results of this study will demonstrate whether the use of PlasmaJet Surgical Device will lead to a greater chance of complete cytoreductive surgery, and whether there is prolonged progression free and overall survival after operations conducted with this device.

The trial aims to study the efficacy of the PlasmaJet, side effects, survival rates and cost effectiveness, in comparison with conventional surgery. Pathology findings such as the presence of microscopic vital tumour after vaporisation with PlasmaJet and the depth of tissue damage after using the device will be studied.

A strength of this single blinded RCT is the use of questionnaires of Quality of Life (EORTC QLQ-30 and EQ-5D) and the involvement of the patient association of women with gynaecological cancer in The Netherlands.

Trial status

Approved by Medical Ethical Committee Medical Ethical Committee Erasmus Medical Centre Rotterdam, The Netherlands on 20-11-2017. Recruitment started on 30-1-2018. Protocol version 3.0.

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4

Adjuvant Use of PlasmaJet Device During Cytoreductive Surgery for Advanced-Stage Ovarian Cancer: Results of the PlaComOv-study, a Randomized Controlled Trial in The Netherlands

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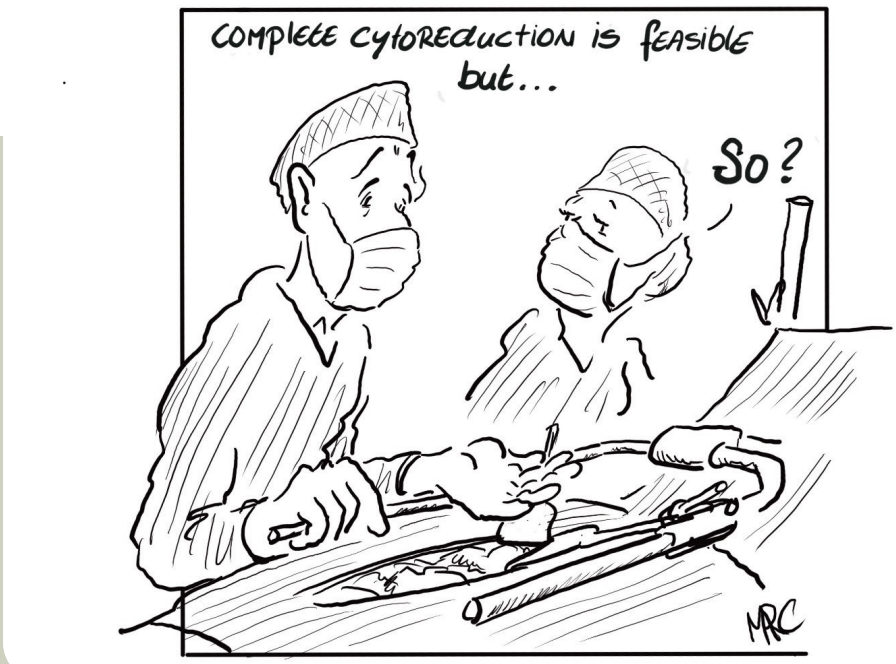

Abstract

Background

Standard surgical treatment of advanced-stage ovarian carcinoma with electrosurgery cannot always result in complete cytoreductive surgery (CRS), especially when many small metastases are found on the mesentery and intestinal surface. We investigated whether adjuvant use of a neutral argon plasma device can help increase the complete cytoreduction rate.

Methods

327 patients with FIGO stage IIIB–IV epithelial ovarian cancer (EOC) who underwent primary or interval CRS were randomized to either surgery with neutral argon plasma (PlasmaJet) (intervention) or without PlasmaJet (control group). The primary outcome was the percentage of complete CRS. The secondary outcomes were duration of surgery, blood loss, number of bowel resections and colostomies, hospitalization, 30-day morbidity, and quality of life (QoL).

Results

Complete CRS was achieved in 119 patients (75.8%) in the intervention group and 115 patients (67.6%) in the control group (risk difference (RD) 8.2%, 95% confidence interval (CI) –0.021 to 0.181; P = 0.131). In a per-protocol analysis excluding patients with unresectable disease, complete CRS was obtained in 85.6% in the intervention group and 71.5% in the control group (RD 14.1%, 95% CI 0.042 to 0.235; P = 0.005). Patient-reported QoL at 6 months after surgery differed between groups in favor of PlasmaJet surgery (95% CI 0.455–8.350; P = 0.029). Other secondary outcomes did not differ significantly.

Conclusions

Adjuvant use of PlasmaJet during CRS for advanced-stage ovarian cancer resulted in a significantly higher proportion of complete CRS in patients with resectable disease and higher QoL at 6 months after surgery. (Funded by ZonMw, Trial Register NL62035.078.17.)

Introduction

Ovarian cancer is the eighth most common cancer in women, with nearly 314,000 new cases in 2020 worldwide(1). The most important independent prognostic factor for survival among patients with advanced-stage epithelial ovarian cancer (EOC) is completeness of cytoreductive surgery (CRS)(2-9). Achieving complete CRS is difficult when many small tumor spots are found on the intestines and mesentery. The use of neutral argon plasma (PlasmaJet, Plasma Surgical, Inc, Roswell, GA), in addition to standard surgical instruments may help achieve complete CRS(10-16). We performed a study designed to assess whether adjuvant use of PlasmaJet would increase the proportion of complete CRS among patients with advanced-stage EOC(17-20).

Patients and Methods

Trial Design

The PlaComOv study is a multicenter, single-blinded, randomized controlled superiority trial. The acronym "PlaComOv" already reveals the study aim: "Will the use of the PLAsmaJet® device improve the rate of COMplete cytoreductive surgery for advanced-stage OVarian cancer"(17).

This trial compared the rates of complete CRS of patients with advanced EOC operated with standard use of electrocoagulation (control group) versus patients operated with adjuvant use of PlasmaJet (intervention group).

Patients from four gynecological oncology centers and nine centers specialized in ovarian cancer surgery in the Netherlands were randomized to either treatment arm. All hospitals had experience in CRS. A gyneco-oncologist from one of the oncology centers was always one of the surgeons. All surgeons were trained to perform operations with the PlasmaJet by following a course where theoretical knowledge of the PlasmaJet was discussed in detail, followed by operations on laboratory animals, concluding with an exam. During the cytoreductive surgery, someone with experience with PlasmaJet was always present.

For practical reasons, randomization was performed prior to surgery. Block randomization in a 1:1 ratio to either the intervention or control group was performed, with stratification according to suspected versus proven advanced-stage EOC, primary CRS (pCRS) versus interval CRS (iCRS), presence of peritoneal carcinomatosis based

on preoperative computed tomography (CT) scan, and hyperthermic intraperitoneal chemotherapy (HIPEC) procedure.

All patients provided written informed consent and were blinded to the arm for which they were selected.

Inclusion and Exclusion Criteria

Patients with suspected advanced-stage EOC, fallopian tube, or peritoneal carcinoma International Federation of Gynecology and Obstetrics (FIGO) stage IIIB–IV who were fit enough to undergo CRS and chemotherapy were eligible for inclusion. The surgical procedure was either pCRS or iCRS(21,22). Actual inclusion in the study was decided if advanced-stage EOC (FIGO IIIB–IV) was diagnosed during surgery. We excluded patients with recurrent disease, a nonepithelial, borderline ovarian tumor, or ovarian metastasis of another primary tumor, as well as patients who did not have surgery after randomization because of their condition.

HIPEC was introduced in the Netherlands in 2019(23). From 2019, all patients younger than 76 years of age with FIGO stage III EOC who underwent iCRS were eligible to receive an additional HIPEC procedure after complete or optimal CRS.

Treatment

Preoperative workup consisted of physical examination and transvaginal ultrasonography. Serum measurement of cancer antigen 125 (CA-125) and carcinoembryonic antigen (CEA), a CT scan of the thorax/abdomen, and if possible a histological biopsy was taken. Workup findings were discussed preoperatively in a multidisciplinary tumor board.

Preoperative CT scans were reported systematically, and criteria were set for nonresectability of disease(24-28). Patients who met those criteria were scheduled for iCRS and received three courses of neoadjuvant chemotherapy (NACT). In case of response or stable disease on a CT scan after three cycles of chemotherapy, patients were eligible for iCRS.

Patients who had been included in this study but had incomplete primary CRS and thus received NACT to enable consecutive surgery remained in the treatment arm as allocated before primary surgery. For analyses, they were assigned to the iCRS group.

The standard chemotherapy regimen consisted of six cycles of intravenous carboplatin (area under the curve of 6 mg ml/min) and paclitaxel (175 mg/m2 body surface area)

with a duration of 3 weeks for each cycle(5). In pCRS, all six cycles were given after surgery. In iCRS, in all cases, three cycles were given prior to and three cycles after surgery. In case of germline or tumor BRCA mutations, patients received maintenance of poly ADP ribose polymerase (PARP) inhibitor in accordance with standard of care as per April 2019.

Diagnostic laparoscopy was performed if the feasibility of complete CRS was doubted.

Surgery included total hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and resection of all visible and palpable tumor. Complete, optimal, and suboptimal CRS was defined as described by the Gynecologic Oncology Group(29,30). Complete CRS was defined as surgery that resulted in no macroscopic disease (residual disease classification, R-1), optimal cytoreduction was defined as postoperative surgical residuum ≤ 1 cm in largest diameter (R-2), and suboptimal cytoreduction as residuum > 1 cm. Unresectable disease was defined as surgery intended to perform CRS but abandoned because tumor was irresectable.

Electrocoagulation, Harmonic Scalpel, Ligasure, scalpel, and scissors were used during conventional surgery to remove any visible tumor and to dissect tumor tissue on peritoneal surfaces.

In the intervention group, the PlasmaJet device could be used as an additional device. With the aim of objectifying surgical completeness, two gynecological oncologists blinded to the patient's treatment arm allocation reviewed photographs from predesignated sites (pelvis, paracolic fossa, diaphragm, and small intestines) taken at the end of surgery.

At the end of each procedure in the intervention group, the gynecological oncologist filled in a questionnaire on the value of the contribution of the PlasmaJet to the surgical outcome.

All histology was coded, and the majority of the slides were reviewed by an experienced gyne-pathologist (P.E.E.-G.).

End Points

The primary outcome was the rate of complete CRS. The secondary outcomes were duration of surgery, blood loss, length of hospitalization, bowel surgery, number of colostomies, complication rate (mortality and 30-day morbidity), and quality of life.

To study self-perceived health status, we asked patients to complete a questionnaire before surgery, and at 4 weeks and 6 months after surgery. The questionnaire consisted of two parts: a descriptive health classifier system on five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression (EQ-5D-5L), and a vertical visual analog scale (EQ-VAS)(31,32).

Statistical Analysis

To demonstrate 15% more cases of complete CRS in the intervention group than in the control group (77% versus 62%) and setting the type I error (alpha) to 5% and type II error (beta) to 20%, we needed to enroll 294 patients. Assuming 12% loss to follow-up, 330 patients were required.

An intention-to-treat (ITT) analysis was performed with data of all included patients. A per-protocol analysis was performed with data of all patients who underwent CRS.

The primary outcome was calculated with a confidence interval based on the Wilson method. Group data were compared using a chi-squared test with continuity correction. The arms of the trial are compared using a generalized linear model with a binomial distribution and identity link adjusting for stratification factors. We further present an unadjusted risk difference together with a 95% confidence interval based on Newcombe's method.

An exploratory subgroup analysis was performed in a subset of patients who underwent HIPEC and patients with ≥ 50 lesions in the abdomen (peritoneal carcinomatosis), which made complete CRS not easily feasible.

Continuous secondary outcomes (duration of surgery, duration of hospital stay, blood loss, and patient-reported quality of life on EQ-VAS and EQ-5D-5L questionnaires) were compared using t-tests; the discrete variables (complication rate, bowel surgery, and colostomies) were compared using chi-square tests with continuity correction, unless an expected count was less than five, in which case Fisher's exact test was used.

P-value < 0.05 on a two-sided test was considered to indicate a significant difference. All analyses were performed using R 4.1 (Foundation for Statistical Computing Vienna, Austria). Multiplicity correction was not performed for this subgroup analysis.

Results

Patients

From February 2018 through September 2020, a total of 383 patients were randomized: 190 to the intervention group and 193 to the control group. All had suspected or proven advanced-stage EOC (Figure 1). Fifty-six patients had to be excluded. The clinical characteristics of the 327 included patients whose data were analyzed according to intention to treat are presented in Table 1. The characteristics are evenly distributed among the two groups.

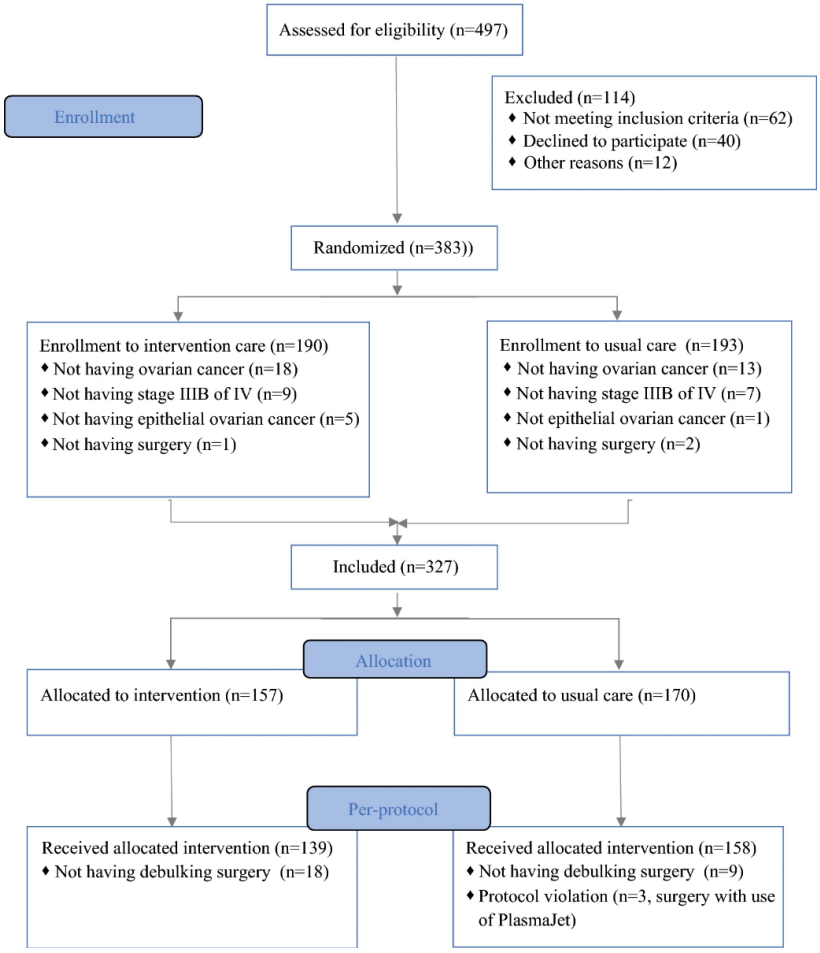

Figure 1 CONSORT 2010 flow diagram

Table 1 Patient characteristics

	Intention-to-treat		Per-Protocol	
	Intervention n=157 (%)	Control n=170 (%)	Intervention n=139 (%)	Control n=158 (%)
Age (years)				
mean [SD]	66.1 [9.6]	65.1 [11.2]	65.8 (9.3)	64.9 (11.3)
median [min, max]	67.6 [28.9, 81.3]	65.9 [20.3, 86.1]	66.9 [35.4, 81.2]	65.7 [20.3, 86.1]
Parity (>AM 24 weeks)				
0	22 (14.0)	34 (20.0)	20 (14.4)	32 (20.3)
1-2	99 (63.1)	83 (48.8)	88 (63.3)	76 (48.1)
>3	34 (21.7)	49 (28.8)	29 (20.8)	46 (29.1)
WHO-performance status				
0	82 (52.2)	90 (52.9)	76 (54.7)	85 (53.8)
1	56 (35.7)	53 (31.2)	46 (33.1)	50 (31.6)
2	9 (5.7)	8 (4.7)	7 (5.0)	5 (3.2)
3	2 (1.3)	5 (2.9)	2 (1.4)	5 (3.2)
4	1 (0.6)	0	1 (0.7)	0
Body Mass Index (kg/m^2)				
mean [SD]	24.8 [5.30]	25.7 [4.37]	24.7 [5.00]	25.9 [4.39]
median [min, max]	24.0 [17.2, 57.1]	24.9 [17.3, 40.6]	24.2 [17.8, 57.1]	24.9 [17.3, 40.6]
Missing	0	1 (0.6)	0	1 (0.6)
CA-125 diagnosis (kU/L)				
mean [SD]	2250 [3710]	1810 [3500]	2220 [3640]	1790 [3530]
median [min, max]	849 [5.0, 25400]	776 [26.0, 31600]	881 [5, 25400]	776 [26, 31600]
Missing	0	4 (2.4)	0	1 (0.6)
CA-125 preoperative (kU/L)				
mean [SD]	426 [1450]	319 [698]	452 [1540]	311 (690)
median [min, max]	92.2 [6.0, 13000]	72.0 [9.0, 5090]	94 [6, 13000]	71 [26, 31600]
Missing	9 (5.7)	6 (3.5)	9 (6.5)	6 (3.8)
CEA pre-operative (µg/L)				
mean [SD]	6.03 [31.2]	3.89 [10.5]	6.53 [33.3]	3.97 (10.8)
median [min, max]	1.75 [0.1, 304]	1.6 [0, 93.0]	1.75 [0.1, 304]	1.6 [0, 93]
Missing	61 (38.9)	65 (38.2)	55 [39.6]	59 (37.3])
Histology				
Sereus adenocarcinoma	149 (94.9)	164 (96.5)	131 (94.2)	152 (96.2)
Mucinous adenocarcinoma	1 (0.6)	1 (0.6)	1 (0.7)	1 (0.6)
Endometroid adenocarcinoma	0	2 (1.2)	0	2 (1.3)
Clearcell adenocarcinoma	5 (3.2)	0	5 (3.6)	0
Mixed epithelial carcinoma	0	1 (0.6)	0	1 (0.6)
Carcinosarcoma	2 (1.3)	2 (1.2)	2 (1.4)	2 (1.3)

Table 1 *(Continued)*

	Intention-to-treat		Per-Protocol	
	Intervention n=157 (%)	Control n=170 (%)	Intervention n=139 (%)	Control n=158 (%)
FIGO stage				
IIIB	11 (7.0)	11 (6.5)	11 (7.9)	10 (6.3)
IIIC	96 (61.1)	109 (64.1)	85 (61.2)	103 (65.2)
IV	50 (31.8)	50 (29.4)	43 (30.9)	45 (28.5)
Primary CRS	20 (12.7)	25 (14.7)	20 (14.4)	22 (13.9)
Interval CRS	137 (87.3)	145 (85.3)	119 (85.6)	136 (86.1)
Suspicion peritoneal carcinomatosis on CT	111 (70.7)	113 (66.5)	96 (69.1)	106 (67.1)
HIPEC-procedure	29 (18.5)	32 (18.8)	29 (20.9)	32 (20.3)

CRS= Cytoreductive surgery, SD=Standard Deviation

In 27 patients (8.3%), a laparotomy was performed but CRS was not performed because of unresectable disease. These 27 patients were not evenly distributed among the two groups, with 18 patients in the intervention group and 9 in the control group. Three others were left out of the analysis because of protocol violation: although they had been randomized to the control group, the PlasmaJet was still used during surgery (Table 1).

Forty-five patients (14.8%) underwent pCRS, and 282 patients (86.2%) iCRS. Twenty-six patients (8%) underwent a diagnostic laparoscopy prior to CRS, in which pCRS was possible in 12 patients. Fourteen patients started with NACT followed by iCRS, being evenly distributed among the groups.

Surgical Outcomes

The intention-to-treat analysis showed that complete CRS was achieved in 75.8% (95% CI 0.685–0.813) of patients in the intervention group versus 67.6% (95% CI 0.603–0.742) in the control group (RD 8.2%, 95% CI –0.021 to 0.181; P = 0.131, adjusted for stratification factors, RD 9.1%, 95% CI –0.01 to 0.20; P = 0.070). Other surgery details are provided in Table 2.

Table 2 Surgical outcomes

	Intention-to-treat			Per-protocol		
	Intervention n=157 (%)	Control n=170 (%)	P-value	Intervention n=139 (%)	Control n=158 (%)	P-value
Surgical outcome						
Complete	119 (75.8)	115 (67.6)	0.001	119 (85.6)	113 (71.5)	0.002
Optimal	12 (7.6)	38 (22.4)		12 (8.6)	38 (24.1)	
Suboptimal	8 (5.1)	8 (4.7)		8 (5.8)	7 (4.4)	
Unresectable	18 (11.5)	9 (5.3)		-	-	
Complete cytoreductive surgery YES	119 (75.8)	115 (67.6)	0.131	119 (85.6)	113 (71.5)	0.005
Start of surgery						
Primary CRS	20 (12.7)	25 (14.7)	0.722	20 (14.4)	22 (13.9)	1
Interval CRS	137 (87.3)	145 (85.3)		119 (85.6)	136 (86.1)	
Operative time (minutes)						
mean [SD]	236 [126]	222 [110]	0.326	254 [121]	230 [109]	0.084
median [min, max]	210 [29, 671]	194 [48, 595]		234 [45, 671]	202 [65, 595]	
Missing	6 (3.8)	4 (2.4)		5 (3.6)	3 (1.9)	
Abdominal drain	35 (22.3)	50 (29.4)	0.259	35 (25.2)	49 (31.0)	0.263
Blood loss (ml)						
mean [SD]	923 [801]	956 [801]	0.712	1020 [803]	995 [805]	0.827
median [min, max]	700 [0, 4300]	845 [0, 6000]		800 [50.0, 4300]	875 [0, 6000]	
Missing	4 (2.5)	1 (0.6)		4 (2.9)	0	
Transfusion during surgery	41 (26.1)	45 (26.5)	0.877	41 (29.5)	45 (28.5)	0.961
Colostomy	9 (5.7)	20 (11.8)	0.092	9 (6.5)	20 (12.7)	0.169
Intensive Care postoperative	34 (21.7)	40 (23.5)	0.785	33 (23.7)	39 (24.7)	0.957
Intensive Care (days)						
mean [SD]	1.9 (1.9)	1.6 (0.9)	0.339	1.9 [1.9]	1.6 [0.9]	0.378
median [min, max]	1.0 [1, 11]	1.0 [1, 5]		1.0 [1, 11]	1.0 [1, 5]	
Hospitalization (days)						
mean [SD]	8.7 [6.5]	7.9 [6.4]	0.221	9.1 [6.7]	8.1 [6.6]	0.175
median [min, max]	6.5 [2, 35]	6.0 [2, 51]		7.0 [2, 35]	6.0 [3, 51]	
missing	3 (1.9)	0		3 (2.2)	0	
Discharge						
Home without nursing care	100 (63.7)	110 (64.7)	0.955	86 (61.9)	101 (63.9)	0.975
Home with nursing care	34 (21.7)	39 (22.9)		31 (22.3)	38 (24.1)	
Nursing home	4 (2.5)	3 (1.8)		3 (2.2)	3 (1.9)	
Rehabilitation center	2 (1.3)	2 (1.2)		2 (1.4)	2 (1.3)	
Hotel providing nursing care	9 (5.7)	12 (7.1)		9 (6.5)	10 (6.3)	
Hospice	1 (0.6)	0		1 (0.7)	0	
Death	0	0		0	0	

CRS=Cytoreductive surgery

In the per-protocol analysis, complete CRS was achieved in 85.6% (95% CI 0.788–0.905) of patients in the intervention group versus 71.5% (95% CI 0.640–0.780) in the control group (RD 14.1%; 95% CI 0.042–0.235; P = 0.005, adjusted for stratification factors, RD 14.0%, 95% CI 0.050–0.231; P = 0.003).

In case of pCRS (n = 42), complete CRS was achieved in 90.0% of patients in the intervention group versus 63.6% in the control group (RD 26.4%, 95% CI –0.032 to 0.506; P = 0.071, adjusted for stratification factors, RD 27.9%, 95% CI 0.057–0.522; P = 0.018). In case of iCRS (n = 255), complete CRS was achieved in 84.9% of patients in the intervention group versus 72.8% in the control group (RD 12.1%, 95% CI 0.014–0.222; P = 0.031, adjusted for stratification factors, RD 12.2%, 95% CI 0.024–0.218; P = 0.015) (Supplementary Table S1).

The median operating time in the intervention group was 33 min longer than in the control group (P = 0.056). As displayed in Supplementary Table S3, on subanalysis, operating time during CRS including HIPEC was longer than in the group without a HIPEC procedure. The median operating time during CRS including HIPEC was 392 min (intervention) versus 372 min (control group). The median operating time during CRS without HIPEC was 219 min (intervention) versus 193 min (control).

There was no significant difference in volume of blood loss and blood transfusion between the groups. The duration of postoperative hospital stay did not statistically significantly differ between the groups.

The number of colostomies was lower in the intervention group (6.5% versus 12.7%) but did not differ significantly (P = 0.169) (Table 2).

In the intervention group, nine women received a colostomy: six a permanent colostomy and three a temporary colostomy. In the control group, 20 women received a stoma: 8 a permanent colostomy, 11 a temporary colostomy, and 1 an ileostomy because the whole colon had to be removed. Twelve months after surgery, none of the women with a temporary colostomy had reversal of their colostomy.

Bowel surgery was performed in about 50% of the patients in both groups. The most common type of resection was rectosigmoid resection (n = 46, 15.7%). The type of surgical procedure (removal of the tumor from the bowel or resection of the organ) did not significantly differ between groups, except for rectal involvement. Rectal involvement was found in 52 of the 139 patients (37.5%) in the intervention group versus 45 of the 158 patients (28.5%) in the control group. To achieve complete CRS,

the rectosigmoid was resected in 8 patients (5.8%) in the intervention group and 15 patients (9.5%) in the control group (P = 0.033) (Supplementary Table S2).

Complications

The surgical complication rate did not significantly differ between the two groups (Table 3). A relaparotomy was performed in eight patients of the intervention group. No relaparotomy was related to the use of the PlasmaJet.

Table 3 Surgical complications within 30-days (per-protocol analysis)

	Intervention group n=139 (%)	Control group n=158 (%)	P-value
Bowel laceration post-operative	2 (1.4)	1 (0.6)	0.597
Bowel obstruction (ileus)			
-Conservative	11 (7.9)	14 (8.9)	1
-Surgery	0	0	
Surgical site infection			
Sepsis	0	4 (2.5)	0.127
Intra-abdominal abscess	1 (0.7)	3 (1.9)	0.627
Urinary tract infection	8 (5.8)	7 (4.4)	0.735
Superficial wound infection	8 (5.7)	4 (2.5)	0.201
Relaparotomy*	8 (5.8)	3 (1.9)	0.143
Medical complication			
Cardiac	6 (4.3)	7 (4.4)	1
Venous thrombo-embolism	1 (0.7)	2 (1.3)	1
Deep venous embolism	1 (0.7)	2 (1.3)	1
Pulmonary embolism	2 (1.4)	3 (1.9)	1
Pulmonary failure	0	0	1
Pneumonia	2 (1.4)	10 (6.3)	0.072
Respiratory insufficiency	7 (5.0)	5 (3.1)	0.551
Renal failure	1 (0.7)	1 (0.6)	1
Ureter laceration	0	0	1
Gastric perforation	1 (0.7)	0	1
Anastomotic leakage	1 (0.7)	1 (0.6)	1
Stroke	1 (0.7)	0	1
Delirium	5 (3.6)	1 (0.6)	0.099
Death (within 30-days)	0	1 (0.6)	0.319

* Indications intervention group: anastomotic leakage (1), suspicion of anastomotic leakage (2), to continue and finish the interval debulking surgery (1), gastric perforation (1), pancreatic leakage (1), intra-abdominal bleeding (1), pelvic abscess (1).
Control group: anastomotic leakage (1) and suspicion of anastomotic leakage (2).

A paralytic ileus developed in 8.5% of all cases, evenly distributed in both groups, and resolved with conservative treatment. Apart from a higher rate of postoperative pneumonia in the control group, there were no significant differences in postoperative complications within 30 days following surgery between the two groups.

The cumulative incidence of mortality within 30 days was 0.003%. One of the patients in the control group died at home the night after discharge from hospital. An autopsy was not performed.

HIPEC

A subset analysis was performed on data of 61 patients with FIGO stage III disease who underwent iCRS combined with HIPEC (Supplementary Table S3). This showed a higher percentage of complete CRS in the intervention group compared with the control group, which was not significant (96.6% compared to 81.2%, P = 0.106).

Peritoneal Carcinomatosis

A subset analysis was performed in a group of patients with disseminated intraabdominal disease, called peritoneal carcinomatosis (Supplementary Table S4). This was defined as ≥ 50 metastatic lesions on either peritoneum, diaphragm, or mesentery. A total of 120 patients had ≥ 50 lesions. The rate of complete CRS of these patients was 72.2% in the intervention group versus 51.5% in the control group (RD 20.7%, 95% CI 0.020–0.373; P = 0.034).

Use of PlasmaJet

In the intervention group, the PlasmaJet was used 104 times during surgery (75%). In 56 of all patients in the intervention group (41%), the gynecological oncologist gave their opinion on whether PlasmaJet was necessary or very useful to achieve complete CRS (Supplementary Table S5). In 12% of the procedures, PlasmaJet was regarded as necessary to achieve complete CRS.

Regarding the learning curve, expertise in using the PlasmaJet did not affect surgical outcome (surgical procedure 1–10 versus > 10) (Supplementary Table S6).

Patient-Reported Outcomes

Patients self-rated their health status before surgery (299 responders, 91.4%), and at 4 weeks (296 responders, 90.5%) and 6 months (262 responders, 80.1%) after surgery. Six months after surgery, patients in the intervention group (n = 120) reported a better health score (EQ-VAS 73.4) than the patients in the control group (n = 142) (EQ-VAS 69.0) (95% CI 0.455–8.350; P = 0.029). Six months after surgery,

patients in the intervention group reported a mean EQ-5D-5L health state of 0.80 compared with 0.76 in the control group (95% CI 0.001–0.092; P = 0.049) (Figure 2).

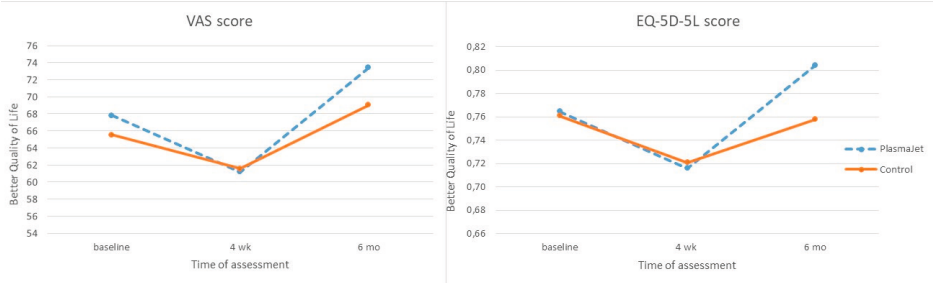

Figure 2 Quality of life

Discussion

In this randomized, multicenter clinical trial on the effectiveness of the PlasmaJet device during CRS for advanced-staged EOC, surgery with adjuvant use of the PlasmaJet was associated with a significantly higher proportion of complete CRS in patients with resectable disease.

This benefit was even stronger in the subset analysis of patients with peritoneal carcinomatosis.

These results are consistent with previous results based on case series of patients with EOC and treated with PlasmaJet(11-16).

A per-protocol analysis was performed in which 27 patients with unresectable disease were excluded, considering that the aim of the study was to examine the effectiveness of the use of the PlasmaJet during CRS.

In 12%, the gynecological oncologists indicated that the PlasmaJet was regarded as “necessary” to achieve complete CRS. In case of many small tumor spots at the small intestines, it is often not possible to remove all tumor lesions without bowel resection. In case of more than two to three anastomosis in often frail, elderly patients or in case of a large small-bowel resection that would lead to a short-bowel syndrome, all those small tumor spots cannot be removed without the help of the PlasmaJet. The same applies to many small tumor spots at the location of the small bowel mesentery. If this has to be removed using electrocoagulation, there is a greater chance of damage to the blood supply of the small intestine than with the use of the PlasmaJet(34). In this study, we see the benefit of the use of the PlasmaJet for surgical outcome

even more strongly in the subset analysis of patients with peritoneal carcinomatosis (Supplementary Table S4).

In 29%, the gynecological oncologists indicated that it was “very useful” to use the PlasmaJet, mainly because the PlasmaJet simplifies the removal of lesions at the location of the diaphragm and peritoneum compared with electrocoagulation. Especially at the location of the diaphragm, the PlasmaJet has added value because it does not cause muscle contractions.

This study is a single-blind RCT. It was impossible to evaluate the completeness of surgery in a double-blind setting, as electrocoagulation and use of the PlasmaJet leave different scars. At the end of surgery, photographs were taken to objectively estimate the result of CRS. Two gynecological oncologists independently reviewed a number of the photographs. The final judgment was hampered by the fact that there was no overview of the complete abdomen and palpation was not feasible. Although this method resulted in a subjective interpretation, the conclusion on surgical outcome seems reliable. Given the high percentage of complete and optimal CRS, a postoperative CT scan would have had no added value, as it does not show small tumor volume.

None of the secondary outcomes differed significantly between the intervention group and the control group. Still, the duration of surgery with the adjuvant use of the PlasmaJet was 32 min longer (P = 0.084). More often, the use of the PlasmaJet made it possible to remove tumor lesions at vulnerable locations. Although this takes more time, a higher percentage of complete CRS can be reached.

Bowel surgery was performed in 50% of the patients in both groups. Patients in the intervention group had more frequent disease involvement of the surface of rectum and rectosigmoid. Disease at these sites was removed more often without the need for resection compared with the control group. Besides a lower proportion of bowel resections in the intervention group, the number of colostomies in the intervention group was lower than in the control group. A colostomy was created when there was no possibility to perform an anastomosis or when such an extensive resection was performed that the surgeon decided that the risk of anastomotic leakage was too high.

Table 2 and Supplementary Table S2 (per-protocol analysis) show that resection of the bowel was performed in 37 of 139 patients (26.6%) in the intervention group,

of whom 9 got a colostomy (6.5%). Of all 37 patients with bowel surgery, 9 got a colostomy (24.3%).

In the control group, bowel resection was performed in 56 of 158 patients (35.4%), of whom 20 got a colostomy (12.7%). Of all 56 patients with bowel surgery, 20 got a colostomy (35.7%). This was not significantly different. Although this study was not powered for differences in bowel surgery, fewer colostomies in the intervention group is an important finding. Further research should demonstrate whether the use of PlasmaJet can avoid bowel surgery and colostomies.

Six months after surgery, patients in the intervention group reported a better health score than the patients in the control group. A possible explanation could be the lower percentage of colostomies in the intervention group (9 versus 20). Another explanation for the more favorable health scores in the intervention group is perhaps the long-term protective effect of PlasmaJet, which results in less tissue damage than coagulation(10,33,34).

Conclusions

In conclusion, in this trial, adjuvant use of the PlasmaJet during CRS for advanced-stage EOC resulted in a higher proportion of complete CRS and is significantly associated with a better patient-reported outcome at 6 months after surgery.
Considering that the surgical outcome has important impact on both PFS and OS,3,6,7 we recommend considering the use of the PlasmaJet during CRS to remove all visible tumor when many small metastases at vulnerable locations are found. Still, survival data need to mature to assess the effect on PFS and OS outcomes.

Supplementary

Table S1 Surgical outcome in case of primary cytoreductive surgery or interval cytoreductive surgery

	Primary CRS			Interval CRS		
	Intervention n=20 (%)	Control n=22 (%)	P-value	Intervention n=119 (%)	Control n=136 (%)	P-value
Complete cytoreduction			0.071			0.029
YES	18 (90.0)	14 (63.6)		101 (84.9)	99 (72.8)	
NO	2 (10.0)	8 (36.4)		18 (15.1)	37 (27.2)	

CRS=Cytoreductive surgery

Table S2 Bowel surgery during cytoreductive surgery

Tumor site	Intervention n=139 (%)	Control n=158 (%)	P-value
Rectum			
No tumor	84 (60.4)	108 (68.4)	0.033
Removal tumor	44 (31.7)	30 (19.0)	
Resection organ	8 (5.8)	15 (9.5)	
Recto-sigmoid			
No tumor	71 (51.1)	85 (53.8)	0.224
Removal tumor	49 (35.3)	42 (26.6)	
Resection organ	18 (12.9)	28 (17.7)	
Cecum			
No tumor	102 (73.4)	109 (69.0)	0.779
Removal tumor	30 (21.6)	39 (24.7)	
Resection organ	6 (4.3)	7 (4.4)	
Appendix			
No tumor	94 (67.6)	119 (75.3)	0.126
Resection organ	44 (31.7)	36 (22.8)	
Ileum			
No tumor	87 (62.6)	108 (68.4)	0.488
Removal tumor	45 (32.4)	41 (25.9)	
Resection organ	5 (3.6)	6 (3.8)	

Table S3 Subset-analysis, cytoreductive surgery with HIPEC procedure

	HIPEC			NON-HIPEC		
	Intervention n=29 (%)	Control n=32 (%)	P-value	Intervention n=110 (%)	Control n=129 (%)	P-value
Surgical outcome			0.106			0.011
Complete	28 (96.6)	26 (81.2)		91 (82.7)	89 (69.0)	
Optimal	1 (3.5)	6 (18.8)		11 (10.0)	32 (24.8)	
Suboptimal	0	0		8 (7.3)	8 (6.2)	
Operative time (mean, minutes) [SD]	392 [135]	372 [94]	0.505	219 [87]	193 [78]	0.019
Blood loss (mean, ml) [SD]	1255 [866]	1332 [737]	0.713	950 [776]	903 [797]	0.646
Hospitalization (days) [SD]	10.5 [4.3]	11.0 [8.2]	0.780	8.7 [7.1]	7.3 [5.9]	0.085
Intensive care (days) [SD]	1.5 [1.1]	1.7 [0.8]	0.736	2.2 [2.4]	1.5 [1.0]	0.294
Colostomy	2 (6.9)	8 (25.0)	0.196	7 (6.4)	12 (9.5)	0.508

Table S4 Sub-analysis, surgical outcome in case of peritoneal carcinomatosis (≥50 lesions)

	≥50 lesions			<50 lesions		
	Intervention n=54 (%)	Control n=66 (%)	P-value	Intervention n=85 (%)	Control n=95 (%)	P-value
Complete cytoreduction			0.034			0.135
YES	39 (72.2)	34 (51.5)		80 (94.1)	82 (86.3)	
NO	15 (27.8)	32 (48.5)		5 (5.9)	13 (13.7)	

Table S5 Surgeons opinion regarding the added value of using the PlasmaJet during surgery per procedure

	n=139 (%)
PlasmaJet has not been used	32 (23)
PlasmaJet used, complete cytoreductive surgery was not possible	13 (9)
PlasmaJet used, but without PlasmaJet complete cytoreductive surgery would have been possible	35 (25)
PlasmaJet used, very useful to achieve complete cytoreductive surgery	40 (29)
PlasmaJet used, necessary to achieve complete cytoreductive surgery	16 (12)
Missing	3 (2)

Table S6 Surgical outcome related to experience in using the PlasmaJet

	Experience PlasmaJet 1-10 procedures			Experience PlasmaJet 11 or more procedures		
	Intervention n=52 (%)	Control n=59 (%)	P-value	Intervention n=87 (%)	Control n=102 (%)	P-value
Complete cytoreduction			0.256			0.013
YES	45 (86.5)	45 (76.3)		74 (85.1)	70 (68.6)	
NO	7 (13.5)	14 (23.7)		13 (14.9)	32 (31.4)	

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5

The effects of neutral argon plasma versus electrocoagulation on tissue in advanced-stage ovarian cancer: a case series

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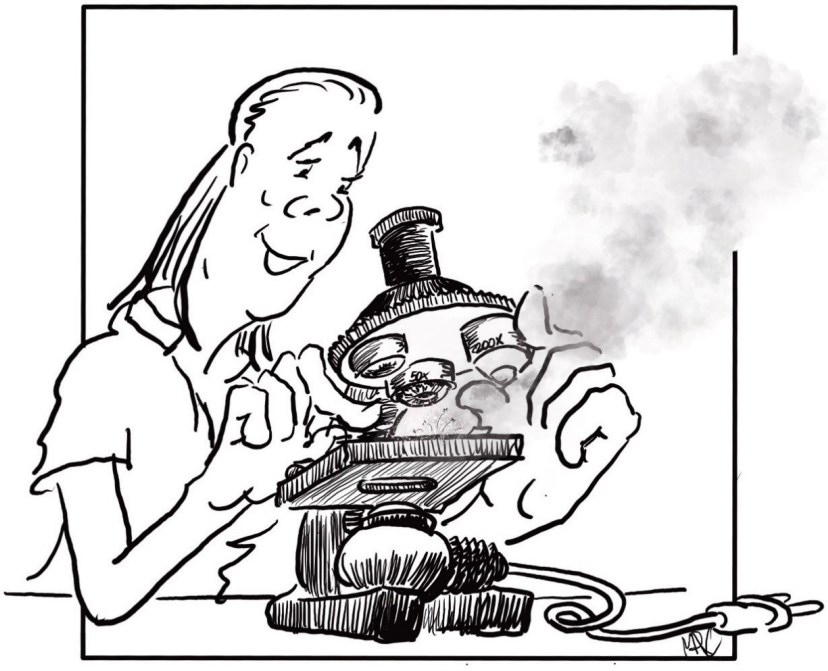

Abstract

Background

The aim of surgery for advanced-stage ovarian cancer is a complete cytoreduction, because this is the most important independent prognostic factor for prolonged survival. Yet this can be difficult to achieve when there are micrometastases on the intestinal mesentery or intestines. The PlasmaJet device is an instrument to remove these micrometastases, but little is known about the depth of damage in human tissue compared to electrocoagulation devices.

Methods

A prospective study was performed for the ex-vivo comparison of the histological depth of thermal damage of neutral argon plasma (PlasmaJet®) and electrocoagulation devices, in a series of 106 histological slides of 17 advanced-stage ovarian cancer patients. Depending on the tissue types resected during complete cytoreductive surgery, samples were collected from reproductive organs (uterus, ovaries), intestines (ileum, colon, rectum) and omentum, intestinal mesentery and peritoneum.

Results

Average thermal damage depth was 0.15 mm (range 0.03–0.60 mm) after use of neutral argon plasma and 0.33 mm (range 0.08–1.80 mm) after use of electrocoagulation ($p < 0.001$). Greater disruption of the tissue surface was often observed after electrocoagulation.

Conclusions

Our case series suggests that the use of neutral argon plasma during cytoreductive surgery produces significantly less thermal damage than electrocoagulation treatment. It is therefore considered a thermally safe alternative, aiding in the achievement of cytoreductive surgery.

Introduction

Ovarian cancer is the fifth leading cause of cancer death in women, with over 14.000 cases yearly in the United States(1). Surgery to remove all visible tumor in combination with chemotherapy is the most common therapy for advanced-stage ovarian cancer (ASOC). The aim of surgery for ASOC is complete cytoreductive surgery (CRS) to no visible disease, as it leads to longer progression free survival (PFS) and overall survival (OS)(2,3). However, it can be challenging to achieve complete CRS in patients with micrometastases on the intestinal mesentery, intestines or if the tumor reaches great vessels. These patients often need radical surgery, including upper abdominal surgery and bowel resection which increases the risk of complications(4,5).

The use of Neutral Argon Plasma (PlasmaJet®, Plasma Surgical, Roswell, GA, USA) is a relatively new device for CRS in ASOC management which may contribute to tissue ablation near to vulnerably locations to improve the percentage complete CRS(6). The PlasmaJet emits a high-energy jet of argon plasma for direct tissue effects and is able to cut or vaporize small tumor foci(7). During this process light, heat and kinetic energy are emitted.

When introducing new instruments, potential hazards of thermal damage like spontaneous bowel perforations and strictures, must be included in the risk analysis. Studies and reviews have indicated that the device is safe and effective for use in the surgical treatment of benign and malignant gynecological conditions with regard to postoperative complications(8-11). The current insight in histological outcome of thermal tissue effects is based on case reports and two studies involving in-vivo porcine models(6,7). Studies quantified thermal tissue effects, and one described occurrence of postsurgical adhesions(7). Only two studies directly compared the PlasmaJet to a second thermal coagulator and presented comparative data on thermal effects(8,9).

The aim of our study was to assess the depth of the thermal tissue effects of the PlasmaJet with those of the ERBE electrocoagulation device. A series of 106 histological slides are described in which the depth of thermal damage was measured in various healthy tissues from reproductive organs (uterus, ovaries), intestines (ileum, colon, rectum) and omentum, intestinal mesentery and peritoneum.

Materials and methods

The patients whose tissue is examined in this case series were included in the PlaComOv-study. The PlaComOv-study is a multicenter randomized controlled trial and compares the rates of complete CRS of patients with ASOC operated with the standard use of electrocoagulation (control group) with patients operated with the adjuvant use of PlasmaJet (intervention group)(12).

The study is carried out in accordance with the standards outlined in the Declaration of Helsinki. Ethics committee approval was granted. All patients were given both verbal and written information by their gynecologist before surgery. Informed consent to allow use of the data for analysis was obtained.

The patients selected for this case series underwent interval CRS because of ASOC between 2018 and 2020. All patients diagnosed with a high grade serous epithelial adenocarcinoma received neoadjuvant chemotherapy consisted of three cycles of intravenously carboplatin (area under the curve of 6 mg per milliliter per minute) and paclitaxel (175 mg per square meter of body-surface area) with a duration of three weeks for each cycle(13). All cases were randomized to the intervention group.

Surgical procedures

Patients randomized to the intervention group (adjuvant use of PlasmaJet during surgery) could be included in this study. Surgery was performed in the Erasmus MC so that the use of the PlasmaJet and ERBE coagulation proceeded in the same way. According to standard cytoreductive surgery for ovarian cancer, hysterectomy, adnexectomy and omentectomy was performed and if required a bowel resection was done in order to remove all visible tumour. Histological examination of the bowel could only be performed if there was visible tumor requiring bowel resection. Because of the research question to compare the depth of tissue infiltration, we only used tissue in which no visible vital tumor was seen. The tissue of interest was processed with the PlasmaJet and with the ERBE electrocoagulation device before removal and was marked with sutures to enable identification for histological research.

The PlasmaJet device was used at power setting 10, for durations ranging between 3 and 4 s. The distance to tissue ranged between 5 and 10 mm. The thermal effects were compared to those of an ERBE electrosurgical unit (VIO 300 D/S, Tübingen, DE), used at a power of 45 W, effect 4–5 for 1–2 s.

Histological analysis

All gross specimens for histological analysis were handled according to the local protocol and transported to the laboratory within one hour after surgery. Blocks were taken from the areas marked with sutures during the operation as having been treated with PlasmaJet or electrocoagulation. The depth of thermal damage was measured on haematoxylin and eosin stained slides from the formalin-fixed, paraffin-embedded tissue blocks. To ensure uniform assessment, measurements were performed by a single blinded experienced gynecopathologist. Thermal damage was quantified as the largest orthogonal distance from the surface to the first layer of unchanged tissue. All slides were reviewed and the measurements checked by two of the authors (GN, PE). For each observed zone three different histological regions were studied in order to average our measurement.

Statistical analysis

For statistical comparison, tissue types were grouped into reproductive organs (uterus, ovaries), intestines (ileum, colon, rectum) and omentum, intestinal mesentery and peritoneum. The results obtained with the PlasmaJet and ERBE electrocoagulation devices were compared in boxplots and evaluated with a Kruskal Wallis, and with Mann–Whitney U tests, using a significance level (α) of 0.05.

Results

A total of 106 histological regions were studied to assess destruction and thermal damage in tissue samples of 17 women who underwent interval CRS (Table 1). In the intestinal mesentery the measurement was not possible after electrocoagulation, as tissues were destroyed totally by using electrocoagulation for one second.

Table 1 Mean (range) depth of thermal damage after use of PlasmaJet and electrocoagulation devices, sorted by tissue type. N = number of samples.

Tissue type		PlasmaJet, damage (mm)	n	Electrocoagulation, damage (mm)	n
Reproduction organs	Uterus	0.08 (0.03-0.20)	8	0.36 (0.15-0.90)	6
	Ovaries	0.43	1	1.09 (0.38-1.80)	2
Intestines	Ileum	0.11 (0.05-0.20)	6	0.44 (0.20-0.70)	5
	Colon	0.13 (0.07-0.20)	8	0.19 (0.10-0.30)	7
	Rectum	0.17 (0.15-0.18)	2	0.09 (0.08-0.10)	2
Omentum		0.15 (0.05-0.30)	16	0.23 (0.08-0.55)	12
Intestinal mesentery		0.50	1	-	-
Peritoneum		0.17 (0.03-0.60)	15	0.35 (0.10-1.00)	13

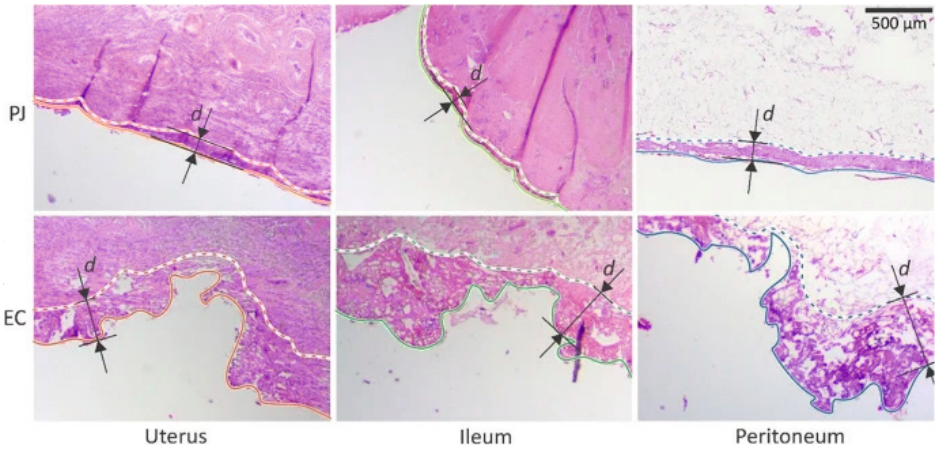

Figure 1 Exemplar histological images of thermal damage after use of the PlasmaJet (PJ) or ERBE electrocoagulation (EC). Depth of thermal damage (d) is indicated by arrows.

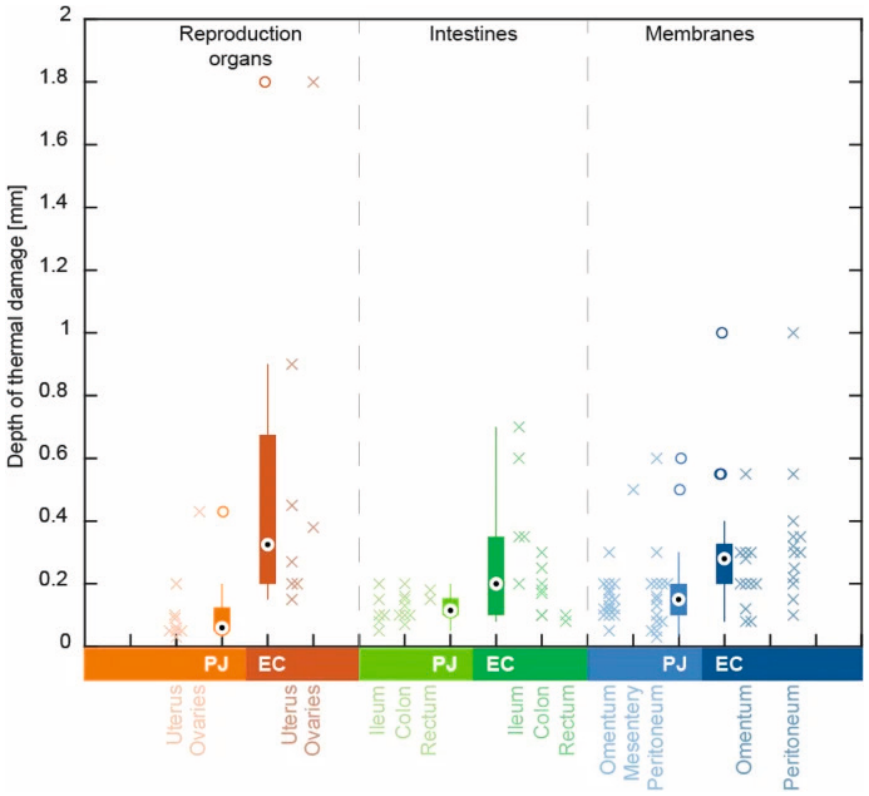

Figure 2 Comparison of depth of thermal damage after use of PlasmaJet (PJ) or ERBE electrocoagulation (EC) devices, for various tissue types, grouped in reproductive organs, intestines and membranes

The data are summarized in boxplots in Figure 2. The mean of the depth of thermal damage after use of PlasmaJet was 0.15 mm (range 0.03–0.60 mm). After use of an electrocoagulation device the mean depth of thermal damage was 0.33 mm (range 0.08–1.80 mm). After clustering, the mean ± standard deviation of depth of thermal damage was 0.12 ± 0.13 mm (PJ) and 0.54 ± 0.56 mm (EC) in reproductive organs, 0.13 ± 0.05 mm (PJ) and 0.26 ± 0.19 mm (EC) in intestines, and 0.17 ± 0.12 mm (PJ) and 0.29 ± 0.19 mm (EC) in the group of omentum, intestinal mesentery and peritoneum. These groups were compared using the Kruskal Wallis test ($p < 0.001$), and the Mann-Whitney U test. These showed that thermal damage was consistently lower after PlasmaJet than after electrocoagulation, i.e. for reproductive organs ($p = 0.003$), intestines ($p = 0.013$) and in the group of omentum, intestinal mesentery and peritoneum ($p < 0.001$).

Discussion

In our case series of 106 histological slides of 17 advanced-stage ovarian cancer patients, mean thermal damage depth was significantly lower when tissue was treated with Neutral Argon Plasma, 0.15 mm (range 0.03–0.60 mm) than with electrocoagulation, 0.33 mm (range 0.08–1.80 mm, $p < 0.001$). Tissue treated with the PlasmaJet often showed a thin regular affected layer along the surface. In contrast, tissue treated with electrocoagulation, the tissue was rugged and disrupted (Figure 1).

Our data correlates well with the findings of Roman et al.(14) (mean: 0.145 mm), Sonoda et al.(11) (mean: 0.13 mm), and the shorter exposure times tested by Madhuri et al.(15) (mean 0.8 mm). Deb et al. report damage values in the 0.5–0.6 mm range(8). However, it is unclear whether they used comparable histological definitions for the depth of thermal effects.

Neutral Argon Plasma enables ablation with a highly controlled tissue effect, allowing treatment of sites previously considered untreatable, e.g. metastases on the intestinal mesentery and serosa of intestines(16). With short application times, energy dissipation to deeper structures can be avoided(8). The PlasmaJet device also eliminates some of the risks of electrosurgical devices because no electrical current passes through the tissue. As the PlasmaJet tip is continuously cooled by circulating water, the risk of inadvertent burns is minimized.

The histological slides in these case series confirm minimal tissue damage from the PlasmaJet on the gut. In particular for the gut, little data on the thermal infiltration depth are publicly available. Until now, it was not possible to remove tumor on the intestines and leave the intestines in situ due to the depth of infiltration of electrocoagulation devices. These measurements show that the infiltration damage from using the PlasmaJet is less than after using electrocoagulation.

A possible explanation for the variations infiltration damage could be related to the difference between the devices. The PlasmaJet emits a high-energy beam of argon plasma for direct tissue effects. Electrocoagulation requires the tissue to be heated rapidly by a required current density achieved by short electrical arcs (sparks) that occur at peak voltages from around 200 V between the electrode and the tissue. The absence of sparks and uncontrolled bursts of energy entering the tissue might explain the reduced deep tissue injury when using the PlasmaJet.

In clinical practice, the effect of less tissue infiltration by using the PlasmaJet may also be reflected in the quality of life. Patients who had surgery using the PlasmaJet showed a higher quality of life six months after the procedure(17). A possible explanation could be that less tissue damage results in a different process of tissue repair and regeneration (inflammation, proliferation by fibrogenesis and angiogenesis and remodeling). In contrast, when there is more tissue damage, it will proceed differently. The surgeon must be aware of the effect of the instrument used, especially when extensive peritoneal stripping is involved in the surgery.

However, in other tissue types (e.g. intestinal mesentery) thermal effects may remain unclear, as sample sizes relied on the clinical necessity of tissue removal. As a result, clustering of data was required. It should also be noted that knowledge about tissue damage is particularly relevant for those tissues that remain in the patient. In this study, the tissues of uterus, adnexa and omentum were included for comparison with data in literature.

A difficulty of our study was the assessment of the depth of histological tissue damage after electrocoagulation treatment, due to disrupted and irregular tissue surfaces. In our analysis, we measured damage as the thickness of the layer of altered tissue (Figure 1). An alternative approach could be to include the depth of disruption, vaporization and charring formed by electrocoagulation, when measuring the depth of effect. This approach would significantly increase the difference seen after using PlasmaJet and electrocoagulation devices. The importance of including exemplary histological images to illustrate the approach used should be emphasized.

The PlasmaJet device was used at power setting 10, for durations ranging between 3 and 4 s. For the PlasmaJet device, depth of vaporization was found to increase with exposure time(11,15). Possibly, vaporization depth is also weakly related to the power setting(11). Lateral thermal spread is likely to be dependent on exposure time, but not on power setting(9,11,15). However, in an in-vitro setting, Deb et al.(8) found no effect of exposure time or power setting on lateral spread or width of the affected zone.

In general, our results correspond to other studies and have demonstrated that the depth of thermal damage of the use of Neutral Argon Plasma remains superficial. Situations where the use of PlasmaJet could clearly be beneficial include the treatment of tissue that would otherwise remain untreated and the treatment of micrometastasis thereby avoiding bowel resection.

Conclusions

Based on our case studies we conclude that a Neutral Argon Plasma device produces significantly less thermal damage than an electrocoagulation device. The PlasmaJet is therefore a thermally safe device that can be used to aid during cytoreductive surgery in patients with advanced-stage ovarian cancer. We recommend subsequent research to evaluate whether microscopic deposits of vital tumor tissue remain on relevant organs such as bowel after vaporization.

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6

Cost Study of the PlasmaJet Surgical Device Versus Conventional Cytoreductive Surgery in Patients With Advanced-Stage Ovarian Cancer

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Abstract

Background

Adjuvant use of Neutral Argon Plasma (PlasmaJet Surgical Device) during cytoreductive surgery (CRS) for advanced-stage epithelial ovarian cancer improves surgical outcomes. The aim of this study is to examine the costs of adjuvant use of the PlasmaJet during surgery compared with conventional CRS in advanced-stage epithelial ovarian cancer.

Methods

The patients were randomly assigned to surgery with or without the PlasmaJet. Analysis of the intra- and extramural health care costs was performed. Costs were divided into three categories: costs of the diagnostic phase (T1), inpatient care up to discharge including costs of surgery (T2), and outpatient care including chemotherapy until 6 weeks after the last cycle of chemotherapy (T3).

Results

Overall, 327 patients underwent CRS (surgery with PlasmaJet: n = 157; conventional surgery: n = 170). The mean total health costs were significantly higher for CRS with adjuvant use of PlasmaJet compared with conventional CRS (€19,414 v €18,165, P = 0.017). Costs are divided into costs of the diagnostic phase (€2,034 v €1,974, P = 0.890), costs of inpatient care (€10,956 v €9,556, P = 0.003), and costs of outpatient care (€6,417 v €6,628, P = 0.147).

Conclusions

Mean total health care costs of the use of PlasmaJet in CRS were significantly higher than those for conventional CRS. This difference is fully explained by the additional surgery costs of the use of PlasmaJet. However, surgery with the use of the PlasmaJet leads to a significantly higher percentage of complete CRS and a halving of stomas. A cost-effectiveness analysis will be performed once survival data are available.

Introduction

Ovarian cancer is the eighth most occurring cancer in women, with, in 2020, almost 314,000 new cases and more than 207,000 deaths worldwide(1). Conventional treatment for advanced-stage epithelial ovarian cancer (EOC) consists of a combination of chemotherapy and cytoreductive surgery (CRS). Completeness of CRS is the most important independent prognostic factor for survival(2-5). In recent years, various additional diagnostics and treatment options have been added to the standard policy. One of the additional options during surgery is the possibility to use Neutral Argon Plasma (PlasmaJet Surgical Device of Plasma Surgical, Inc, Roswell, GA), which increases the number of complete cytoreduction(6). Even previous studies showed that the adjuvant use of the PlasmaJet during CRS for advanced-stage EOC resulted in a significantly higher percentage of complete CRS compared with conventional treatment without the use of the PlasmaJet(7-10).

The costs of treatment of advanced-stage ovarian cancer can range from €20,000 for only surgery up to €200,000 and even higher for treatment with both surgery and chemotherapy(11). A study that was performed by an insurance company in the United States estimated the mean cost of care during the first year after diagnosis of ovarian cancer at approximately €55,000(12). Koole et al.(13) performed a cost-effectiveness study in the Netherlands, which focused on the use of hyperthermic intraperitoneal chemotherapy (HIPEC) during surgery for advanced-stage EOC, reporting costs of approximately €70,000, which comprises all costs from diagnosis to recurrent disease. Costs of surgery with the PlasmaJet, however, have not been studied before.

The health care system in the Netherlands is managed by the government and supplemented by nonprofit health insurance companies. All residents are entitled to have a basic insurance package regardless of their income. In addition, employees and the self-employed contribute to the Dutch health care costs depending on their company and income. The Dutch health insurance entitles to free medical treatment in the Netherlands. Care for ovarian cancer including CRS and chemotherapy is fully reimbursed. The hospitals negotiate individually with the insurers about the rates of their health care products for each year. These health care products consist of a diagnosis-treatment combination. Agreements by the Dutch Healthcare Authority, the rate table for health care products, and other health care products lead to a declaration system and determine the reimbursed costs for specialist medical care in the Netherlands.

When a new product is added to a treatment, the costs are for the hospital unless otherwise has been negotiated with the Dutch Healthcare Authority. With the current knowledge that surgery with the use of the PlasmaJet improves surgical outcomes and hypothetically leads to longer survival, it is important to determine the increase of operative costs.

The aim of this study is to examine the total medical costs of adjuvant use of the PlasmaJet compared with conventional CRS in patients with advanced-stage EOC.

Methods

Patient Data

A cost analysis was performed in a population of women with advanced-stage EOC, who were included in the PlaComOv study. This multicenter randomized controlled trial in the Netherlands investigated whether the use of the PlasmaJet Surgical Device compared with conventional CRS increased the rate of a successful cytoreduction in women with advanced-stage EOC(14).

The PlaComOv study was approved by the Medical Ethical Committee of the Erasmus Medical Center, the Netherlands, METC 2017-500, NL62035.078.17, on November 20, 2017. The study was performed according to the standards outlined in the Declaration of Helsinki. All patients provided written informed consent.

Patients were randomly assigned into two groups: CRS with the use of the PlasmaJet (intervention) or conventional CRS (control). All surgeons (gyneco-oncologists) had experience in performing CRS, and all were trained in the use of the PlasmaJet device in 11 hospitals. In other two hospitals, patients could only be randomly assigned for this study, but no surgery was performed for ovarian cancer.

Inclusion and Exclusion Criteria

Patients with advanced-stage EOC, fallopian tube or peritoneal carcinoma International Federation of Gynecology and Obstetrics (FIGO) stage IIIB-IV who underwent both CRS and chemotherapy, were eligible for inclusion in this cost analysis. The surgical procedure was either primary CRS or interval CRS. Actual inclusion in the study was decided on if advanced-stage EOC (FIGO stage IIIB-IV) was diagnosed before or during surgery. According to the intention-to-treat principle, patients with proven FIGO stage IIIB-IV EOC who underwent surgery with the intention to perform CRS, but in whom surgery was discontinued because of unresectable disease, remained in the study.

Patients with a nonepithelial, borderline ovarian tumor and ovarian metastasis of another primary tumor were excluded.

Diagnostics and Treatment

Diagnostic tests for EOC consisted of physical examination and transvaginal ultrasonography. Furthermore, laboratory research including serum measurement of cancer antigen-125 (CA-125) and carcino-embryonic antigen was achieved, a computed tomography (CT) scan of thorax/abdomen was performed, and, if possible, histologic biopsy was taken.

Patients who met radiologic criteria for nonresectable disease or were diagnosed with FIGO stage IV disease were scheduled for interval CRS and received three courses of neoadjuvant chemotherapy(15,16). In the case of radiologic tumor regression or stable disease on a CT scan after three cycles of chemotherapy, patients were eligible for interval CRS.

Diagnostic laparoscopy was performed if the feasibility of surgery was unclear.

The standard chemotherapy regimen consisted of six cycles of carboplatin and paclitaxel with a duration of 3 weeks for each cycle(5). In primary CRS, all six cycles were given after surgery. In interval CRS, three cycles were given before surgery and three cycles after surgery. HIPEC was introduced in the Netherlands in 2019(17). From 2019, all patients age ≤ 75 years with FIGO stage III EOC who underwent interval CRS were eligible to receive an additional HIPEC procedure after complete or optimal CRS.

Cost Calculations

Medical costs from the first appointment at the outpatient clinic up to 6 weeks after the end of the last cycle of chemotherapy as first-line treatment were calculated by multiplying volumes of health care use with the corresponding unit prices. A comparison was made between costs of CRS using the PlasmaJet surgical device versus conventional surgery without the PlasmaJet. Total medical costs consisted of three categories: costs of the diagnostic phase (T1), inpatient care to discharge including costs of surgery (T2), and outpatient care including chemotherapy (T3). A detailed overview of the cost categories is given in Supplementary Table S1.

Total costs of surgery using the PlasmaJet and conventional CRS without the PlasmaJet were calculated on the basis of detailed measurement of labor investments, equipment, housing, and overhead. Costs per hour of labor by health

care suppliers were estimated on the basis of salary schemes of hospitals. Equipment costs included costs of depreciation and maintenance costs of the PlasmaJet device and were based on an economic life expectancy of 10 years. The cost of a PlasmaJet handpiece is only included if the PlasmaJet has been used during CRS.

Total medical costs per patient consisted of total inpatient and outpatient health care costs. Inpatient care included total costs of surgery using either the PlasmaJet or conventional surgery and costs of care up to hospital discharge, including costs related to a colostomy, diagnostic activities (eg, CT scan and laparoscopy), and postoperative care in the hospital or rehospitalization within 30 days after surgery. Costs of outpatient care included home care and costs of chemotherapy during day treatment. Costs were analyzed from a health care perspective, meaning that societal costs, such as productivity costs, were not taken into account.

Extramural health care use was retrieved from case report forms. Unit prices of the most relevant cost items were determined by following the microcosting method, in which a detailed inventory and measurement of all resources used are made(18). For instance, duration of surgery was measured to determine costs of health personnel spend on the intervention. Costs of stay at a hospital were determined using the cost manual(19). A distinction in cost price was made for general and university hospitals. We chose not to invest much time and effort in exploring costs that were unlikely to make any difference to the study results because they were low in price and volume(20). In the Netherlands, a detailed fee-for-service registration system is used for the reimbursement of medical interventions and diagnostic procedures. Costs were calculated in the European currency (Euro) and corrected for inflation for the year 2020.

Sensitivity Analysis

Since 2019, HIPEC treatment became common practice in patients with FIGO stage III ovarian cancer age ≤ 75 years who undergo interval CRS. Therefore, we performed a sensitivity analysis adding costs of HIPEC to this group, even when HIPEC was not actually applied, to provide a real estimation of current costs of patients with ovarian cancer.

Statistical Analysis

Analyses were performed using an intention-to-treat approach to express the real clinical situation of CRS. Patient characteristics on a categorical level were compared between the intervention and control group using the $\chi 2$ test. Continuous variables were compared using the Mann-Whitney U test. A P value of $< .05$ was considered statistically significant.

The total expenditures were reported as means with standard deviation for the diagnostic phase, inpatient costs, and outpatient costs. Differences in costs between the intervention and control group were compared using the Mann-Whitney U test since costs were not normally distributed. No correction for multiplicity was applied since analyses were of exploratory nature. All analyses were performed using SPSS version 25.

Results

Patients

From February 2018 through September 2020, a total of 383 patients were randomly assigned, 190 to the intervention group and 193 to the control group. All randomly assigned patients had suspected or proven advanced-stage EOC (Figure 1). Overall, 56 patients had to be excluded because they did not meet the inclusion criteria. The clinical characteristics of the 327 included patients in the intention-to-treat analyses are presented in Table 1 and Supplementary Table S2.

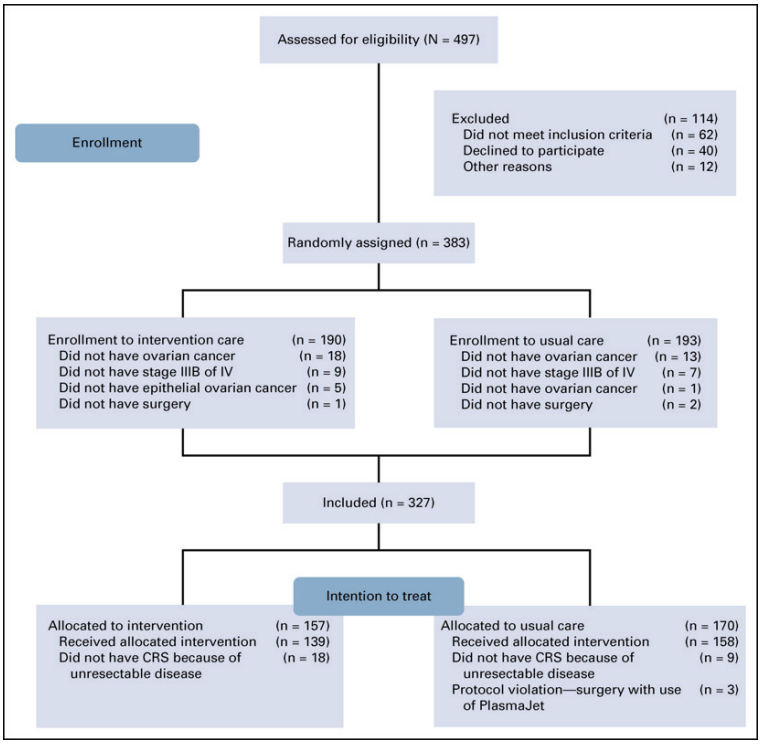

Figure 1 CONSORT flow diagram. CRS= cytoreductive surgery.

Table 1 Patients characteristics

Patient characteristics	CRS with PlasmaJet n=157 (%)	Conventional CRS n=170 (%)
Age (years)		
mean [SD]	66.1 [9.6]	65.1 [11.2]
median [min, max]	67.6 [28.9, 81.3]	65.9 [20.3, 86.1]
WHO-performance status		
0	82 (52.2)	90 (52.9)
1	56 (35.7)	53 (31.2)
2	9 (5.7)	8 (4.7)
3	2 (1.3)	5 (2.9)
4	1 (0.6)	0
FIGO stage		
IIIB	11 (7.0)	11 (6.5)
IIIC	96 (61.1)	109 (64.1)
IV	50 (31.8)	50 (29.4)
Primary CRS	20 (12.7)	25 (14.7)
Interval CRS	137 (87.3)	145 (85.3)
HIPEC-procedure	29 (18.5)	32 (18.8)

CRS= Cytoreductive surgery, FIGO= Federation of Gynecology and Obstetrics, HIPEC= hyperthermic intraperitoneal chemotherapy, SD=Standard Deviation

Forty-five patients (14.8%) underwent primary CRS, and 282 patients (86.2%) interval CRS. A diagnostic laparoscopy was performed in 26 patients (8%) before CRS, in which primary CRS was possible in 12 patients and 14 patients underwent interval CRS.

Costs

Considering costs of diagnostics (T1), it was found that costs were comparable for the intervention and the control group. Costs of preoperative consultation comprised more than half of total costs of diagnostics, for both the intervention and control group (€995 in both groups).

Costs of surgery (part of T2) were found to be significantly higher for the intervention group (€4,020 v €2,951, P < .001; Table 2). The higher costs were mainly driven by the cost of the PlasmaJet itself, of which 11 were available in all participating hospitals in the study. Other cost components of surgery were not significantly different between the intervention and control group.

Table 2 Detailed costs of CRS using the PlasmaJet or conventional CRS without the PlasmaJet in euro's (2020)

Cost category	CRS with PlasmaJet Mean [95% CI]	Conventional CRS Mean [95% CI]	P-value
Personnel	1161 [1036, 1268]	1130 [1021, 1239]	0.886
Equipment[a]	908 [873, 944]	-	<0.001*
Housing/overhead	1951 [1783, 2118]	1821 [1685, 1958]	0.314
Total costs	**4020 [3726, 4314]**	**2951 [2716, 3186]**	**<0.001***

[a]Equipment consists of costs of the PlasmaJet availability and the use of a PlasmaJet handpiece. CRS= Cytoreductive surgery, CI=confidence interval.

Total costs of inpatient care (T2), including surgery, were found to be higher for the intervention group compared with the control group (€10,956 v €9,556, P = .003; Table 3).

Table 3 Average health care use and costs per patient in 2020 € for CRS using the PlasmaJet or conventional CRS without the PlasmaJet

Categories`	**CRS with PlasmaJet (n=157)**		**Conventional CRS (n=170)**		**P-value**
	Health care use mean [95% CI]	*Costs*	*Health care use mean [95% CI]*	*Costs*	
Diagnostics					
Pre-operative vulnerability analysis	0.3 [0.2, 0.4]	123 [74, 171]	0.3 [0.2, 0.4]	144 [92, 199]	0.865
Pre-operative intake[a]	3.0 [3.0, 3.0]	995 [995, 995]	3.0 [3.0, 3.0]	995 [995, 995]	-
Diagnostic laparoscopy	0.1 [0.1, 0.2]	386 [197, 590]	0.1 [0.0, 0.1]	249 [115, 390]	0.396
Diagnostic laparotomy	0.0 [0, 0]	58 [-15, 94]	0.0 [0.0, 0.1]	107 [22, 194]	0.372
X-thorax	0.0 [0, 0]	1 [0, 2]	0.0 [0, 0]	1 [1, 2]	0.936
CT scan	1.1 [1.0, 1.1]	172 [164, 177]	1.1 [1.1, 1.2]	179 [171, 188]	0.206
MRI	0.0 [0.0, 0.1]	9 [2, 17]	0.0 [0.0, 0.1]	10 [3, 18]	0.891
Echo	0.7 [0.6, 0.8]	63 [56, 69]	0.6 [0.6, 0.7]	59 [52, 66]	0.372
Pre-operative diagnostic scan other[b]	2.1 [2.0, 2.3]	228 [178, 282]	2.3 [2.1, 2.4]	230 [180, 281]	0.985
Total diagnostics	-	2,034 [1825, 2255]	-	1,974 [1802, 2152]	0.890
Inpatient care					
Surgery	-	4,020 [3726, 4314]	-	2,951 [2716, 3186]	<0.001*
Hospital days PACU	0.2 [0.1, 0.3]	259 [159, 370]	0.2 [0.1, 0.3]	263 [169, 363]	0.814
Hospital days ICU	0.4 [0.2, 0.6]	917 [506, 1335]	0.4 [0.3, 0.5]	821 [563, 1099]	0.721
Hospital days ward	7.4 [6.6, 8.3]	4,058 [3547, 4550]	7.1 [6.2, 8.0]	3,958 [3364, 4594]	0.410
HIPEC	0.2 [0.1, 0.2]	905 [589, 1193]	0.2 [0.1, 0.2]	922 [639, 1227]	
In-hospital scans	0.6 [0.5, 0.8]	58 [45, 73]	0.5 [0.4, 0.6]	52 [38, 66]	0.537
Re-laparotomy	0.1 [0, 0.1]	154 [50, 265]	0.0 [0, 0]	53 [-7, 115]	0.096

Table 3 *(Continued)*

Categories`	**CRS with PlasmaJet (n=157)**		**Conventional CRS (n=170)**		**P-value**
	Health care use mean [95% CI]	*Costs*	*Health care use mean [95% CI]*	*Costs*	
Re-hospitalization days ward	1.0 [0.4, 1.7]	548 [185, 919]	0.9 [-0.1, 1.9]	486 [-14, 998]	0.409
Re-hospitalization scans	0.3 [0.2, 0.4]	34 [22, 46]	0.2 [0.1, 0.3]	25 [12, 38]	0.026*
Total inpatient care	-	10,956 [9817, 12176]	-	9,556 [8401, 10712]	0.003*
Outpatient care					
Stoma	0.1 [0, 0.1]	179 [66, 300]	0.1 [0.1, 0.2]	368 [217, 527]	0.056
Chemotherapy	6.0 [6.0, 6.0]	6,150 [6150, 6150]	6.0 [6.0, 6.0]	6,150 [6150, 6150]	-
Homecare hours	1.4 [0.9, 1.9]	87 [56, 122]	1.8 [1.0, 2.5]	110 [64, 160]	0.769
Total outpatient care	-	6,417 [6292, 6552]	-	6,628 [6461, 6801]	0.147
TOTAL COSTS	-	**19,414 [18161, 20668]**	-	**18,165 [16920, 19409]**	**0.017***

[a]Includes: consults with gynecologist, medical-oncologist and anesthesiologist
[b]Includes: CA-125, CEA, PET-CT, histological puncture (ultrasound-guided), histological puncture (CT-guided), cytological puncture (ultrasound-guided), colonoscopy, CR-BOZ, cytological ascites, EBUS, echo biopsy, gastroscopy, histology, pleural puncture, trans esophageal ultrasound, pathological tests.
CRS= Cytoreductive surgery, CI=confidence interval.

Costs of outpatient care (T3) were, like costs of diagnostics, not significantly different between the intervention and control group (€6,417 v €6.628, P = .147). Outpatient costs consisted mainly of costs of chemotherapy.

Comparing total costs of care between patients who underwent surgery with the PlasmaJet and patients who underwent conservative CRS, it was found that costs of care when the PlasmaJet was available during surgery were significantly higher than costs of care when conventional CRS was applied (€19,414 v €18,165, P = .017).

Sensitivity Analysis

Sensitivity analysis with the inclusion of costs of the HIPEC procedure in patients who met the previously mentioned criteria resulted in total costs of €21,674 for the intervention group versus €20,247 for the control group (P = .019; Table 4). The number of additional patients who would receive HIPEC in the hypothetical situation did not differ significantly between the PlasmaJet and the standard CRS group because the age and FIGO stage were equally distributed between the two groups.

Table 4 Number of patients with HIPEC treatments and total costs (2020 €) for sensitivity analysis

HIPEC[a]	CRS with PlasmaJet	Conventional CRS	P-value
n(%)	50 (32%)	49 (29%)	0.552
Mean total cost including additional HIPEC [95% CI]	21,674 [20338, 23009]	20,247 [18885, 21609]	0.019*

NOTE: HIPEC treatment was added to the total costs for all patients aged <76 years with stage III ovarian cancer who underwent interval CRS and who had not had HIPEC in their actual treatment.
[a]Includes both patients who actually received HIPEC treatment and patients who would receive HIPEC treatment with current treatment protocols.
CRS= Cytoreductive surgery, HIPEC= hyperthermic intraperitoneal chemotherapy, CI=confidence interval.

Discussion

This study provided a detailed overview of the total medical costs of CRS with the use of the PlasmaJet compared with CRS without the use of the PlasmaJet in patients with advanced-stage EOC.

The total medical costs in the intervention group were significantly higher than the costs in the control group (€19,414 v €18,165; P = .017). This significant difference is fully explained by the additional surgery costs of the use of PlasmaJet. This includes the one-time purchase of the PlasmaJet, the annual costs for maintenance, and the variable costs of the handpiece that are charged per patient. Costs of the diagnostic phase (T1), inpatient care up to discharge including costs of surgery minus costs of the PlasmaJet (part of T2), and outpatient care including chemotherapy until 6 weeks after the last cycle of chemotherapy (T3) did not differ.

All data in this article were derived from the PlaComOv study. In this study, the patients were randomly assigned to the intervention group (CRS with PlasmaJet) or the control group (conventional CRS without PlasmaJet). If the use of the PlasmaJet is no longer limited to patients randomly assigned to the intervention arm, we suspect that surgeons are likely to use the PlasmaJet in more patients. Therefore, fixed costs of using the PlasmaJet can then be divided among more patients. This will reduce the additional costs per person of surgery using the PlasmaJet.

Whether this difference is also financially significant will depend on a number of things. First, this depends on the number of CRS performed in a hospital. If hospitals can perform other procedures with the PlasmaJet, this will also reduce the fixed costs per procedure and probably, the handpieces can be ordered for an decreased price. Finally, if the hospital bears the extra costs per procedure with the PlasmaJet in addition to the savings from fewer colostomies, the difference will not be financially

significant. Most importantly, cost-effectiveness will be calculated in the future to establish the amount of gained disability-adjusted life year.

At the moment, there have been no negotiations with the Dutch Healthcare Authority. This is why the costs of the PlasmaJet will not be reimbursed by health care insurance. In the short term, the cost of this new clinical intervention will be paid by the departments of Gynecologic Oncology, whereas the savings on colostomy care will benefit insurers.

From 2019, halfway through the PlaComOv study, HIPEC was introduced in the Netherlands for patients age ≤ 75 years with FIGO stage III disease undergoing interval CRS. Because random assignment was stratified for the use of HIPEC, the percentage of HIPEC was equally divided between the two groups. Nowadays, all patients age ≤ 75 years with FIGO stage III EOC undergoing interval CRS would be eligible for the HIPEC procedure. The sensitivity analysis showed that the costs in both groups will be higher than the calculated costs from this study(13,17).

Despite performing a diagnostic laparoscopy in 26 of 327 patients, the number of total futile laparotomies in this study was still 27 (8%). Prevention of performing useless laparotomies could therefore potentially further reduce costs without negatively affecting the quality of life. However, identification of patients eligible for CRS remains a challenge. A Dutch randomized controlled trial previously studied the cost-effectiveness of laparoscopy as a diagnostic tool before primary CRS in ovarian cancer, but found no difference in direct medical costs over a 6-month time horizon although it reduced the number of useless laparotomies(21). An alternative strategy could be the radiologic selection of patients eligible for CRS. Better predictors in both CT scans and MRIs for complete or optimal CRS would reduce costs. To date, no effective imaging strategies are available that offer effective prevention against futile laparotomies.

Gynecologist-oncologists and other surgeons should be trained to use the PlasmaJet. One day of training is required to use the PlasmaJet. The costs of this training during our study were paid from the subsidy awarded to the PlaComOv study and have not been included in this cost calculation. It seems obvious that the one-off costs of a training will be part of the purchase of the PlasmaJet.

A limitation of this study is that the indirect costs because of productivity losses and informal caregiver costs are not included in the analysis. The median age at diagnosis was 67 years and was equally distributed among both groups. The percentage of

women under age 67 years who were employed at diagnosis and experienced loss of productivity is unknown.

To determine whether the costs will turn out differently in the long term, a study should be performed with a longer follow-up period. In that study, costs of poly(adenosine diphosphate-ribose) polymerase inhibitors, which are currently prescribed as maintenance therapy at the end of primary treatment, should be added(22).

Costs for molecular diagnostics on the tumor tissue and for genetic research should also be included in a study with a longer follow-up period(23,24). These tests on tumor tissue could not be claimed from the insurer at the time of our study. Because the costs would be the same for both groups, this does not influence the outcome of this study.

Finally, in a long-term analysis, the difference in progression-free and overall survival between the two study groups will become clear.

Conclusions

In conclusion, the mean total health care costs of using PlasmaJet during CRS (€19,414) were significantly higher than those for conventional CRS (€18,165) in advanced-stage EOC. This study showed a difference in costs between the two groups of €1,249, which only consists of the additional costs of the PlasmaJet and was not due to an increased demand for care because of complications or a longer hospitalization. In authors' opinion, the benefits of implementing the PlasmaJet outweigh the increase of these costs. The PlasmaJet is promising with a greater chance of complete CRS.

Supplementary

Table S1 Overview of cost prices in 2020 € (19)

Item	Unit	Price
Pre-operative consult (for example geriatrician, cardiologist etc)	Consult	€461
Consult gynecologist	Consult	€461
Consult oncologist	Consult	€461
Pre-operative consult anesthesiologist	Consult	€74
Laboratory tests (diagnostic)	Test	€12
CA-125	Test	€13
CEA	Test	€8
Ultrasound	Scan	€92
CT scan thorax-abdomen	Scan	€159
MRI-scan abdomen	Scan	€244
PET-CT	Scan	€1138
X-ray thorax	Scan	€65
X-ray abdomen	Scan	€46
Trans esophageal ultrasound	Scan	€865
Cystogram	Scan	€183
Electrocardiogram	Scan	€384
Pyelogram	Scan	€169
Histological puncture – CT	Puncture	€654
Histological puncture – ultrasound	Puncture	€136
Cytological ascites/ Abcess puncture – ultrasound	Puncture	€206
Cytological pleural puncture -ultrasound	Puncture	€289
Colonoscopy	Scopy	€267
Gastroscopy	Scopy	€263
Ultrasound-bronchoscopy	Scopy	€783
Pathological examination	Test	€129
Laparoscopy	Treatment	€3028
Laparotomy	Treatment	€3028
Relaparotomy	Treatment	€3028
HIPEC	Treatment	€4900
Packed cells	Pack	€238
Platelets	Pack	€574
Fresh Frozen Plasma	Pack	€205
Stay at post-anesthesia care unit	Day	€1313
Stay at intensive care unit	Day	€2216
Stay at hospital ward (academic)	Day	€706

Table S1 *(Continued)*

Item	Unit	Price
Stay at hospital ward (general)	Day	€487
Chemotherapy per cycle	Treatment	€1025
Parenteral nutrition	Day	€289
Enteral nutrition (fixed)	Stay	€67
Enteral nutrition (variable)	Day	€25

Table S2 Outcome of inpatient care (for cost calculation T2) of patients who underwent CRS with PlasmaJet compared to conventional CRS without PlasmaJet

Categories of inpatient care	CRS with PlasmaJet n=157 (%)	Conventional CRS n=170 (%)	P-value
Operative time (minutes)			
mean [SD]	236 [126]	222 [110]	0.326
median [min, max]	210 [29, 671]	194 [48, 595]	
Missing	6 (3.8)	4 (2.4)	
Transfusion during surgery	41 (26.1)	45 (26.5)	0.877
Colostomy	9 (5.7)	20 (11.8)	0.092
Intensive Care postoperative	34 (21.7)	40 (23.5)	0.785
Intensive Care (days)			
mean [SD]	1.9 (1.9)	1.6 (0.9)	0.339
median [min, max]	1.0 [1, 11]	1.0 [1, 5]	
Hospitalization (days)			
mean [SD]	8.7 [6.5]	7.9 [6.4]	0.221
median [min, max]	6.5 [2, 35]	6.0 [2, 51]	
Missing	3 (1.9)	0	
Discharge			
Home without nursing care	100 (63.7)	110 (64.7)	0.955
Home with nursing care	34 (21.7)	39 (22.9)	
Nursing home	4 (2.5)	3 (1.8)	
Rehabilitation center	2 (1.3)	2 (1.2)	
Hotel providing nursing care	9 (5.7)	12 (7.1)	
Hospice	1 (0.6)	0	
Death	0	1 (0.6)	

CRS = Cytoreductive surgery, SD=standard deviation

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7

Cytoreductive Surgery with the PlasmaJet improved Quality-of-Life for Advanced Stage Ovarian Cancer patients

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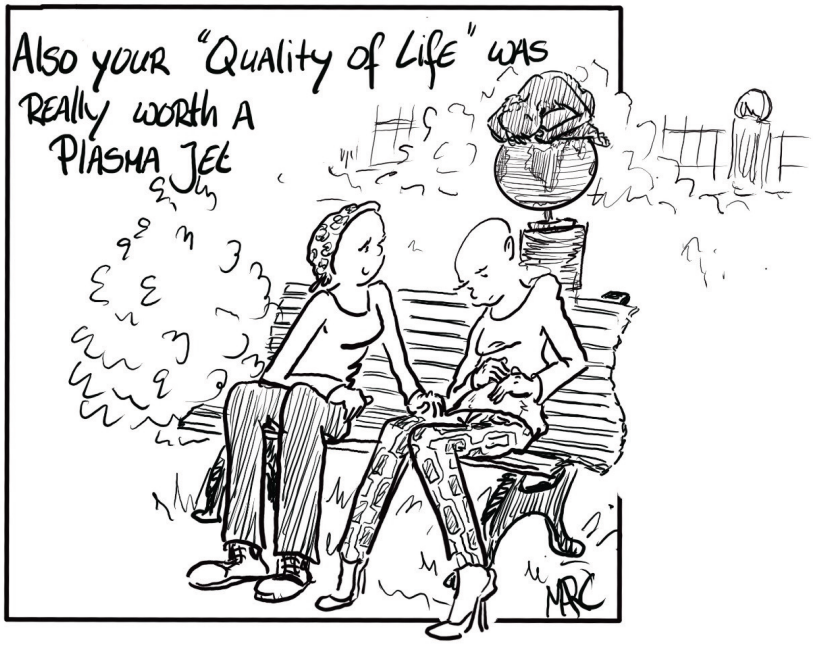
Submitted



Abstract

Background

Knowledge on Quality-of-Life (QoL) after cytoreductive surgery (CRS) is important to counsel patients with advanced-stage epithelial ovarian cancer (ASEOC) prior to surgery. The aim of this study was to determine whether the use of the PlasmaJet Surgical device during CRS has an effect on the QoL.

Methods

Data included in this prospective observational study were derived from the PlaComOv-study, in which patients with ASEOC were randomly assigned to have CRS with or without adjuvant use of the PlasmaJet. QoL was measured before surgery and one, six, 12 and 24 months after surgery with three questionnaires: the EORTC QLQ-C30, QLQ-OV28 and EQ-5D-5L.

Results

Between 2018 and 2020, 326 patients were enrolled into the trial. The overall response rate was high with the lowest response rate at 24 months of 77%. At 6 months, the QoL was higher in the intervention group (95%CI 0.009; 0.081, p=0.045). At 12 months, the QoL was higher in the intervention group with fewer symptoms of fatigue, appetite loss and diarrhoea (95%CI 0.6;10,0, p=0.027), similarly patients in the intervention group reported a better body image (95%CI -14.2; -3.0, p=0.003) and a higher score on the visual analogue scale (95%CI 1.99;11.15, p=0.005). At 24 months post-operatively, no further difference was found between the two groups except for pain (95%CI -12.9;-0.8, p=0.027) and body image (95%CI -13.808;-0.733, p=0.029). A higher QoL in the intervention group was partially explained by the mediator 'surgery outcome'.

Conclusions

This study demonstrated knowledge of patients' QoL until two years after CRS to fully inform patients preoperatively. Even after adjustment for the mediator of surgical outcome, a higher QoL was seen in patients who had surgery with the use of the PlasmaJet device.

Introduction

While cytoreductive surgery (CRS) is considered an effective method for treating patients with advanced stage epithelial ovarian cancer (ASEOC), CRS is a complex treatment which may have a considerable impact on patient's quality of life (QoL) after surgery(1-3). Patients are selected for the procedure using quantitative prognostic indicators, such as imaging findings, CA-125 level, response on neoadjuvant chemotherapy and comorbidity(4-11). To fully inform patients before CRS in the process of shared decision making, knowledge on the effect of QoL after CRS is required(12-14). In particular, QoL after surgery may be a decisive factor in choosing to perform CRS with or without a particular device, such as the PlasmaJet, which has been found to increase the percentage of complete CRS without an increase of complications(15).

Studies related to QoL in women who had undergone CRS with the addition of bevacizumab or hyperthermic intraperitoneal chemotherapy (HIPEC) showed that the surgery did not adversely impact QoL(16-18). Also, no clinical difference in QoL was found between patients who underwent primary CRS and patients who underwent interval CRS(19). Furthermore, a recent surgery-related study found no difference in QoL between patients who had undergone surgery of lower complexity and those who had undergone extensive surgery(1-3).

All studies had a follow-up between 12 and 16 months postoperatively.

While these studies indicated that CRS as such did not affect patients' QoL, so far, no study has been published which compared the QoL of patients who underwent a conventional CRS and a CRS with the use the PlasmaJet Surgical device(20). The PlasmaJet emits a high-energy jet of argon plasma for direct tissue effects and is able to cut or vaporize small tumor foci(21).

The aim of this study was to determine whether the use of the PlasmaJet Surgical device during CRS leads to a higher QoL than surgery without the PlasmaJet. The primary research question was whether a difference in QoL was seen in women undergoing CRS with or without the PlasmaJet Surgical device at 12 and 24 months postoperatively. Secondary outcomes were the effects of the mediators 'surgical outcome' and 'having of a colostomy' on QoL.

Methods

Study population

Data included in this study were derived from the PlaComOv study, a single blinded multicenter randomized controlled trial(22). In thirteen cancer centers in the Netherlands, patients with International Federation of Gynecology and Obstetrics (FIGO) stage IIIB-IV ovarian cancer were included in the study who were suitable to receive standard treatment, which consists of CRS and chemotherapy(23). Those patients were randomized to CRS with or to CRS without the adjuvant use the of PlasmaJet device(15). The PlaComOv study evaluated the effectiveness of the PlasmaJet surgical device in the treatment of ASEOC. The study was approved by the Medical Ethics Review Board of the Erasmus University Medical Center Rotterdam, the Netherlands (NL62035.078.17).

Quality of life assessment

QoL was assessed preoperatively and one, six, 12 and 24 months postoperatively(22). Patients had the choice to receive the questionnaires digitally or by post. If the questionnaires were not fully completed after 1 week, an automatic reminder was sent. The online questionnaires were sent by GEMS Tracker (GEneric Medical Survey Tracker), a software package for the distribution of questionnaires and forms during clinical research and quality registrations in healthcare. GEMS Tracker is developed at the Erasmus MC, The Netherlands in collaboration with several partners. The software is published under an open source licence (new BSD).

Quality of life was measured by three validated questionnaires: the QLQ-C30 and QLQ-OV28 of the European Organization for Research and Treatment of Cancer (EORTC) and the EuroQol five-dimensional questionnaire (EQ-5D-5L)(24-26).

The first questionnaire, the QLQ-C30 (version 3), is a 30-item questionnaire used for patients with cancer(24). This questionnaire consists of a global health scale, functioning scales (physical, role, emotional, cognitive and social) and a symptom scale (fatigue, nausea/vomiting, pain, dyspnoea, insomnia, appetite loss, constipation and diarrhoea. The QLQ-C30 scores were transformed to continuous scales from 0 to 100. Higher scores on the global health scale and the functioning scales indicate a higher level of functioning and a better QoL.

The second questionnaire, the QLQ-OV28, is a 28-item questionnaire designed as a supplement of the QLQ-C30 questionnaire for patients with ovarian cancer(25). The QLQ-OV28 consists of seven symptom scales associated with ovarian cancer:

abdominal/gastrointestinal symptoms, peripheral neuropathy, hormonal, body image, attitude to disease/treatment, chemotherapy side-effects and sexuality.

Higher scores on the symptom scales of both QLQ-C30 and QLQ-OV28 indicate a higher level of symptoms or problems. A change in score of five to ten points on the QLC-C30 and QLQ-OV28 global scale is considered small, a change of ten to 20 points is considered moderate and a change of more than 20 points is considered large(27,28).

The third questionnaire, the EQ-5D-5L, is a descriptive measurement of health and consists of five dimensions covering mobility, self-care, usual activities, pain/discomfort and anxiety/depression(26). Each dimension has five response levels. These response levels expresses the severity of each dimension: no problem, slight problems, moderate problems, severe problems and extreme problems. The total score for all dimensions is converted in a health state profile. The EQ-5D-5L questionnaire also includes a visual analogue scale (VAS), which provides a quantitative measure (0 to 100 scale) of the patients' perceptions of their overall health on the day of assessment. The endpoints are labelled between 'The worst health you can imagine'(0) and 'The best health you can imagine'(100).

Statistical analysis

All analyses were performed following the intention-to-treat principle. Patient characteristics and response rates at each follow-up were evaluated using descriptive statistics. Descriptive statistics were also used to graphically present the mean QoL scores over time stratified for the intervention.

For the primary study objective, a generalized estimation equations (GEE) analysis with an independent correlation matrix was performed to determine the effect of CRS with the PlasmaJet compared to the control group on QoL one, six, 12 and 24 months postoperative. Time was added as categorical variable presented by dummy variables. Interaction terms between intervention and time were added as fixed covariates to assess the difference in QoL per time point. The analysis was adjusted for baseline scores by adding the time-independent baseline QoL variables. Women who were no longer alive at the time of analysis were removed from the analysis. For non-responders, data were imputed.

For the secondary outcomes a mediation analysis was performed to investigate if surgical outcome and colostomy mediated the effect of CRS with the PlasmaJet on QoL (Figure S1). The direct effect of the PlasmaJet on QoL (c') was analyzed by adding

the mediators as independent fixed variables to the existing GEE model (Figure S1). The effect of the mediators on the QoL (b) at 12 and 24 months was analyzed with a new GEE model with an independent correlation matrix.

Descriptive analyses were performed in IBM SPSS Statistics 28, all other analyses were performed with Rstudio version 3. P-values $p<0.05$ were considered statistically significant.

Results

From February 2018 through September 2020, a total of 326 patients were included in the PlaComOv-study. Table 1 presents the baseline characteristics, which were equally divided between the two groups. The mean age was 65.7 (SD10.4) years. The mean body mass index was 25.3 (SD4.9) kg/m2. FIGO stage III disease was present in 226 patients (69%), FIGO stage IV disease was present in 100 patients (31%). World Health Organization (WHO) performance status was predominantly 0-1 (86%). A primary CRS was performed in 13% of the patients and an interval CRS in 87%. A HIPEC procedure was applied in 19% of the patients.

Table 1 Patient characteristics

	Total n=326 (%)	PlasmaJet n=157 (%)	Control n=169 (%)
Age (years)			
Mean [SD]	65.7 [10.4]	66.1 [9.6]	65.3[11.2]
Median [min, max]	66.7 [20.4, 86.1]	67.5 [28.9, 81.3]	66.2 [20.4, 86.1]
BMI			
Mean [SD]	25.3 [4.9]	24.8 [5.3]	25.7 [4.4]
Median [min, max]	24.6 [17.2, 57.1]	24.0 [17.2, 57.1]	24.9 [17.3, 40.7]
FIGO stage			
IIIB	22 (6.7)	11 (7.0)	11 (6.5)
IIIC	204 (62.6)	96 (61.1)	108 (63.9)
IV	100 (30.7)	50 (31.8)	50 (29.6)
WHO-performance status			
0	171 (52.8)	82 (52.2)	89 (53.3)
1	109 (33.6)	56 (35.7)	53 (31.7)
2	17 (5.2)	9 (5.7)	8 (4.8)
3	7 (2.2)	2 (1.3)	5 (3.0)
4	1 (0.3)	1 (0.6)	0 (0.0)

Table 1 *(Continued)*

	Total n=326 (%)	PlasmaJet n=157 (%)	Control n=169 (%)
Surgery			
Primary CRS	44 (13.5)	20 (12.7)	24 (14.2)
Interval CRS	282 (86.5)	137 (87.3)	145 (85.8)
HIPEC	61 (18.7)	29 (18.5)	32 (18.9)
Surgical outcomes			
Complete CRS	233 (71.5)	119 (75.8)	114 (67.5)
Optimal CRS	50 (15.3)	12 (7.6)	38 (22.5)
Suboptimal CRS	16 (4.9)	8 (5.1)	8 (4.7)
Unresectable	27 (8.3)	18 (11.5)	9 (5.3)
Colostomy	32 (9.8)	11 (7.0)	21 (12.4)

Of all patients, 157 patients (48%) were randomised into the intervention group and 169 patients (52%) into the control group (Figure 1). Complete CRS was reached in 76% of the patients in the intervention group and in 68% of the control group (p=0.096). A colostomy was performed in 11 patients (7%) of the intervention group and in 21 patients (12%) of the control group (p=0.100).

Response rate

About half of the patients (52%) completed the questionnaire digitally and all other respondents preferred to receive and submit their questionnaire on paper. Figure 1 presents the response rates for completing the three questionnaires. The overall response rate was high, with the lowest percentage of 172 respondents (77%) of all patients surviving 24 months postoperatively. Of all patients who did not respond, 17%, 41% and 56% had a recurrence at respectively six, 12 and 24 months postoperatively.

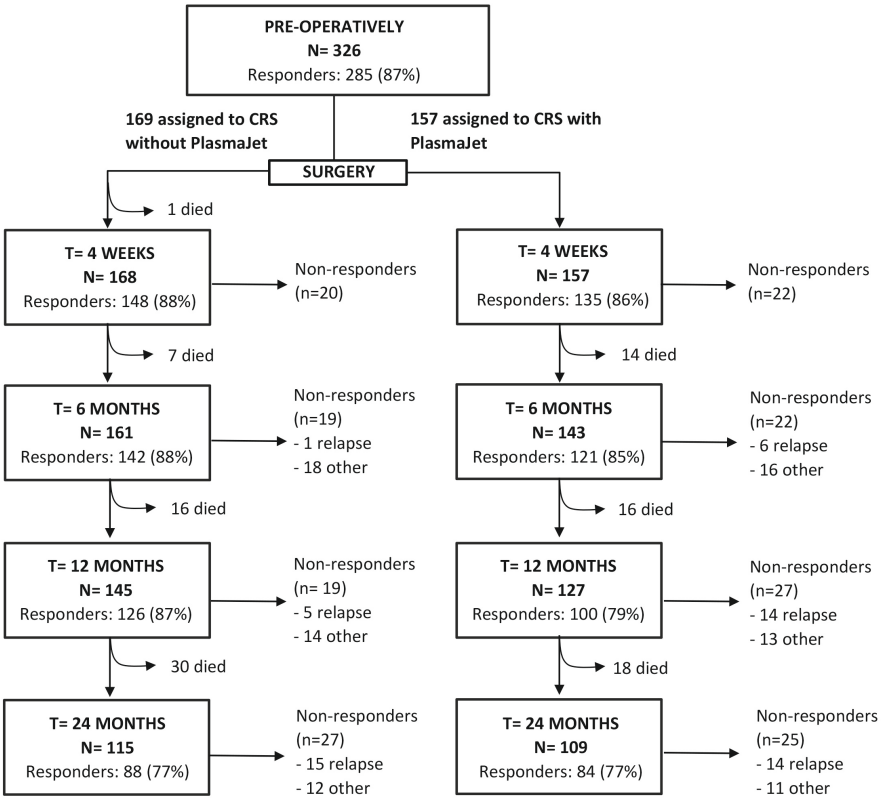


Figure 1 Flow chart of inclusions: responders and non-responders

EORTC QLQ-C30

At 12 months postoperatively, the mean score for global health in the EORTC QLQ-C30 in the intervention group was 77.9 and in the control group 71.0 (Figure 2). Adjustment for the baseline score, in both groups revealed a difference of 5.3 points (95%CI 0.60;10.01, p=0.027). At 24 months postoperatively, the mean score for global health in the intervention group was 75.1 and in the control group 68.0, with a difference of 4.8 points (p=0.083) (Table 2).

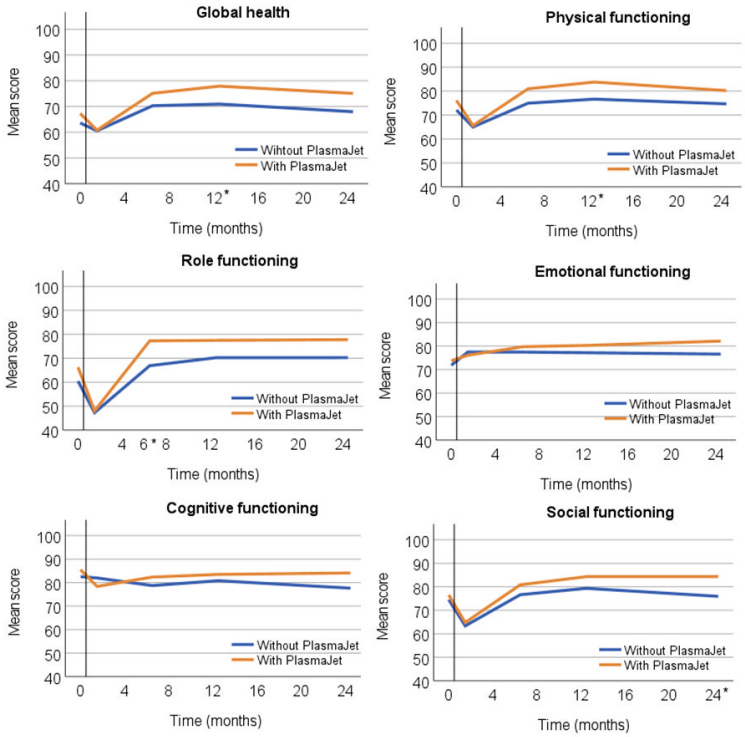


Figure 2 Outcome EORTC QLQ-C30 for every domain at five different time-points (preoperative and 1, 6, 12 and 24 months postoperative) for patients who had surgery with or without the PlasmaJet. * P < 0.05.

Table 2 Mean scores of the EORTC QLQ-C30, QLQ-OV28 and EQ-5D-5L 12 and 24 months after surgery for patients who underwent surgery with or without the PlasmaJet

	Mean score		Total effect	P-value	Direct effect	P-value
	PlasmaJet	Control	(95%CI)		(95%CI)	
EORTC QLQ-C30						
Global health						
12 months	77.9	71.0	5.3 (0.6;10.0)	0.027*	4.4 (-0.3;9.0)	0.064
24 months	75.1	68.0	4.8 (-0.6;10.3)	0.083	3.9 (-1.5;9.3)	0.160
EORTC QLQ-OV28						
Abdominal						
12 months	18.5	22.5	-3.9 (-8.2;0.4)	0.074	-3.6 (-7.9;0.7)	0.099
24 months	21.6	23.9	-1.1 (-5.7;3.5)	0.631	-0.8 (-5.5;3.9)	0.728
Peripheral neuropathy						
12 months	23.6	31.4	-5.9 (-11.7;-0.2)	0.043*	-5.3 (-11.0;0.5)	0.076
24 months	25.4	31.0	-3.0 (-9.1;3.0)	0.328	-2.3 (-8.5;3.9)	0.462

Table 2 *(Continued)*

	Mean score		Total effect	P-value	Direct effect	P-value
	PlasmaJet	Control	(95%CI)		(95%CI)	
Chemo side effects						
12 months	14.4	18.3	-3.6 (-6.9;-0.3)	0.032*	-3.3 (-6.7;-0.01)	0.049*
24 months	16.4	19.2	-2.4 (-6.7;2.0)	0.292	-2.081 (-6.5;2.4)	0.359
Hormonal						
12 months	16.3	22.9	-5.5 (-11.3;0.2)	0.060	-5.6 (-11.4;0.2)	0.058
24 months	18.3	27.6	-4.6 (-11.8;2.7)	0.215	-4.6 (-11.9;2.6)	0.211
Body image						
12 months	16.7	26.4	-8.6 (-14.2;-3.0)	0.003*	-8.4 (-14.1;-2.7)	0.004*
24 months	19.1	39.8	-7.3 (-13.8;-0.7)	0.029*	-7.1 (-13.6;-0.5)	0.036*
Attitude to disease						
12 months	47.2	50.8	-1.4 (-7.5;4.6)	0.645	-0.5 (-6.5;5.5)	0.863
24 months	44.0	54.3	-5.7 (-12.2;0.9)	0.091	-4.7 (-11.3;1.8)	0.158
Sexuality						
12 months	87.4	87.1	-0.7 (-5.0;3.7)	0.759	-0.5 (-4.8;3.9)	0.830
24 months	88.6	87.2	-0.8 (-5.2;3.6)	0.717	-0.6 (-4.9;3.8)	0.791
EQ-5D-5L						
Health status						
12 months	0.80	0.76	0.021 (-0.029;0.071)	0.402	0.012 (-0.037;0.061)	0.439
24 months	0.80	0.77	0.011 (-0.043;0.066)	0.678	0.002 (-0.052;0.056)	0.890
VAS						
12 months	75.8	68.3	6.6 (2.0;11.2)	0.005*	5.8(1.2;10.4)	0.014*
24 months	72.0	68.9	2.4 (-3.0;7.8)	0.385	1.563 (-3.8;6.9)	0.569

Total effect: score corrected for preoperative score. Direct effect: score corrected for preoperative score and effect of the mediators 'Surgical outcome' and 'Colostomy'. * = p<0.05.

Postoperatively, all functioning scales in the EORTC QLQ-C30 showed higher scores in the intervention group than in the control group, which were significantly higher for physical functioning (4.7 points at 12 months, 95%CI 0,12;9,18, p=0.044), role functioning (7.8 points at 6 months, 95%CI 1.6;13.9, p=0.014) and social functioning (7.7 points at 24 months, 95%CI 0.5;14.8, p=0.048) (Table S1). During all the time points, equal QoL scores were found between the groups with regard to cognitive and emotional functioning (Figure 2).

Postoperatively, the symptom scales in the EORTC QLQ-C30 showed fewer symptoms in the intervention group with regard to symptoms of fatigue (-8.0 points at 12 months, 95%CI -13.2;-2.9, p=0.002), appetite loss (-6.1 points, 95%CI-11.4;-0.8, p=0.024) and diarrhoea (-5.2 points, 95%CI -10.0;-0.5, p=0.031). At 24 months postoperatively,

the EORTC QLQ-C30 showed fewer symptoms of pain in the intervention group (-6.8 points, 95%CI -12.9;-0.8, p=0.027) (Table S1).

EORTC QLQ-OV28

At 12 and 24 months postoperatively, the symptom scores in the EORTC QLQ-OV28 showed a better score in the intervention group for body image than in the control group (-8.6 points, 95%CI -14.3;-3.0, p=0.003) (Table 2). The differences for abdominal symptoms and attitude to disease were -3.9 points (p=0.074) and -5,7 points (p=0.091) respectively (Figure 3).

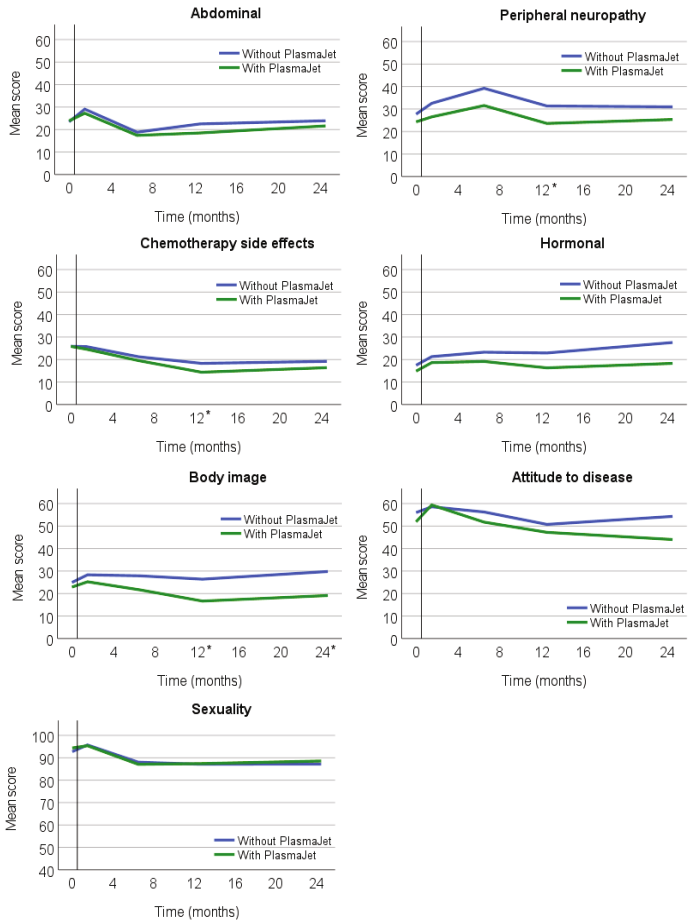


Figure 3 Outcome EORTC QLQ-OV28 for every domain at five different time-points for patients who had surgery with or without the PlasmaJet. * P < 0.05.

EQ-5D-5L

At six months postoperatively, the EQ health status demonstrated a higher score for the intervention group (0.80 vs 0.76, 95%CI0.009;0.081, p=0.045) (Table 2). At 12 months postoperatively, the EQ VAS showed a higher score for the intervention group (75.8 versus 68.3 points (95%CI 2.0;11.2, p=0.005, Figure S2).

Secondary outcomes

A mediation analysis was performed to investigate if surgical outcome and colostomy mediated the effect on QoL (Figure S1). Table S2 shows the effect of surgical outcome on QoL. At 12 months postoperatively, the mean score for global health in the EORTC QLQ-C30 was 77.1 in the group with a complete CRS and 62.8 in the group without a complete CRS (95%CI 5.6;18.1, p=0.002). At 24 months postoperatively, no difference in the mean score for global health was seen.

Table S3 shows the effect of a colostomy on QoL. No differences in the mean scores for global health in the EORTC QLQ-C30 were seen at 12 or 24 months postoperatively.

Table 2 and Table S1 demonstrate the total and the direct effect of the PlasmaJet on QoL. Because the total effect on QoL is partially explained by the surgical outcome, the direct effect of the PlasmaJet on QoL is lower. However, the direct effect of the PlasmaJet on the QoL remained statistically significant on role functioning, fatigue, diarrhoea, body image and the VAS score.

Discussion

The aim of this study was to determine whether the use of the PlasmaJet Surgical device during CRS leads to a higher QoL than conventional surgery with electrocoagulation only. In our single blinded randomized PlaComOv-study, 326 patients with advanced stage ovarian cancer were requested to complete QoL-questionnaires until two years after CRS.

The response rate in this study was high, and even at 24 months postoperatively, 172 of 224 (77%) patients completed the questionnaires. A possible explanation for the high response rate was that patients had the choice to receive the questionnaires digitally or by post and a reminder was sent if the patients did not complete their questionnaires within one week.

In general, four weeks after CRS a lower QoL was seen for all patients compared to QoL before surgery (Figure 2-4). During follow-up, however, patients indicated a QoL that was equal or higher than at diagnosis. This finding was in line with previous studies(1-3).

At six months postoperatively, the EQ-health status was significantly higher in the intervention group. At 12 months postoperatively, the mean global health score was significantly higher in the intervention group than in the control group. Patients in the intervention group had a significantly better body image at 12 and 24 months postoperatively. At 12 months postoperatively, the EQ-VAS was higher in the intervention group.

The difference in QoL between the groups was clinically small by modern criteria but statistically significant(27,28). Nevertheless, in patients with a high risk of recurrence of ovarian cancer within two years, any improvement in QoL is relevant.

At 12 months postoperatively, the highest differences in scores between the intervention and the control group were seen for body image with 8.6 points and fatigue with 8.0 points.

Mediators

To our knowledge, the finding that QoL is affected by the use of a medical instrument during surgery for patients with ASEOC has never been described. The mediation analysis showed that the direct effect of the PlasmaJet on the QoL was indeed less pronounced after correction for the mediated effect of higher rates of CRS and less colostomies, compared to the total effect. This suggests that the mediators could partially explain the effect of the PlasmaJet on the QoL.

In a subset analysis to analyse the effect of a colostomy on QoL, no significant differences in the mean scores for global health were seen between patients with or without a colostomy. However, the number of colostomies in this study was small. In addition, not every patient with a colostomy completed the questionnaires. As a result, we could not comment on the effect of a colostomy on QoL.

No sensitivity analysis was performed for all patients who really underwent surgery with the use of the PlasmaJet. Patients with less extensive disease and in whom the PlasmaJet was not used would be transferred to the control group. In this case, more patients in the control group would have less extensive disease and the QoL would automatically be higher in this group.

It is notable that the difference in QoL between the groups is mainly in physical and role functioning, fatigue and pain. A possible explanation could be the differences in tissue damage when working with different equipment during surgery. The PlasmaJet infiltrates the tissue less deeply than electrosurgery.29 With less tissue damage, the process of tissue repair (inflammation, proliferation by fibrogenesis and angiogenesis and remodeling) will proceed differently than when there is more tissue damage. Especially in surgery involving extensive peritoneal stripping, the surgeon must be aware of the effect of the instrument used.

CRS with the PlasmaJet improved various QoL outcomes. At 12 months postoperatively, the adjuvant use of the PlasmaJet for ASEOC resulted in a higher QoL which was partially explained by the mediator 'surgical outcome'. This means that the use of the PlasmaJet can be considered, despite a higher cost per procedure(30).

Strengths

Our study used an additional short validated questionnaire, the EQ-5D-5L in contrast to other studies among QoL of patients with ASEOC(1,16-18).

This study demonstrated data up to 24 months postoperatively in contrast to previous studies that described QoL up to a maximum of 16 months postoperatively. The overall response rate was high, with the lowest response rate at 24 months postoperatively: 172 of 224 patients alive (77%) completed the questionnaires. The number of non-responders was the same in both groups. A logical dropout rate was because patients died of the disease. In contrast to other studies, the percentage of the non-responders who had a relapse was known (Figure 1).

Limitations

A limitation of this study is that it was impossible to apply a correction for the QoL of the non-respondents. Previously Stark et al., made a correction for the non-responders who had recurrence of disease(18). We waived this because there is insufficient scientific evidence to fill in a fictitious value for QoL. A proportion of our non-responders had a relapse and it is plausible that they would have a lower QoL than the median QoL. On the other hand, the non-responders without disease and in relatively good health could have had a better QoL, improving the overall outcome in QoL.

Future research

Further research should specifically be focused on the difference in QoL of patients who will undergo CRS and those who will decline surgery. Knowledge of patients'

QoL of both groups, combined with survival data, is needed to fully inform patients in the process of shared decision-making. Thereafter, patients can make an informed decision to undergo or to refuse a CRS.

Obtaining more data on the effect of a colostomy on QoL in patients with ASEOC may be possible if a specific instrument about stoma care would be used. More information about QoL in patients with a colostomy after CRS could help the surgical team in peroperative decision making.

Conclusions

This study demonstrated knowledge of patients' QoL until two years after CRS to fully inform patients preoperatively. Even after adjustment for the mediator of surgical outcome, a higher QoL was seen in patients who had surgery with the use of the PlasmaJet device at 12 months postoperatively.

Supplementary

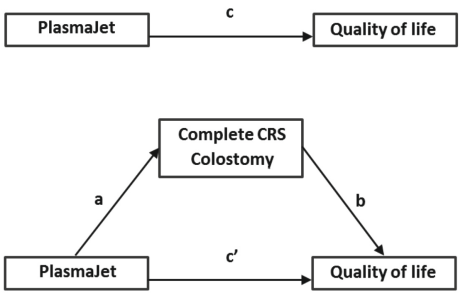


Figure S1 Mediation analysis

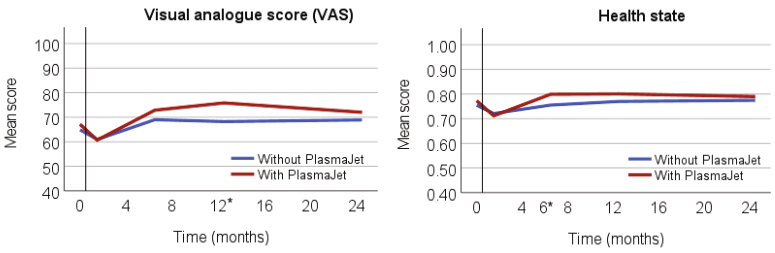


Figure S2 Outcome EQ-5D-5L for patients who had surgery with or without the PlasmaJet. * P < 0.05.

Table S1 Mean scores of the EORTC QLQ-C30, QLQ-OV28 and EQ-5D-5L for every domain at five different time-points (preoperative and 1, 6, 12 and 24 months postoperative) for patients who had surgery with or without the PlasmaJet

	Mean score		Total effect (95%CI)	P-value	Direct effect (95%CI)	P-value
	PlasmaJet	Control				
EORTC QLQ-C30						
Global health						
Pre-op	67.34	63.63				
4 weeks	60.80	60.59	-0.638 (-4.819;3.543)	0.765	-1.234 (-5.395;2.927)	0.561
6 months	75.14	70.30	3.310 (-1.159;7.780)	0.146	2.591 (-1.839;7.020)	0.251
12 months	77.92	70.97	5.305 (0.595;10.014)	0.027*	4.374 (-0.256;9.004)	0.064
24 months	75.10	67.99	4.828 (-0.627;10.282)	0.083	3.876 (-1.533;9.285)	0.160
Physical functioning						
Pre-op	76.16	72.12				
4 weeks	65.63	65.05	-0.692 (-4.867;3.483)	0.745	-1.098 (-5.245;3.049)	0.604
6 months	80.99	74.98	3.689 (-0.185;7.564)	0.062	3.237 (-0.630;7.104)	0.101
12 months	83.80	76.67	4.652 (0.123;9.181)	0.044*	4.115 (-0.338;8.568)	0.070
24 months	80.24	74.70	3.344 (-2.098;8.786)	0.228	2.786 (-2.635;8.207)	0.314
Role functioning						
Pre-op	66.30	60.47				
4 weeks	48.02	47.30	0.173 (-6.049;6.395)	0.956	-0.574 (-6.800;5.651)	0.857
6 months	77.27	66.90	7.757 (1.581;13.932)	0.014*	6.880 (0.671;13.089)	0.030*
12 months	77.50	70.24	5.362 (-1.133;11.857)	0.106	4.268 (-2.220;10.756)	0.197
24 months	77.78	70.27	5.800 (-1.523;13.123)	0.120	4.668 (-2.710;12.046)	0.215
Emotional functioning						
Pre-op	73.78	71.85				

Table S1 *(Continued)*

	Mean score		Total effect (95%CI)	P-value	Direct effect (95%CI)	P-value
	PlasmaJet	Control				
4 weeks	76.11	77.48	-1.039 (-4.805;2.728)	0.589	-1.324 (-5.045;2.397)	0.485
6 months	79.75	77.47	1.133 (-3.201;5.466)	0.608	0.771 (-3.505;5.047)	0.724
12 months	80.33	77.18	2.378 (-2.401;7.156)	0.329	1.902 (-2.853;6.658)	0.433
24 months	82.14	76.61	2.256 (-2.192;8.703)	0.241	2.767 (-2.649;8.184)	0.316
Cognitive functioning						
Pre-op	85.52	82.55				
4 weeks	78.39	81.98	-3.579 (-7.754;0.597)	0.093	-3.561 (-7.744;0.623)	0.095
6 months	82.37	78.76	2.356 (-2.144;6.857)	0.305	2.393 (-2.105;6.891)	0.297
12 months	83.50	80.82	1.631 (-2.927;6.189)	0.483	1.695 (-2.844;6.234)	0.464
24 months	84.13	77.65	4.020 (-1.676;9.716)	0.166	4.085 (-1.630;9.801)	0.161
Social functioning						
Pre-op	76.52	74.55				
4 weeks	64.81	63.40	1.678 (-3.697;7.051)	0.541	1.087 (-4.302;6.476)	0.692
6 months	80.85	76.64	3.312 (-2.778;9.402)	0.286	2.604 (-3.459;8.667)	0.400
12 months	84.33	79.36	4.025 (-1.694;9.745)	0.168	3.123 (-2.423;8.669)	0.270
24 months	84.33	75.95	7.662 (0.488;14.836)	0.036*	6.782 (-0.444;13.901)	0.066
Fatigue						
Pre-op	34.71	39.94				
4 weeks	47.49	49.32	-0.675 (-5.878;4.527)	0.799	-0.243 (-5.458;4.971)	0.927
6 months	25.99	35.45	-6.458 (-11.588;-1.329)	0.014*	-5.888 (-11.046;-0.729)	0.025*

Table S1 *(Continued)*

	Mean score		Total effect (95%CI)	P-value	Direct effect (95%CI)	P-value
	PlasmaJet	Control				
12 months	24.78	35.54	-8.047 (-13.207;-2.886)	0.002*	-7.265 (-12.409;-2.120)	0.006*
24 month	27.25	36.99	-6.042 (-12.972;0.888)	0.087	-5.234 (-12.206;1.738)	0.141
Nausea and vomiting						
Pre-op	9.37	7.32				
4 weeks	15.06	13.29	1.027 (-4.425;6.480)	0.712	1.534 (-3.869;6.983)	0.578
6 months	7.30	4.34	2.918 (-0.867;6.702)	0.131	3.536 (-0.268;7.340)	0.068
12 months	4.83	7.01	-1.823 (-5.613;1.967)	0.346	-1.039 (-4.786;2.709)	0.587
24 months	6.94	9.09	-1.687 (-7.277;3.902)	0.554	-0.876 (-6.489;4.738)	0.760
Pain						
Pre-op	21.41	21.85				
4 weeks	30.62	29.05	0.425 (-5.119;5.968)	0.881	1.031 (-4.515;6.578)	0.715
6 months	14.46	17.25	-2.885 (-8.260;2.490)	0.293	-2.142 (-7.523;3.240)	0.435
12 months	15.33	19.97	-5.028 (-11.252;1.195)	0.113	-4.060 (-10.120;2.000)	0.189
24 months	13.10	21.40	-6.846 (-12.932;-0.760)	0.027*	-5.847 (-11.874;0.181)	0.057
Dyspnoea						
Pre-op	17.03	20.04				
4 weeks	20.25	20.95	0.468 (-5.084;6.020)	0.869	0.480 (-5.135;6.095)	0.867
6 months	15.43	19.72	-3.052 (-8.756;2.652)	0.294	-3.042 (-8.831;2.747)	0.303
12 months	18.00	20.90	-2.553 (-8.686;3.581)	0.415	-2.546 (-8.790;3.697)	0.424
24 months	18.65	22.73	-2.282 (-9.172;4.608)	0.516	-2.275 (-9.175;4.624)	0.518

Table S1 *(Continued)*

	Mean score		Total effect (95%CI)	P-value	Direct effect (95%CI)	P-value
	PlasmaJet	Control				
Insomnia						
Pre-op	28.71	26.58				
4 weeks	31.85	30.85	-2.001 (-7.599;3.597)	0.483	-1.441 (-7.030;4.147)	0.613
6 months	25.62	24.41	-0.071 (-5.779;5.637)	0.981	0.581 (-5.161;6.323)	0.843
12 months	27.67	29.63	-4.003 (-11.817;3.810)	0.315	-3.199 (-11.009;4.611)	0.422
24 months	25.79	27.27	-1.368 (-8.706;5.970)	0.715	-0.541 (-7.850;6.768)	0.885
Appetite loss						
Pre-op	19.95	17.12				
4 weeks	27.41	28.83	-2.504 (-9.350;4.341)	0.473	-1.809 (-8.660;5.041)	0.605
6 months	9.92	9.62	-0.592 (-5.948;4.763)	0.828	0.253 (-5.038;5.545)	0.925
12 months	7.33	12.43	-6.085 (-11.385;-0.785)	0.024*	-4.994 (-10.319;0.332)	0.066
24 months	11.11	17.42	-7.141 (-14.406;0.125)	0.054	-6.012 (-13.322;1.299)	0.107
Constipation						
Pre-op	17.76	14.86				
4 weeks	24.69	22.97	0.794 (-5.693;7.280)	0.810	0.542 (-5.886;6.970)	0.869
6 months	9.37	11.03	-1.727 (-6.216;2.763)	0.451	-1.893 (-6.363;2.578)	0.407
12 months	11.67	14.81	-3.923 (-9.552;1.706)	0.172	-3.975 (-9.619;1.670)	0.167
24 months	14.28	13.64	0.093 (-5.964;6.149)	0.976	0.033 (-6.003;6.069)	0.991
Diarrhoea						
Pre-op	8.03	7.66				

Table S1 *(Continued)*

	Mean score		Total effect (95%CI)	P-value	Direct effect (95%CI)	P-value
	PlasmaJet	Control				
4 weeks	11.36	14.86	-3.139 (-8.719;2.441)	0.270	-2.818 (-8.337;2.701)	0.317
6 months	6.61	4.69	1.776 (-2.127;5.679)	0.372	2.133 (-1.754;6.019)	0.282
12 months	6.33	11.11	-5.249 (-10.012;-0.487)	0.031*	-4.829 (-9.531;-0.127)	0.044*
24 months	5.95	10.98	-5.249 (-10.795;0.296)	0.063	-3.820 (-10.303;0.664)	0.085
Financial difficulties						
Pre-op	5.35	8.33				
4 weeks	6.17	6.08	1.045 (-1.898;3.989)	0.486	1.070 (-1.890;4.031)	0.478
6 months	7.16	8.22	0.033 (-3.826;3.891)	0.987	0.084 (-3.832;4.001)	0.966
12 months	8.20	8.00	0.729 (-4.010;5.467)	0.763	0.821 (-3.841;5.483)	0.730
24 months	6.35	9.85	-2.056 (-7.402;3.290)	0.451	-1.960 (-7.248;3.329)	0.467
EORTC QLQ-OV28						
Abdominal						
Pre-op	23.88	23.45				
4 weeks	27.26	29.09	-2.839 (-6.534;0.856)	0.132	-2.576 (-6.267;1.115)	0.171
6 months	17.42	18.85	-1.774 (-5.370;1.821)	0.333	-1.505 (-5.119;2.108)	0.414
12 months	18.50	22.51	-3.908 (-8.191;0.375)	0.074	-3.622 (-7.926;0.681)	0.099
24 months	21.63	23.92	-1.131 (-5.742;3.480)	0.631	-0.832 (-5.531;3.867)	0.728
Peripheral neuropathy						
Pre-op	24.33	27.74				
4 weeks	26.53	32.58	-4.377 (-8.859;0.105)	0.056	-3.896 (-8.370;0.579)	0.088

Table S1 *(Continued)*

	Mean score		Total effect (95%CI)	P-value	Direct effect (95%CI)	P-value
	PlasmaJet	Control				
6 months	31.57	39.24	-5.951 (-11.934;0.032)	0.051	-5.396 (-11.433;0.642)	0.080
12 months	23.61	31.38	-5.930 (-11.684;-0.176)	0.043*	-5.250 (-11.047;0.548)	0.076
24 months	25.38	30.99	-3.032 (-9.114;3.049)	0.328	-2.323 (-8.509;3.865)	0.462
Chemo side effects						
Pre-op	25.86	25.92				
4 weeks	24.59	25.75	-1.428 (-4.811;1.955)	0.408	-1.226 (-4.620;2.168)	0.479
6 months	19.52	21.24	-1.697 (-5.327;1.933)	0.359	-1.473 (-5.124;2.178)	0.429
12 months	14.38	18.32	-3.602 (-6.900;-0.303)	0.032*	-3.338 (-6.663;-0.013)	0.049*
24 months	16.40	19.21	-2.355 (-6.743;2.033)	0.292	-2.081 (-6.527;2.365)	0.359
Hormonal						
Pre-op	14.84	17.46				
4 weeks	18.66	21.32	-2.567 (-7.076;1.942)	0.264	-2.580 (-7.105;1.946)	0.264
6 months	23.29	19.17	-3.184 (-8.841;2.473)	0.270	-3.215 (-8.922;2.491)	0.269
12 months	16.32	22.93	-5.535 (-11.293;0.224)	0.060	-5.595 (-11.374;0.185)	0.058
24 months	18.31	27.59	-4.579 (-11.820;2.661)	0.215	-4.641 (-11.917;2.634)	0.211
Body image						
Pre-op	22.87	24.94				
4 weeks	25.25	28.34	-4.081 (-9.260;1.098)	0.122	-3.879 (-9.051;1.293)	0.141
6 months	27.90	21.67	-4.912 (-10.695;0.871)	0.096	-4.709 (-10.525;1.108)	0.112
12 months	16.67	26.40	-8.613 (-14.248;-2.978)	0.003*	-8.401 (-14.082;-2.721)	0.004*

Table S1 *(Continued)*

	Mean score		Total effect (95%CI)	P-value	Direct effect (95%CI)	P-value
	PlasmaJet	Control				
24 months	19.14	39.81	-7.270 (-13.808;-0.733)	0.029*	-7.052 (-13.633;-0.470)	0.036*
Attitude to disease						
Pre-op	51.91	56.01				
4 weeks	59.37	58.58	1.129 (-3.223;5.480)	0.611	1.835 (-2.450;6.121)	0.401
6 months	51.76	56.26	-1.146 (-6.749;4.456)	0.688	-0.376 (-5.937;5.184)	0.894
12 months	47.22	50.76	-1.424 (-7.482;4.634)	0.645	-0.529 (-6.530;5.472)	0.863
24 months	44.03	54.32	-5.653 (-12.214;0.908)	0.091	-4.731 (-11.303;1.841)	0.158
Sexuality						
Pre-op	94.40	92.74				
4 weeks	95.40	95.75	-1.175 (-3.791;1.441)	0.379	-1.044 (-3.691;1.603)	0.439
6 months	87.03	88.06	-2.069 (-5.735;1.596)	0.268	-1.910 (-5.592;1.773)	0.309
12 months	87.41	87.13	-0.681 (-5.038;3.675)	0.759	-0.474 (-4.803;3.856)	0.830
24 months	88.58	87.22	-0.804 (-5.158;3.551)	0.717	-0.590 (-4.941;3.762)	0.791
EQ-5D-5L						
Health status						
Pre-op	0.77	0.75				
4 weeks	0.71	0.72	-0.004 (-0.046;0.038)	0.842	-0.011 (-0.052;0.030)	0.605
6 months	0.80	0.76	0.041 (0.009;0.081)	0.045*	0.034 (-0.007;0.074)	0.105
12 months	0.80	0.77	0.021 (-0.029;0.071)	0.402	0.012 (-0.037;0.061)	0.633
24 months	0.79	0.77	0.011 (-0.043;0.066)	0.678	0.002 (-0.052;0.056)	0.945

Table S1 *(Continued)*

	Mean score		Total effect (95%CI)	P-value	Direct effect (95%CI)	P-value
	PlasmaJet	Control				
VAS						
Pre-op						
4 weeks	67.16	64.90	-0.754 (-4.518;3.009)	0.694	-1.253 (-5.009;2.502)	0.513
6 months	72.88	69.01	3.175 (-0.514;6.863)	0.091	2.563 (-1.123;6.248)	0.173
12 months	75.84	68.26	6.571 (1.992;11.150)	0.005*	5.774 (1.177;10.370)	0.014*
24 months	72.03	68.91	2.387 (-3.006;7.781)	0.385	1.563 (-3.815;6.940)	0.569

Total effect: score corrected for preoperative score. Direct effect: score corrected for preoperative score and effect of the mediators 'Surgical outcome' and 'Colostomy'. * = $p<0.05$.

Table S2 Outcome of the EORTC QLQ-C30 of patients with complete cytoreductive surgery

	Mean score			
	Complete CRS (n=233)	Non-complete CRS (n=93)	95%CI	P-value
EORTC QLQ-C30				
Global health				
12 months	77.1	62.8	11.8 (5.6;18.1)	0.002*
24 months	72.7	65.8	3.7 (-4.3;11.7)	0.368

CRS= cytoreductive surgery

Table S3 Outcome of the EORTC QLQ-C30 of patients who received a colostomy

	Mean score			
	Colostomy (n=32)	No Colostomy (n=294)	95%CI	P-value
EORTC QLQ-C30				
Global health				
12 months	71.7	74.3	-2.4 (-11.2;6.4)	0.588
24 months	71.1	71.5	-2.4 (-5.6;10.4)	0.557

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8

Preoperative Cancer Antigen 125 Level as Predictor for Complete Cytoreduction in Ovarian Cancer: A Prospective Cohort Study and Systematic Review

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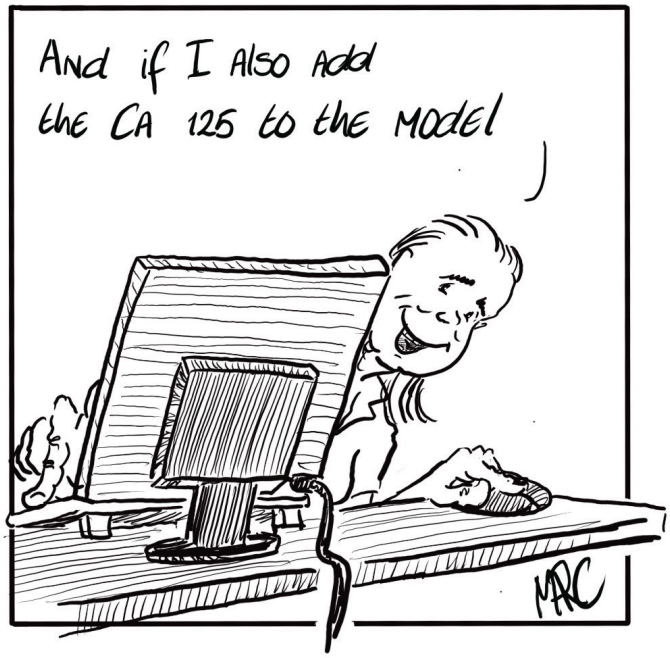

Abstract

Background

The tumor marker 'cancer antigen 125' (CA-125) plays a role in the management of women with advanced stage ovarian cancer. This study aims to describe the predictive value of pre-treatment CA-125 level and the reduction after neoadjuvant chemotherapy (NACT) on surgical outcome.

Methods

A systematic review and a prospective clinical study were performed. Multiple databases were searched from database inception to April 2022. The clinical study is part of a randomized controlled trial named "PlaComOv-study". A regression analysis was performed to demonstrate correlations between preoperative CA-125 levels, CA-125 reduction after NACT, and surgical outcome.

Results

Fourteen relevant articles were analyzed of which eleven reported that lower preoperative CA-125 levels were associated with a higher probability of complete cytoreduction. In the clinical study, 326 patients with FIGO stage IIIB-IV ovarian cancer who underwent CRS were enrolled from 2018 to 2020. Patients who underwent interval CRS with preoperative CA-125 levels ≤ 35 kU/L had higher odds of achieving complete CRS than patients with CA-125 level >35 kU/L (85% vs. 67%, OR 2.79, 95%CI 1.44–5.41, p = 0.002). In multivariable analysis with presence of ascites and peritoneal carcinomatosis, normalized preoperative CA-125 did not appear as a significant predictor for complete CRS.

Conclusions

In literature, preoperative CA-125 levels ≤ 35 kU/L were associated with a significant higher percentage of complete CRS in univariable analysis. According to our cohort study, preoperative CA-125 level ≤ 35 kU/L cannot independently predict surgical outcome either for primary or interval CRS.

Introduction

The tumor marker 'cancer antigen 125' (CA-125) plays a role in the management of women with advanced stage ovarian cancer. For those patients, the cornerstone treatment is the combination of cytoreductive surgery (CRS) and chemotherapy. How much value can we give to the CA-125 level to predict surgical outcome, and can we use CA-125 to decide to start neoadjuvant chemotherapy (NACT) or to perform a primary CRS? More than 300,000 women worldwide were diagnosed with epithelial ovarian cancer (EOC) in 2020. Unfortunately, 75% of them were initially diagnosed with advanced stage(1,2).

CA-125 is a tumor marker that is elevated in 80–90% of patients with EOC(3,4). Patients with EOC will commonly undergo blood CA-125 analysis preceding treatment. Previous studies have shown that a lower level of preoperative CA-125 was associated with a higher probability of achieving optimal CRS(5–7). During the past several years, the definition of 'optimal cytoreduction' after CRS has been changed from a maximum residual tumor diameter of 3 cm to one less than 1 cm(8). Currently, we aim to achieve a complete CRS without any macroscopic residual disease when performing either primary or interval CRS.

The predictive value of CA-125 level for complete CRS is still inconclusive. Furthermore, we do not know whether normalization of CA-125 is a predictor of complete CRS or whether a particular drop can also be used as a predictor of surgical outcome.

To help fill this knowledge gap, we performed a systematic review and a prospective cohort study. The aim of this study was to demonstrate whether we can use CA-125 as a predictor of complete CRS for patients with advanced stage EOC. The secondary aim was to determine the predictive value of the CA-125 reduction rate after neoadjuvant chemotherapy on the surgical outcome for interval CRS.

Materials and Methods

Systematic Review

Search Strategy

This review is reported in accordance with the Preferred reporting items for systematic reviews and meta-analyses (Prisma) Checklist(9), and the Prisma-S extension to the PRISMA Statement for Reporting Literature Searches in Systematic Reviews(10).

Embase.com, Medline Ovid, Web of Science Core Collection, Cochrane Central Register of Trials, and Google Scholar from which the most relevant 50 references were included, were searched from database inception to April 2022. The search strategy contained terms for 1) CA-125; 2) ovarian cancer and 3) CRS. The search strategy is presented in Supporting information Supplementary Table S1.

Eligibility Criteria

The key inclusion criteria were patients with International Federation of Gynecology and Obstetrics (FIGO) stage IIIB-IV ovarian cancer, English-language studies, complete surgical outcome, the correlation of preoperative CA-125 level or the changes of CA-125 level after NACT with surgical outcome. Exclusion criteria were patients with FIGO stage I-IIA ovarian cancer, recurrence of disease, and an optimal or suboptimal CRS or survival as primary outcome.

Data Extraction

The retrieved electronic citations were de-duplicated, and the titles and abstracts were screened on relevance for the review independently by two researchers (PB and GN) using EndNote X9. Subsequently, the full texts of eligible citations were screened for relevance to the review. Any disagreements between both researchers were resolved through discussion. The reference lists of retrieved articles were searched for possibly missed relevant studies. Extracted data included FIGO staging, type of CRS (primary or interval), surgical outcome, level of CA-125 and reduction of CA-125 after NACT (when applicable), and optimal cut-off value of CA-125.

Quality Assessment

Quality of the included studies was assessed with the Quality In Prognosis Studies (QUIPS) tool(11). Risk of study bias in studies of prognostic factors was appraised in five important domains: study participation, prognostic factor measurement, outcome measurement, study confounding, statistical analysis, and reporting. Each domain was rated and then classified as low, moderate, or high risk of bias. Low risk means least risk of bias: results are generally considered valid, there is clear description of population (>100), setting, inclusion criteria, interventions, comparison groups, and statistics are clearly defined.

Moderate risk means susceptible risk to some bias: studies may not meet all the criteria for the low risk of bias rating, but do not show flaws that could cause major bias. The study population is 50–100 people. The study may also lack information, making it difficult to assess limitations and potential problems. High risk means significant deficiencies that may invalidate the results: deficiencies in design,

analysis or reporting, small sample size, large amounts of missing information, and discrepancies in reporting.

Prospective Study

The second part of the study consisted of a prospective cohort study within the framework of a multicenter randomized controlled trial named "PlaComOv-study"(12). The aim of PlaComOv-study was to evaluate the effectiveness of the PlasmaJet surgical device in the treatment of advanced stage ovarian cancer. Participants were randomized to the additional use of the PlasmaJet surgical device during surgery or only the conventional surgical devices. The study was conducted in four gynecological oncology centers and nine centers specialized in ovarian cancer surgery in the Netherlands. The standard chemotherapy regimen given after primary CRS consisted of six cycles of intravenously carboplatin (area under the curve of 6 mg per milliliter per minute) and paclitaxel (175 mg per square meter of body-surface area) with an interval of three weeks for each cycle. The regimen for interval CRS consisted of three cycles of NACT given prior to surgery and three cycles given after surgery in all cases(13).

Inclusion and Exclusion Criteria

Patients with suspected advanced stage EOC, fallopian tube or peritoneal carcinoma FIGO stage IIIB-IV who were fit enough to undergo CRS and chemotherapy were eligible for inclusion. The surgical procedure was either primary CRS or interval CRS. Subjects were included in the study if advanced stage EOC (FIGO IIIB-IV) was pathologically reported. Patients were excluded with recurrent disease, a non-epithelial, borderline ovarian tumor, ovarian metastasis of another primary tumor, as well as patients who did not have surgery after randomization because of their comorbidity. Informed consent was obtained from all subjects involved in the PlaComOv-study.

Data Collection

Clinical characteristics and operative reports of the participants of the PlaComOv-study were stored in an electronic database management platform called 'Open Clinica'. The preoperative levels of blood CA-125 were related to type of surgery, either primary or interval CRS. Normal CA-125 level was defined as <35 kU/L, as this cut-off value is used in general practice(14). The reduction of CA-125 level after NACT was calculated and presented as a percentage. Blood CA-125 level was determined in 13 different laboratories using five different automated immunochemistry platforms. While all assays use the same general analytical principle (automated sandwich assays with monoclonal capture), the antigen-binding sites of the antibodies as well as the signal technology for quantifying tumor markers concentrations may

be disparate. The detailed methods of each platform used to analyze CA-125 are presented in Supporting information Supplementary Table S2.

The surgical outcome was classified in four categories: complete CRS, optimal CRS, suboptimal CRS, and unresectable disease. Complete CRS was defined as no macroscopic residual disease after surgery. Optimal CRS was defined as residual tumor lesions of ≤1 cm. Suboptimal CRS was defined as residual tumor lesions > 1 cm. Unresectable disease was defined as surgery with the intention to perform CRS, but which the surgeon stopped when after exploration resection proved not possible.

In addition, preoperative CA-125 levels were categorized as ≤35 kU/L vs. >35 kU/L. The reduction of CA-125 level after NACT among patients who underwent interval CRS was categorized as ≤95% change vs. >95% change.

Statistical Analyses

Continuous variables were analyzed using the one-way ANOVA or the Kruskal–Wallis test. Categorical variables were compared using the chi-squared test. Univariable analysis with binary logistic regression was conducted to compare variables between categories of CA-125 level as well as between categories of surgical outcome. Multivariable analysis with binary logistic regression was conducted to identify variables independently predicting complete CRS. All variables in univariable analysis were included in the multivariable model. ROC analysis with cross-validation was performed to evaluate the combined value of significant predictors of complete CRS. Cross-validation was applied, and it was considered that ROC curves were created with a selection of variables. Differences with a two-tailed *p*-value of $p < 0.05$ were considered statistically significant. All statistical analyses were performed in IBM SPSS Statistics Version 25 (SPSS Inc., Chicago, IL, USA).

Results

Systematic Review

General Characteristics of the Studies

The searches revealed 580 potentially relevant articles. After excluding duplicates and screening on relevance, 14 articles met the inclusion criteria (Figure 1). Records were excluded because of the following reasons: conference paper, editorials, letter and short communications, not ovarian malignancy, not English language, recurrence of ovarian cancer, survival as primary outcome, optimal versus suboptimal CRS, and

inclusion of FIGO stage I-IIA. The QUIPS quality assessment outcomes of the included studies are reported in Supporting information Supplementary Table S3. Generally, the risk of bias was low for most studies (8,15–24). The risk of bias was moderate for only three studies (25,27).

The characteristics of the included studies are summarized in Table 1. Two studies were prospective cohort studies (15,25); the other twelve studies were retrospective cohort studies (8,16-24,26,27). Four out of 14 studies reported the results of patients who underwent primary CRS (15-17,25), and nine studies reported the results of patients who underwent interval CRS (8,18-24,26). One study reported patients undergoing either primary or interval CRS (27) Generally, patients were diagnosed with FIGO stage IIIA-IV EOC (10,24,26–36), and the majority of patients in all studies were diagnosed with a serous tumor.

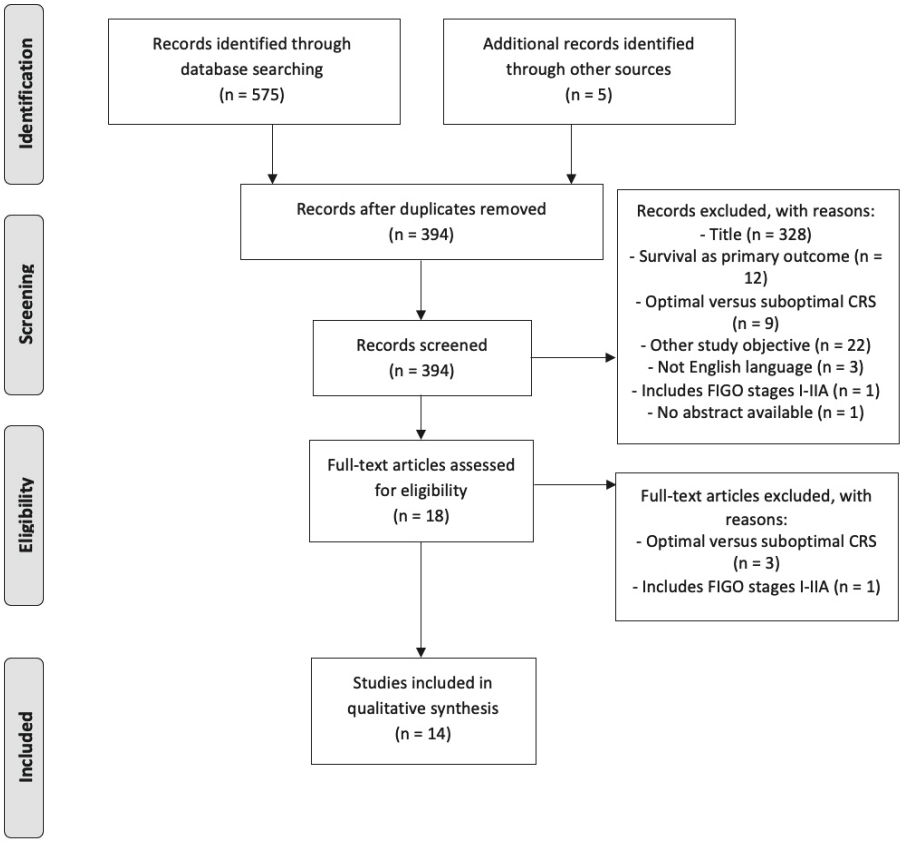

Figure 1 Flowchart of study selection

Table 1 Summary of study characteristics

Authors	Journal, Publication Year	Sample Size	FIGO Staging	Primary Outcome Measures	Type of CRS	CA-125 Reduction after NACT
Eltabbakh et al. [14]	Gynecol Oncol, 2004	72	15.3% Stage IIIA 5.6% Stage IIIB 61.1% Stage IIIC 18.1% Stage IV	Relation between preoperative CA-125 and surgical outcome	Primary CRS	N/A-
Risum et al.[22]	Int J Gynecol Cancer, 2009	75	86.7% Stage III 13.3% Stage IV	The predictive value of preoperative CA-125 on incomplete CRS	Primary CRS	N/A
Rodriguez et al. [19]	Gynecol Oncol, 2012	103	40.5% Stage IIIC 59.5% Stage IV	Relation between change of CA-125 in patients undergoing NACT and surgical outcome	Interval CRS	Overall percentage change, >80% change from presentation to operation and prior to each NACT cycle
Furukawa et al. [18]	J Gynecol Oncol, 2013	75	6.7% Stage IIIA 93.3% Stage IIIC	Relation between CA-125 after NACT and surgical outcome Relation between changes of CA-125 levels during NACT and surgical outcome	Interval CRS	Rates of changes prior to each NACT cycle
Jung et al. [12]	Gynecol Oncol, 2013	358	12.1% Stage IIC 71.5% Stage III 15.1% Stage IV 0.3% undocumented	Developing a model to predict non-complete CRS with CA-125, CT scan, age and surgical skill index	Primary CRS	N/A
Pelissier et al.[17]	Gynecol Oncol, 2014	148	72.3% Stage IIIC 23.6% Stage IV	Relation between kinetic CA-125 levels during NACT and surgical outcome	Interval CRS	Percentage decrease in CA-125
Karlsen et al. [11]	Tumor Biol, 2016	150	78.7% Stage IIIC 21.3% Stage IV	Relation between preoperative CA-125, HE4, age, presence of ascites and performance status and the surgical outcome	Primary CRS	N/A

Surgical Outcome	Number of NACT Cycles	Results for Preoperative CA-125	Results for CA-125 Reduction after NACT	Optimal CA-125 Cut-Off Value	Additional Information
Complete vs. non-complete CRS	N/A	In univariable analysis, preoperative levels of CA-125 predict complete CRS ($p < 0.001$). In multivariable analysis, preoperative CA-125 was not significantly associated with complete CRS.	N/A	≤500 kU/L preoperative	No or small amount of ascites significantly correlated with complete CRS ($p < 0.001$) in univariable analysis. In multivariable analysis, the only independent predictor of complete CRS was p53 expression ($p < 0.001$).
Complete vs. non-complete CRS	N/A	Preoperative CA-125 levels are significantly lower in patients undergoing complete CRS ($p = 0.03$).	N/A	N/A	Intestinal carcinosis was found in 92% of incomplete CRS and in only 13% of complete CRS.
Complete vs. optimal CRS	Median: 3 cycles, Range: 1–8 cycles	Lower preoperative CA-125 levels, especially ≤100 kU/L, significantly correlate with complete CRS ($p = 0.04$).	No significant relation between decrease in CA-125 during NACT and complete CRS.	≤100 kU/L preoperative	
Complete vs. non-complete CRS	3 cycles: 100%	Preoperative CA-125 levels are significantly lower in patients undergoing complete CRS ($p < 0.001$) in both univariable and multivariable analysis.	In univariable analysis, (pre-NACT CA-125—pre-2nd NACT CA-125)/pre-NACT CA-125 ($p = 0.01$) and (pre-NACT CA-125—pre-3rd NACT CA-125)/pre-NACT CA-125 ($p = 0.008$) significantly predicted complete CRS. In multivariable analysis, there was no significant relation between decrease in CA-125 during NACT and complete CRS.	≤20 kU/L preoperative	
Complete vs. non-complete CRS	N/A	Higher preoperative CA-125 levels significantly predict non-complete CRS ($p = 0.001$).	N/A	N/A	CA-125 ($p = 0.001$), two CT factor scores and surgical skill index were included in the model.
Complete vs. non-complete CRS	Median: 6 cycles, Range: 1–9 cycles	In univariable analysis, preoperative CA-125 ($p = 0.001$) significantly predicts complete CRS, but not according to multivariable analysis.	In univariable analysis, level of CA-125 after 3 cycles of NACT ($p = 0.00001$), cycle to nadir ($p = 0.001$) and percentage decrease ($p = 0.01$) significantly predict complete CRS. Multivariable analysis shows that only CA-125 after 3 cycles of NACT independently predicts complete CRS ($p = 0.04$).	<75 kU/L after 3 cycles of NACT	
Complete vs. non-complete CRS	N/A	In univariable analysis, preoperative CA-125 are significantly lower in patients undergoing complete CRS ($p = 0.001$).	N/A	N/A	CA-125 was excluded from the prediction model (no significant contribution to the model ($p = 0.166$)). Included in the model were: age, HE4 and performance status.

Morimoto et al. [23]	Jpn J Clin Oncol, 2016	139	59.7% Stage IIIC 40.3% Stage IV (Primary ovarian, fallopian tube and peritoneal)	Relation between CA-125 after NACT, presence of ascites and response rate and the surgical outcome	Interval CRS	N/A
Zeng et al. [8]	J Cancer, 2016	118	84.7% Stage III 15.3% Stage IV (Primary ovarian, fallopian tube and peritoneal)	Relation between preoperative CA-125 and surgical outcome Relation between changes in CA-125 during NACT and surgical outcome	Interval CRS	Percentage reduction after the first NACT cycle and >30% reduction, overall percentage reduction, >80% reduction after all NACT cycles
Matsuhashi et al. [16]	J Nippon Med Sch, 2017	107	55.1% Stage III 44.9% Stage IV	Relation between CA-125 after NACT and surgical outcome	Interval CRS	Number of NACT cycles needed for CA-125 levels to halve or reduce to <35 U/mL
Ghisoni et al. [20]	J Ovarian Res, 2018	93	9.7% Stage IIIA 15% Stage IIIB 62.4% Stage IIIC 12.9% Stage IV	Developing a predictive score of cytoreductive outcome	Interval CRS	<96% reduction in CA-125
Gupta et al. [15]	South Asian J Cancer, 2020	406	71.5% Stage III 28.5% Stage IV	Relation between preoperative CA-125 and surgical outcome Relation between percent fall of CA-125 after NACT and surgical outcome	Interval CRS	>95% vs. <95% decrease in CA-125
Nakamura et al. [21]	World J Surg Oncol, 2020	63	68.3% Stage IIIC 31.7% Stage IV	This study aimed to use CA-125 and CT scanning to generate a model of predicting complete cytoreduction	Interval CRS	N/A
Merlo et al. [24]	Radiol Oncol, 2021	253	Primary CRS: 89.5% Stage IIIC 10.5% Stage IV Interval CRS: 66.6% Stage IIIC 33.4% Stage IV	Relation between pre-operative CA-125 and surgical outcome	Primary CRS and Interval CRS	Percentage reduction

CRS = cytoreductive surgery, CT = computed tomography, FIGO = international federation of gynecology and obstetrics, N/A = not applicable, NACT = neoadjuvant chemotherapy. * = not mentioned in the article.

	Complete vs. non-complete CRS	Median: 4 cycles Range: 3–6 cycles	Preoperative CA-125 levels are significantly lower in patients undergoing complete CRS ($p < 0.001$).	N/A	≤25.8 kU/L preoperative	Presence of preoperative ascites leads to a significant lower complete CRS rate ($p < 0.0001$).
	Complete vs. non-complete CRS	1–3 cycles: 97.5% ≥4 cycles: 2.5%	In univariable analysis, preoperative value of CA-125 ≤200 kU/L ($p = 0.000$) predicts complete CRS. This was also significant in multivariable analysis ($p = 0.012$).	In univariable analysis, >80% reduction of CA-125 after NACT ($p = 0.000$) predicts complete CRS. This was not significant in multivariable analysis ($p = 0.059$).	≤200 kU/L preoperative	
	Complete/optimal vs. suboptimal CRS	6 cycles: >70%, ≤5 cycles: <30%	Lower preoperative CA-125 levels ($p = 0.003$), especially <35 kU/L ($p = 0.0029$), significantly correlate with complete/optimal CRS.	No significant difference in frequency of NACT cycles for CA-125 levels to halve or to drop below 35 U/mL between complete/optimal vs. suboptimal CRS ($p > 0.05$).	<35 kU/L preoperative	
	Complete vs. non-complete CRS	N/A *	In univariable analysis, preoperative CA-125 >33 kU/L significantly predicted non-complete CRS ($p = 0.002$). This was not significant in multivariable analysis.	In univariable analysis, <96% reduction in CA-125 after NACT significantly predicted non-complete CRS ($p = 0.034$). This was not significant in multivariable analysis.	<33 kU/L preoperative >96% reduction	Age >60 years ($p = 0.007$), CA-125 at diagnosis ≥550 kU/L ($p = 0.014$) and peritoneal cancer index assessed at laparoscopy of >16 ($p < 0.001$) were included in the prediction model.
	Complete vs. optimal and vs. suboptimal CRS	<3 cycles: >60%, >3 cycles: <40%	Rate of complete CRS is significantly higher in preoperative levels of CA-125 <100 kU/L ($p = 0.00$).	Rate of complete CRS is significantly higher in >95% fall of CA-125 after NACT ($p = 0.00$).	<100 kU/L preoperative >95% decrease in CA-125 after NACT	Mucinous carcinomas were excluded.
	Complete vs. non-complete CRS	Median: 6 cycles Range: 1–14 cycles	Pre-operative levels of CA-125 were significantly lower in patients with complete CRS ($p = 0.015$).	N/A	N/A	Extra-ovarian implants ($p = 0.009$) and omental tumors at CT after NACT ($p = 0.038$) are significantly associated with complete CRS.
	Complete vs. optimal and vs. suboptimal CRS	N/A *	Primary CRS: Lower preoperative levels of CA-125 are associated with complete/optimal CRS. Interval CRS: Lower preoperative levels of CA-125 are associated with complete/optimal CRS ($p = 0.020$).	The probability of complete/optimal CRS is higher in patients with a CA-125 reduction >96.4%.	<500 kU/L preoperative	

Primary Cytoreductive Surgery and CA-125 Level

The study of Risum et al. compared preoperative CA-125 levels between patients with complete CRS vs. non-complete CRS. The authors demonstrated that patients who underwent complete CRS had significantly lower preoperative CA-125 levels in (p = 0.03)(25). Eltabbakh et al. reported a significant effect of lower preoperative CA-125 levels on complete CRS in univariable analysis, but not in multivariable analysis(17). Merlo et al. reported a higher rate of complete CRS in patients with lower preoperative CA-125 levels(27). Karlsen et al. and Jung et al. reported CA-125 level as part of a prediction model of factors predicting surgical outcome of CRS. While Karlsen et al. excluded preoperative CA-125 levels from their prediction model after multivariable analysis. Jung et al. reported that high preoperative levels of CA-125 were correlated with non-complete CRS (p = 0.001). The authors found that the use of preoperative CA-125 level, computed tomography (CT) factor scores, and surgical skill resulted in a C-statistic of 0.73 (95%CI 0.67–0.79)(15,16).

Interval Cytoreductive Surgery and CA-125 Level

Five studies reported a significant relation between lower preoperative CA-125 levels and a complete CRS rate after interval CRS(21,22,24,26,27). Matsuhashi et al. reported a significant relation between lower preoperative CA-125 levels and complete/optimal CRS (p = 0.003)(19). Gupta et al. demonstrated higher rates of complete CRS in patients with preoperative levels of CA-125 < 100 kU/L (p = 0.00) (18), whereas Zeng et al. reported the cut off level of CA-125 level ≤ 200 kU/L (p = 0.012)(8). In two studies, preoperative CA-125 was not a significant predictor of surgical outcome in multivariable analysis(20,23). Additionally, patients in the studies received NACT before surgery, varying from 1–14 cycles. Only one study reported 3 cycles before interval CRS for all patients(21).

Eight studies demonstrated the effect of preoperative levels of CA-125 change after NACT on surgical outcome(8,18–23,27). After adjusting for potential confounders, Gupta et al. found a significant correlation between >95% decrease rate of preoperative CA-125 and complete CRS(18). Pelissier et al. also reported a significant relation between a level of CA-125 after three cycles of NACT and complete CRS in multivariable analysis(19). Furthermore, Merlo et al. reported an association between >96.4% reduction of CA-125 after NACT and complete CRS(26). Nevertheless, other studies did not find the decrease in CA-125 level after NACT to be an independent predictor for complete CRS(8,19,21–23). Ten studies reported an optimal cut-off value of CA-125 level, either prior to primary CRS or interval CRS(8,17–23,26,27). The cut-off values of preoperative CA-125 ranged from ≤20 kU/L [21] to ≤500 kU/L(17,27).

Prospective Study

Patient Characteristics and Surgical Outcomes

Of the 383 patients randomized for the PlaComOv-study between 2018 and 2020, 326 patients were included in our study (Figure 2). Patients' baseline characteristics were analyzed according to the intention-to-treat protocol and are presented in Table 2. Complete CRS was achieved in 71.8% (n = 234). The majority of patients had been diagnosed with FIGO stage IIIB/IIIC (69.3%) and serous histology (96.0%). Non-seroius tumors were mucinous, endometrioid, clear cell, mixed epithelial, or carcinosarcoma. The PlasmaJet surgical device was used in 119 patients (50.9%) with complete CRS, in 12 patients (24.5%) with optimal CRS and in eight patients (50.0%) with suboptimal CRS (p = 0.002). In case of unresectable disease, cytoreductive surgery was omitted. The extent of surgery required to achieve the outcome was also documented. These results can be found in the original article of the PlaComOv-study(28).

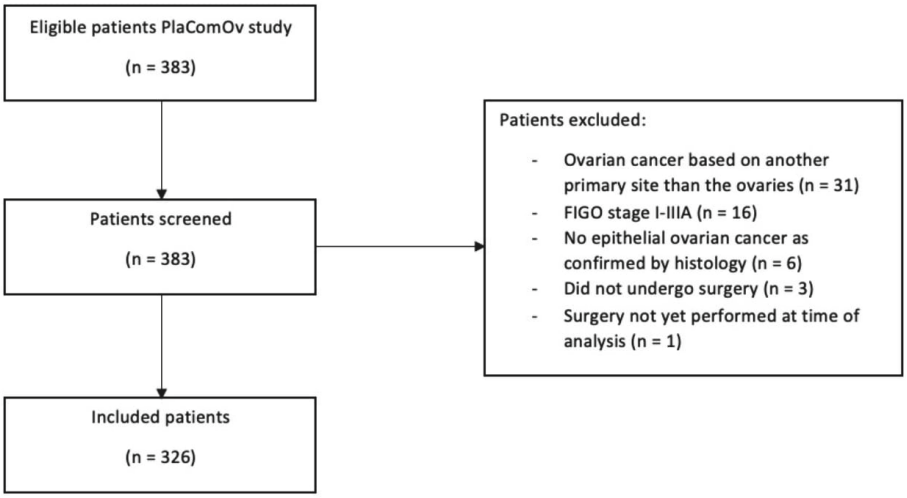

Figure 2 Flowchart of patient selection

Table 2 Patients characteristics (*N* = 326)

Characteristics	Complete CRS (*n* = 234, 71.8%)	Optimal CRS (*n* = 49, 15.0%)	Suboptimal CRS (*n* = 16, 4.9%)	Unresectable Disease (*n* = 27, 8.3%)	*P*-Value
Median AGE (IQR), years	65 (15)	67 (9)	66 (18)	72 (12)	0.038
Median BMI (IQR), kg/m^2	24.7 (6.2)	24.5 (5.6)	24.5 (3.7)	22.5 (7.9)	0.424
WHO performance, *n* (%)					NS
0	130 (55.6)	26 (53.1)	7 (43.8)	9 (33.3)	
1	75 (32.1)	17 (34.7)	4 (25.0)	13 (48.2)	
≥2	14 (5.9)	3 (6.1)	4 (25.0)	4 (14.8)	
Type of surgery, *N* (%)					NS
Primary CRS	33 (14.1)	8 (16.3)	4 (25.0)	0 (0.0)	
Interval CRS	201 (85.9)	41 (83.7)	12 (75.0)	27 (100.0)	
FIGO stage, *n* (%)					0.082
IIIB/IIIC	169 (72.2)	28 (57.1)	13 (81.3)	16 (59.3)	
IV	65 (27.8)	21 (42.9)	3 (18.7)	11 (40.7)	
Histology, *n* (%)					NS
Serous	226 (96.6)	46 (93.9)	14 (87.5)	27 (100.0)	
Non-serous	8 (3.4)	3 (6.1)	2 (12.5)	0 (0.0)	
Randomization: PlasmaJet, *n* (%)	119 (50.9)	12 (24.5)	8 (50.0)	N/A	0.002
Peritoneal carcinomatosis on CT, n (%)	159 (67.9)	34 (69.4)	12 (75.0)	19 (70.4)	0.940
Presence of ascites, n (%)	60 (25.6)	19 (38.8)	11 (68.8)	23 (85.2)	<0.001
Median ascites volume (IQR), ml	100 (350)	250 (400)	300 (450)	250 (400)	0.578
Presence of peritoneal carcinomatosis, *n* (%)	65 (27.8)	34 (69.4)	12 (75.0)	24 (88.9)	<0.001
Primary CRS					
Median preoperative CA-125 (IQR), kU/L	297.4 (602.3)	171.0 (388.2)	185.9 (1828.6)	N/A	0.868
Interval CRS					
Median preoperative CA-125 (IQR), kU/L	67.0 (178.0)	77.5 (166.8)	252.5 (532.5)	81.0 (209.0)	0.026
Median percentage of CA-125 reduction after NACT (IQR), %	91.1 (21.8)	89.9 (13.8)	78.0 (44.0)	88.6 (40.2)	0.388

BMI = body mass index, CA-125 = cancer antigen 125, CRS = cytoreductive surgery, FIGO = international federation of gynecology and obstetrics, IQR = interquartile range, N/A = not applicable, NS = non-significant, WHO = world health organization.

Primary Cytoreductive Surgery and CA-125 Level

A total of 45 patients (13.8%) underwent primary CRS. The median preoperative level of CA-125 was 297.4 kU/L in patients with complete CRS, 171.0 kU/L in patients with optimal CRS, and 185.9 kU/L in patients with suboptimal CRS ($p = 0.868$). All four patients with CA-125 level ≤ 35 kU/L at time of primary cytoreductive surgery had a complete cytoreduction. However, the level of preoperative CA-125 did not show an association with surgical outcome in primary CRS (Supporting information Supplementary Table S4).

Interval Cytoreductive Surgery and CA-125 Level

A total of 281 patients (86.2%) underwent interval CRS. Among these patients, the median preoperative CA-125 was 67.0 kU/L in those with a complete CRS, 77.5 kU/L in those with an optimal CRS, and 252.5 kU/L in those with a suboptimal CRS ($p = 0.026$). The median percentage of CA-125 reduction after NACT was 91.1% in the complete CRS group, 89.9% in the optimal CRS group, 78.0% in the suboptimal CRS group, and 88.6% in the unresectable disease group ($p = 0.388$).

Reduction of CA-125 Level after NACT

Supporting information in Supplementary Table S5 demonstrates factors associated with the normalization of CA-125 level after 3 cycles of NACT. In 85 patients (30.8%) who received NACT, the levels of CA-125 decreased to less than 35 kU/L. Having ascites and/or peritoneal carcinomatosis significantly decreased the chance of having a CA-125 reduction to normal level, (12.9% vs. 36.6%; OR 0.25, 95%CI 0.13–0.50, $p < 0.001$)) and (23.5% vs. 48.7%; OR 0.31, 95%CI 0.18–0.55, $p < 0.001$)) respectively. When using a 95% decrease in CA-125 after NACT [18], no significant factors were found (OR 1.28, 95%CI 0.71–2.31, $p = 0.42$). In 30% of the patients, the level of CA-125 had been reduced > 95% between diagnosis and preoperative interval CRS (Supporting information Supplementary Table S6).

Multivariable Analysis

Table 3 shows the univariable and multivariable analysis of factors predicting a complete interval CRS. Preoperative CA-125 levels ≤ 35 kU/L before interval CRS significantly predicted complete CRS (OR 2.79, 95%CI 1.44–5.41, $p = 0.002$). Furthermore, perioperative absence of ascites and peritoneal carcinomatosis both significantly predicted complete CRS in univariable analysis ($p < 0.001$). In multivariable analysis, patients with normalized level of CA-125 had higher odds of complete CRS than patients with elevated level of CA-125 (OR 1.74, 95%CI 0.74–4.09, $p = 0.207$). The absence of ascites ($p < 0.001$) and peritoneal carcinomatosis ($p < 0.001$) independently predicted complete CRS. Other significant independent

predictors were FIGO stage IIIB/IIIC ($p = 0.002$), a serious histology ($p = 0.013$) and the additional use of the PlasmaJet during surgery ($p = 0.026$).

Table 3 Univariable and multivariable analysis of factors predicting complete interval CRS

Factor	Univariable		Multivariable	
	OR [95%CI]	*P*-value	OR [95%CI]	*P*-value
AGE (IQR),	0.99 [0.97–1.01]	0.417	1.00 [0.96–1.03]	0.768
BMI (IQR),	1.03 [0.98–1.09]	0.226	1.07 [0.99–1.16]	0.092
WHO performance status				
0 (ref)				
1	0.71 [0.42–1.22]	0.214	1.10 [0.53–2.30]	0.800
≥2	0.41 [0.17–0.98]	0.044	0.54 [0.16–1.80]	0.318
FIGO stage,				
IIIB/IIIC (ref)				
IV	0.63 [0.38–1.04]	0.072	0.29 [0.14–0.63]	0.002
Histology				
Serous (ref)				
Non-serous	0.62 [0.20–1.93]	0.407	0.12 [0.02–0.64]	0.013
Randomization: PlasmaJet	1.47 [0.90–2.40]	0.121	2.26 [1.10–4.61]	0.026
Presence of peritoneal carcinomatosis on CT,	0.88 [0.52–1.49]	0.636	1.05 [0.49–2.27]	0.893
Presence of ascites	0.25 [0.15–0.42]	<0.001	0.26 [0.13–0.55]	<0.001
Presence of peritoneal carcinomatosis	0.11 [0.06–0.19]	<0.001	0.10 [0.05–0.23]	<0.001
Median preoperative CA-125	1.00 [1.00–1.00]	0.990	1.00 [1.00–1.00]	0.628
Preoperative CA-125 ≤ 35 kU/L	2.79 [1.44–5.41]	0.002	1.74 [0.74–4.09]	0.207

CA-125 = Cancer Antigen 125, CI = confidence interval, CRS = cytoreductive surgery, IQR = interquartile range, OR = odds ratio, REF = reference.

ROC Analysis

ROC curves were created with preoperative CA-125 level < 35 kU/L, FIGO staging, histology, perioperative presence of ascites and peritoneal carcinomatosis, and with the use of PlasmaJet. The area under the curve (AUC) was 0.876 for primary CRS. After applying cross-validation, the mean AUC was 0.801 (Supplementary Figure S1). For interval CRS, the overall AUC was 0.837. After applying cross-validation, the mean AUC was 0.798 (Supplementary Figure S2).

Discussion

The results of our systematic review indicated a significant relation between lower preoperative level of CA-125 and complete CRS in patients who underwent an interval CRS(8,18,19,21,22,24,26,27). Studies of patients who underwent a primary CRS demonstrated an inconsistent correlation between the CA-215 level and surgical outcome(15–17,25,27). It must be noted, however, that definitions of the normal value of CA-125 and optimal cut-off values of CA-125 reduction varied among studies in the literature, which implies that the effect of CA-125 reduction rate after NACT on the surgical outcome could not be directly compared between the existing studies.

In our prospective cohort study of 326 patients, normalized values of CA-125 in patients receiving interval CRS showed a significant relation with complete CRS in univariable analysis. Complete CRS was achieved in 84.7% (*n* = 72) of patients CA-125 levels ≤ 35 kU/L, whereas this was only 66.5% (*n* = 127) of patients with CA-125 levels > 35 kU/L. However, only the absence of ascites and peritoneal carcinomatosis during surgery, FIGO stage IIIB/IIIC and serious histology were the significant independent predictors of complete interval CRS as presented in multivariable analysis. Furthermore, use of the PlasmaJet surgical device was an independent predictor of complete CRS, which is in line with the results of the PlaComOv study(12,28).

The studies included in our systematic review did not report the effect of ascites or peritoneal carcinomatosis(5–12,14–23,25,27,29–36), and lacked a multivariable analysis(19,24–27). Fortunately, the risk of bias was generally low among most studies. Our finding was in contrast to that of Gupta et al., in that we did not find a significant relation between >95% decrease in CA-125 level after NACT and complete CRS(18). Surprisingly, in patients who underwent primary CRS, preoperative CA-125 level did not appear as a significant predictor for complete cytoreduction, although 73.3% of the patients underwent complete cytoreduction and all patients with normal preoperative CA-125 levels had a complete CRS. This is probably because the population of patients with primary CRS was only 14% of our cohort. However, we expect interval CRS to be performed more frequently in the future, as studies have shown that overall survival is similar to that of primary CRS and there tends to be a decreased risk of postoperative complications(13). Therefore, we still decided to include this patient group in our research.

The results of our clinical study and some studies in the systematic review are remarkably inconsistent, likely due to selection bias or missing data due to the

retrospective nature of most of the included studies. It is quite possible that other studies that have determined the value of CA-125 on surgical outcome, but which have not shown significant outcomes, have not been published. Furthermore, in our clinical study, we have focused on a CA-125 cut-off value of 35 kU/L. This value is generally accepted as cut-off point(14). We additionally applied cut-off values suggested in our systematic review to our study population, but these were found to be non-significant. Moreover, we found no supporting evidence in the literature that the proposed cut-off values are valuable.

We performed both a carefully constructed systematic review through multiple databases and a clinical investigation. Conducting a meta-analysis was not possible since we could not obtain raw data from each study. The clinical data of our cohort have been prospectively collected for the PlaComOv-study. All variables in the univariable analysis were selected for the multivariable logistic regression to identify all independent predictors of complete CRS. The use of the PlasmaJet surgical device, which has been reported to increase the rate of complete CRS (28), was evenly distributed among all groups.

Nevertheless, some limitations need to be addressed. First, CA-125 levels of patients who were not eligible for interval CRS were lacking because of the progressive disease during chemotherapy or because of health deterioration. Second, ROC analysis implied that the combination of significant independent predictors and CA-125 is an acceptable prediction model. However, since CA-125 ≤ 35 kU/L was not a significant predictor in multivariable analysis, we do not know the added value of this variable in the prediction model. Third, the participating hospitals used different methods to measure the level of CA-125 in each. The reliability of CA-125 results depends on precision and trueness, where trueness is of particular importance for the comparability of CA-125 results between laboratories and hospitals. In general, immuno assays, including tumor marker assays, are poorly standardized resulting in a marginal trueness. This is caused in part by differences in antibody-antigen binding characteristics which can differ significantly per used method. During our analyses, we compared the different methods of CA-125 determination. This made no difference to the described results. Therefore, we decided to include all patients in the study to be able to analyze a larger group. It is striking that the articles included in the systematic review do not provide a description of the way in which the CA-125 has been determined in their method. Therefore, we advise researchers considering follow-up research to use standardized tumor marker assays and to describe this clearly in their methods section

Conclusions

In conclusion, the value of CA-125 as a preoperative predicting factor for surgical outcome of primary CRS in advanced stage EOC is inconclusive. Still, the normalization of CA-125 after NACT (≤35 kU/L) was significantly associated with a higher percentage of complete CRS in patients who underwent interval CRS, in line with the literature. Nevertheless, CA-125 level for surgical outcome prediction should be used with caution. Preoperative CA-125 level should not be used as an isolated predictive parameter.

Supplementary

Table S1 The searching strings

Database	
Embase.com	('ovary carcinoma'/exp OR ('ovary tumor'/de AND ('carcinoma'/de OR 'adenocarcinoma'/de)) OR (((epithelial* OR mucinous* OR serous* OR endometrioid*) NEAR/6 (ovar*) NEAR/6 (carcinoma* OR adenocarcinoma*))):ab,ti,kw) AND ('cytoreductive surgery'/de OR (cytoreduc* OR debulking*):ab,ti,kw) AND ('CA 125 antigen'/de OR 'cancer antigen 125'/de OR 'carcinoembryonic antigen'/de OR (ca-125 OR ca125 OR cancer-antigen-125 OR cancer-antigen125 OR carcinoembryonic-antigen* OR CEA OR Mucin-16*):ab,ti,kw) AND (((advanced OR 2b OR 2c OR 3 OR 3a OR 3b OR 3c OR 4 OR iib OR iic OR iii OR iiia OR iiib OR iiic OR iv OR 2-b OR 2-c OR 3-a OR 3-b OR 3-c OR ii-b OR ii-c OR iii-a OR iii-b OR iii-c) NEAR/3 (stag*))):ab,ti,kw NOT [conference abstract]/lim
Medline Ovid	(Carcinoma, Ovarian Epithelial/ OR (((epithelial* OR mucinous* OR serous* OR endometrioid*) ADJ6 (ovar*) ADJ6 (carcinoma* OR adenocarcinoma*))).ab,ti,kf.) AND (Cytoreduction Surgical Procedures/ OR (cytoreduc* OR debulking*).ab,ti,kf.) AND (CA-125 Antigen/ OR (ca-125 OR ca125 OR cancer-antigen-125 OR cancer-antigen125 OR carcinoembryonic-antigen* OR CEA OR Mucin-16*).ab,ti,kf.) AND (((advanced OR 2b OR 2c OR 3 OR 3a OR 3b OR 3c OR 4 OR iib OR iic OR iii OR iiia OR iiib OR iiic OR iv OR 2-b OR 2-c OR 3-a OR 3-b OR 3-c OR ii-b OR ii-c OR iii-a OR iii-b OR iii-c) ADJ3 (stag*))).ab,ti,kf. NOT (letter* OR news OR comment* OR editorial* OR congres* OR abstract* OR book* OR chapter* OR dissertation abstract*).pt.
Web of science	TS=(((((epithelial* OR mucinous* OR serous* OR endometrioid*) NEAR/5 (ovar*) NEAR/5 (carcinoma* OR adenocarcinoma*)))) AND ((cytoreduc* OR debulking*)) AND ((ca-125 OR ca125 OR cancer-antigen-125 OR cancer-antigen125 OR carcinoembryonic-antigen* OR CEA OR Mucin-16*)) AND (((advanced OR 2b OR 2c OR 3 OR 3a OR 3b OR 3c OR 4 OR iib OR iic OR iii OR iiia OR iiib OR iiic OR iv OR 2-b OR 2-c OR 3-a OR 3-b OR 3-c OR ii-b OR ii-c OR iii-a OR iii-b OR iii-c) NEAR/2 (stag*))))
Cochrane Central	((((epithelial* OR mucinous* OR serous* OR endometrioid*) NEAR/6 (ovar*) NEAR/6 (carcinoma* OR adenocarcinoma*))):ab,ti,kw) AND ((cytoreduc* OR debulking*):ab,ti,kw) AND ((ca NEXT 125 OR ca125 OR cancer NEXT antigen NEXT 125 OR cancer NEXT antigen125 OR carcinoembryonic NEXT antigen* OR CEA OR Mucin NEXT 16*):ab,ti,kw) AND (((advanced OR 2b OR 2c OR 3 OR 3a OR 3b OR 3c OR 4 OR iib OR iic OR iii OR iiia OR iiib OR iiic OR iv OR 2 NEXT b OR 2 NEXT c OR 3 NEXT a OR 3 NEXT b OR 3 NEXT c OR ii NEXT b OR ii NEXT c OR iii NEXT a OR iii NEXT b OR iii NEXT c) NEAR/3 (stag*))):ab,ti,kw
Google Scholar	"epithelial ovarian carcinoma|adenocarcinoma" cytoreductive|debulking "ca 125"|ca125|"carcinoembryonic antigen"|CEA "advanced|2b|2c|3a|3b|3c|4 stage|staging"

Table S2 Detailed methods of each platform used to analyze CA-125

	Roche	Abbott	Beckman Coulter	Siemens	Thermo Fischer
Platform	E601, E801	Architect i2000	Dxl 800	Centaur	Kryptor Compact
Method	ECLIA	MEIA	CLEIA	CLEIA	TRACE
Signal technology	Ruthenium	AP	AP	Acrid-Fluor	Cryp-Acc

ECLIA = Electro-Chemiluminescent Immuno Assay; MEIA = Microparticle Enzyme Immuno Assay; CLEIA = Chemiluminiscent Enzyme Immuno Assay; AP = Alkaline Phosphatase; Acrid-Fluor = Acrdinium-Fluorescein; TRACE = Time Resolved Amplified Cryptate Emission; Cryp-Acc = Cryptate-Acc.

Table S3 Outcome of quality assessment

Green = low risk of bias; Yellow = moderate risk of bias

Table S4 Univariable analysis of factors predicting normal levels of preoperative CA-125 before primary CRS

	Preoperative CA-125 ≤35 kU/L (n=4, 9.1%)	Preoperative CA-125 >35 kU/L (n=40, 90.9%)	Unadjusted OR [95%CI]	*P*-value
Median AGE (IQR), years	66 (22)	59 (17)	1.07 [0.96-1.20]	0.208
Median BMI (IQR), kg/m^2	22.2 (7.5)	24.8 (6.7)	0.89 [0.69-1.15]	0.373
WHO performance, n (%)				
0 (ref)	4 (100.0)	25 (62.5)	N/A*	N/A*
1	0 (0.0)	11 (27.5)	N/A*	N/A*
≥2	0 (0.0)	3 (7.5)		
FIGO stage, n (%)				
IIIB/IIIC (ref)	4 (100.0)	37 (92.5)	N/A*	N/A*
IV	0 (0.0)	3 (7.5)		
Histology, n (%)				
Serous (ref)	3 (75.0)	39 (97.5)	13.00 [0.64-263.82]	0.095
Non-serous	1 (25.0)	1 (2.5)		
Presence of peritoneal carcinomatosis on CT, n (%)	2 (50.0)	22 (55.0)	0.82 [0.11-6.40]	0.848
Presence of ascites, n (%)	1 (25.0)	30 (75.0)	0.11 [0.01-1.19]	0.070
Median ascites (IQR), ml	20 (-)	400 (700)	0.94 [0.76-1.17]	0.570
Presence of peritoneal carcinomatosis, n (%)	1 (25.0)	18 (45.0)	0.41 [0.04-4.26]	0.453
Surgical outcome, n (%)				
Complete CRS	4 (100.0)	28 (70.0)	N/A*	N/A*
Non-complete CRS (ref)	0 (0.0)	12 (30.0)		

CA-125 = Cancer Antigen 125, CI = confidence interval, CRS = cytoreductive surgery, IQR = interquartile range, N/A = not applicable, OR= odds ratio, REF = reference

* = odds-ratio or *P*-value could not be calculated

Table S5 Univariable analysis of factors predicting normalized preoperative CA-125 level before interval CRS

	Preoperative CA-125 ≤35 kU/L (n=85, 30.8%)	Preoperative CA-125 >35 kU/L (n=191, 69.2%)	Unadjusted OR [95%CI]	*P*-value
Median AGE (IQR), years	68 (14)	67 (12)	1.00 [0.98-1.03]	0.884
Median BMI (IQR), kg/m^2	24.6 (5.8)	24.5 (6.0)	1.00 [0.95-1.06]	0.905
WHO performance, n (%)				
0 (ref)	48 (60.0)	93 (52.0)	0.84 [0.48-1.466]	0.536
1	29 (36.3)	67 (37.4)	0.31 [0.09-1.09]	0.067
≥2	3 (3.8)	19 (10.6)		
FIGO stage, n (%)				

Table S5 *(Continued)*

	Preoperative CA-125 ≤35 kU/L (n=85, 30.8%)	Preoperative CA-125 >35 kU/L (n=191, 69.2%)	Unadjusted OR [95%CI]	*P*-value
IIIB/IIIC (ref)	56 (65.9)	124 (64.9)	0.96 [0.56-1.64]	0.877
IV	29 (34.1)	67 (35.1)		
Histology, n (%)				
Serous (ref)	84 (98.8)	183 (95.8)	0.27 [0.03-2.21]	0.224
Non-serous	1 (1.2)	8 (4.2)		
Presence of ascites/peritoneal carcinomatosis on CT, n (%)	57 (67.1)	140 (73.3)	0.74 [0.43-1.29]	0.291
Presence of ascites, n (%)	11 (12.9)	70 (36.6)	0.25 [0.13-0.50]	<0.001
Median ascites (IQR), ml	100 (185)	200 (300)	1.00 [0.99-1.00]	0.228
Presence of peritoneal carcinomatosis, n (%)	20 (23.5)	93 (48.7)	0.31 [0.18-0.55]	<0.001
Surgical outcome, n (%)				
Complete CRS	72 (84.7)	127 (66.5)	2.79 [1.44-5.41]	0.002
Non-complete CRS (ref)	13 (15.3)	64 (33.5)		

CA-125 = Cancer Antigen 125, CI = confidence interval, CRS = cytoreductive surgery, IQR = interquartile range, OR= odds ratio, REF = reference

Table S6 Univariable analysis of factors predicting >95% reduction in CA-125 after NAC

	>95% decrease in preoperative CA-125 (n=81, 29.6%)	≤95% decrease in preoperative CA-125 (n=193, 70.4%)	Unadjusted OR [95%CI]	*P*-value
Median AGE (IQR), years	66 (15)	68 (12)	0.98 [0.96-1.01]	0.251
Median BMI (IQR), kg/m^2	24.5 (5.3)	24.6 (6.3)	0.97 [0.91-1.02]	0.228
WHO performance, n (%)				
0 (ref)	50 (61.7)	89 (46.1)	0.56 [0.31-1.00]	0.052
1	23 (28.4)	73 (37.8)	0.40 [0.13-1.23]	0.110
≥2	4 (4.9)	18 (9.3)		
FIGO stage, n (%)				
IIIB/IIIC (ref)	50 (61.7)	128 (66.3)	1.22 [0.71-2.09]	0.467
IV	31 (38.3)	65 (33.7)		
Histology, n (%)				
Serous (ref)	79 (97.5)	186 (96.4)	0.67 [0.14-3.31]	0.626
Non-serous	2 (2.5)	7 (3.6)		

Table S6 *(Continued)*

	>95% decrease in preoperative CA-125 (n=81, 29.6%)	≤95% decrease in preoperative CA-125 (n=193, 70.4%)	Unadjusted OR [95%CI]	*P*-value
Presence of peritoneal carcinomatosis on CT, n (%)	57 (70.4)	138 (71.5)	0.95 [0.54-1.67]	0.850
Presence of ascites, n (%)	15 (18.5)	66 (34.2)	0.44 [0.23-0.83]	0.011
Median ascites (IQR), ml	200 (200)	200 (300)	1.00 [1.00-1.001]	0.459
Presence of peritoneal carcinomatosis, n (%)	30 (37.0)	83 (43.0)	0.77 [0.45-1.32]	0.347
Surgical outcome, n (%)				
Complete CRS	61 (75.3)	136 (70.5)	1.28 [0.71-2.31]	0.416
Non-complete CRS (ref)	20 (24.7)	57 (29.5)		

CA-125 = Cancer Antigen 125, CI = confidence interval, CRS = cytoreductive surgery, IQR = interquartile range, OR= odds ratio, REF = reference

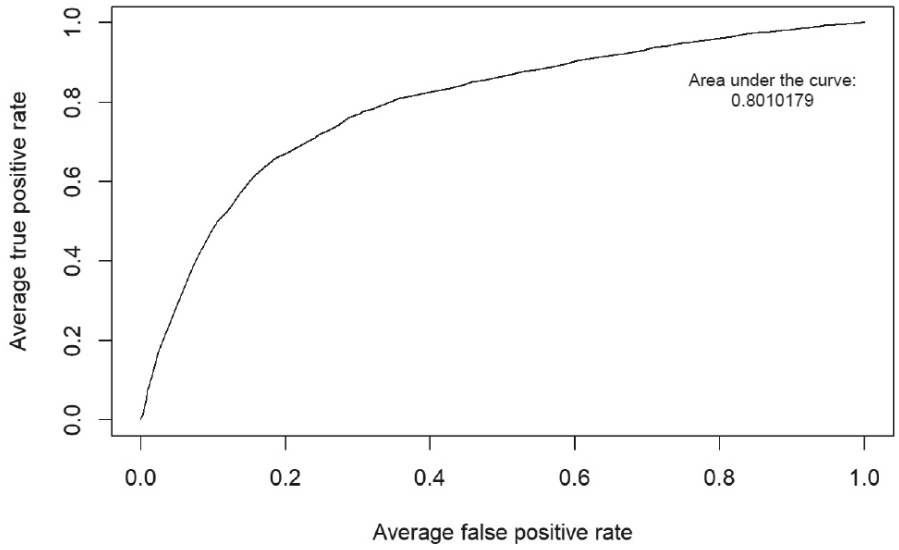

Figure S1 Cross-validated ROC-curve for primary CRS

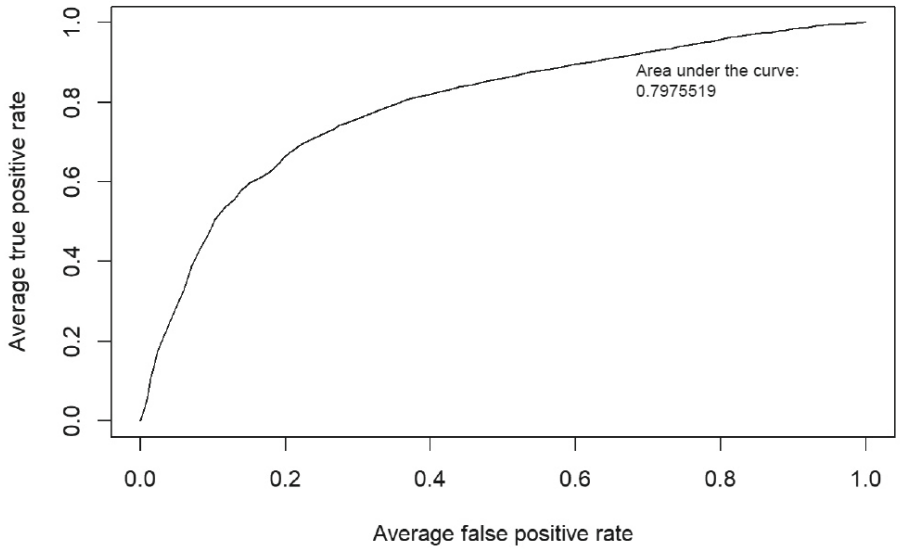

Figure S2 Cross-validated ROC-curve for interval CRS

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9

Indispensable Radiological Parameters associated with Surgical outcome in Advanced Stage Ovarian Cancer Patients: A Systematic Review

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Submitted

Abstract

Background

Preoperative computed tomography (CT) scans are used to identify prognostic features associated with the inability to achieve a complete primary or interval cytoreductive surgery for primary advanced stage epithelial ovarian cancer.

Methods

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Studies reporting CT imaging features for advanced epithelial ovarian cancer in relation to complete cytoreductive surgery were included from databases inception to December 2022. Identified reports were critically appraised according to the Newcastle-Ottowa Quality Assessment Scale.

Results

Six studies were included in this review (1,016 patients). The presence of ascites was examined in all studies. There were significant associations between an incomplete cytoreductive surgery and ascites and tumor deposits at the omentum in four and three studies, respectively, followed by tumor deposits at the peritoneum and diaphragm in two studies. There was a heterogeneity in the descriptions of the reported CT features, therefore a meta-analysis was impossible.

Conclusions

The most commonly reported features associated with the inability to a complete cytoreductive surgery were ascites and tumor deposits at the omentum, peritoneum and diaphragm.

Introduction

Computed tomography (CT) is the most commonly used imaging modality for preoperative staging of epithelial ovarian cancer(1, 2). Worldwide, approximately 240,000 women are diagnosed with ovarian cancer each year, and 80% of them have advanced stages of the disease(3). The treatment consists of a combination of cytoreductive surgery and chemotherapy(4,5). The presence of certain CT features in advanced stage epithelial ovarian cancer indicates the inability to perform a complete primary cytoreductive surgery(1,6-9), and alternatively neoadjuvant chemotherapy (NACT) is started. After three courses of NACT a radiological assessment on a follow-up CT scan is performed(4,10,11).

In patients with advanced stage epithelial ovarian cancer, residual disease after cytoreductive surgery is the most important prognostic factor(12-14). A complete cytoreductive surgery with no residual disease results in the best overall survival rate. In several studies, CT features were shown to be useful to identify patients who can undergo optimal cytoreductive surgery (residual disease <1 cm). Nowadays, guidelines recommend to aim for a complete cytoreductive surgery and studies about an optimal cytoreductive surgery are no longer appropriate(8,15).

Earlier studies assumed the benefit of primary cytoreductive surgery and focus only on the possibility of primary cytoreductive surgery(1). As an interval cytoreductive surgery has been recognized as a non-inferior procedure for survival in FIGO stage IIIC-IV epithelial ovarian cancer, interval cytoreductive surgery has become an alternative to primary cytoreductive surgery(4).

The purpose of this study was to identify CT features associated with the inability to complete cytoreductive surgery for primary and interval cytoreductive surgery based on the literature.

Methods

Data sources and searches

A systematic review was conducted and the search was performed from inception to December 2022 in Embase, Medline, Web-of-Science, Cochrane and Google scholar library. The search strategy included the following keywords: ‘computed assisted tomography’, ‘interpretation’, ‘predictive value’, ‘surgical outcome’, ‘cytoreductive surgery’, and ‘ovary cancer’. The search strategy can be found in Table S1. No study

registries were searched, but Cochrane Central retrieves the contents of ClinicalTrials.gov and the World Health Organization`s International Clinical trials Registry Platform. No authors or subject experts were contacted and unindexed journals in the field were not consulted. The searches in Embase, Medline, Web-of-Science were limited to exclude conference papers and animal only articles. The study protocol was registered in INPLASY (registration number INPLASY 202310059). In accordance with the journal's guidelines, we will provide our data for independent analysis by a selected team by the Editorial Team for the purposes of additional data analysis or for the reproducibility of this study in other centers if such is requested.

Study identification and selection

Studies published in English with adequate information, in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology statement(16), were included in the review. Four authors (GN, MK, AB and DP) independently screened the titles and abstracts of the retrieved electronic citations. Next, they retrieved the full text documents and evaluated potentially eligible articles. All selected articles were read and evaluated by GN, MK, AB, DP. Any disagreements between authors were resolved through discussion and arbitration by a fifth author (HD). The reference lists of retrieved articles were searched for missed relevant studies. We included retrospective and prospective cohort studies as well as clinical trials that report CT-based radiological factors associated with complete cytoreduction in primary epithelial ovarian cancer. Studies published as conference abstracts, narrative review, editorials, letters and short communications were excluded. All significant CT features found in literature were compared with CT features recommended by the guidelines of the European Society of Urogenital Radiology to be part of the CT report for preoperative staging of ovarian cancer(1). This structured report should include the description of size, morphology and uni- or bilaterality of the ovarian mass with a statement of whether the mass demonstrates features of malignancy, uterine endometrial thickening, bladder and bowel invasion or pelvic side-wall invasion, evidence of complications such as bowel obstruction, hydronephrosis or venous obstruction/thrombosis, ascites in the pelvis or upper abdomen and amount of ascites, omental metastases, site and size of other peritoneal/serosal depositions outside the pelvis, involvement of the small bowel mesentery including contraction or tethering of bowel loop, supracolic sites of disease including the gastrohepatic, gastrosplenic and splenocolic ligaments, site of lymph nodes with a short-axis diameter of >1 cm, or suspicious clusters of smaller lymph nodes, cardiophrenic lymph nodes with a short-axis diameter of >5 mm, surface, subcapsular or parenchymal liver and spleen metastases, invasion of the abdominal wall, presence and size of pleural effusion

and stage according to the International Federation of Gynecology and Obstetrics (FIGO) classification(1).

Data extraction and quality assessment

We extracted the following study characteristics: name of first author, year of publication, country, study design, inclusion period, sample size, FIGO stage, surgery, number of evaluated CT features. Primary outcomes were CT features associated with the inability for complete cytoreductive surgery during a primary or interval cytoreductive surgery. The quality and the risk of bias in the observational studies include in our study was assessed independently by MK and DP according to The Newcastle-Ottawa Quality Assessment Scale(17).

Results

General characteristics

The primary search retrieved 3758 articles. After removing duplicates, 3299 records were screened on title. Out of 111 abstracts, 11 full text articles were retrieved for a comprehensive review. Finally, six articles were included in the review based on our inclusion and exclusion criteria (Figure 1).

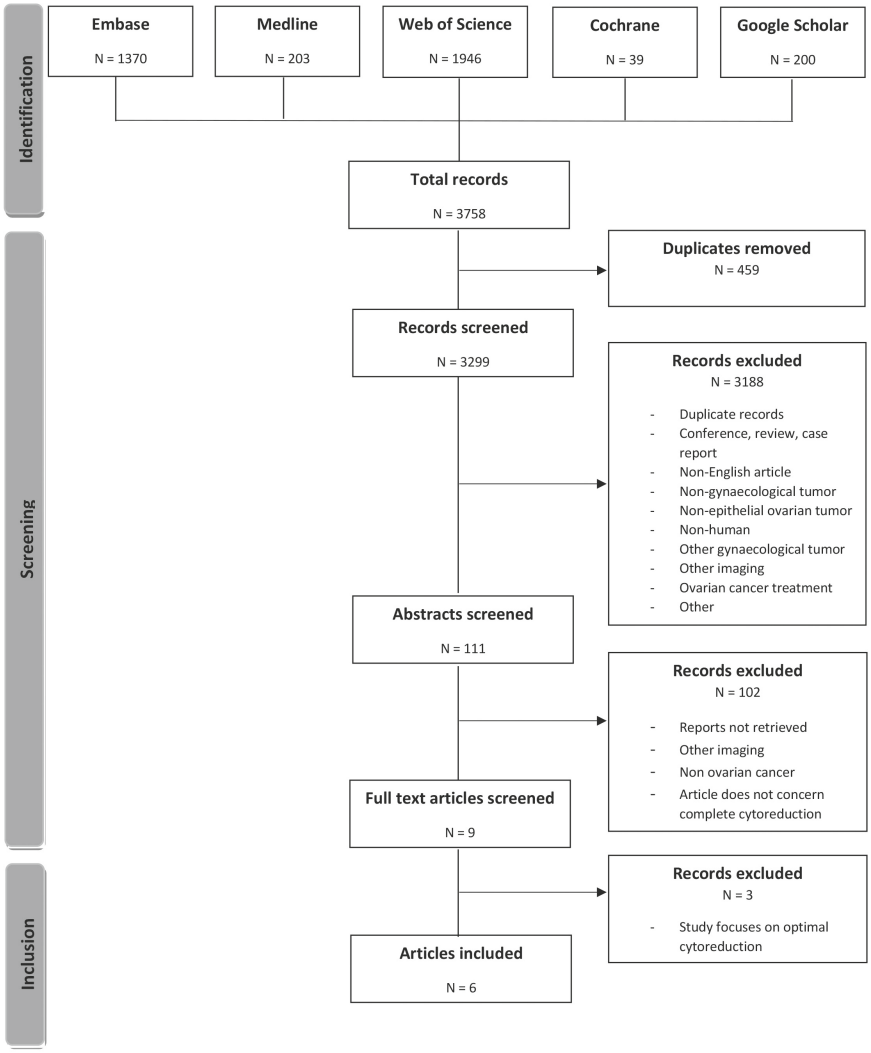

Figure 1 Flowchart included articles

Table 1 demonstrates the characteristics of the included studies. Three articles were retrospective studies, three were prospective studies. In total, 1,016 patients were included in the studies and underwent cytoreductive surgery. Most studies included patients with FIGO stage III-IV, one study included patients with FIGO stage I-IV(18). Table 2 demonstrates the characteristics of the study population and the procedure of the CT scan.

Table 1 Characteristics of included studies

Author	Year of publication	Country	Study design	Surgery	Inclusion period	Sample size	FIGO stage	no. of evaluate CT-features	Outcome
Chesnais	2017	France	Retrospective cohort study	PDS	2008 - 2013	247	I - IV	9	Extent of residual disease
Fuso	2018	Italy	Retrospective cohort study	PDS/ IDS	2011 - 2017	61	IIIC - IV	17	Extent of residual disease
Janco	2015	USA	Prospective cohort study	PDS	2003 - 2011	279	IIIC - IV	9	Extent of residual disease
Rema	2018	India	Prospective observational study	IDS	2016 - 2017	51	IIIC	13	Extent of residual disease
Stachs	2020	Germany	Retrospective cohort study	PDS	2010 - 2014	28 (complete CRS)	IIC - IV	11	Extent of Macroscopic residual tumor and residual tumor 0-1 and >1 cm
Suidan	2017	USA	Prospective trial	PDS	2001 - 2012	350	III - IV	18	Extent of residual disease

CRS= cytoreductive surgery; IDS= interval CRS; PDS= primary CRS

Table 2 Characteristics of the study population and the procedure of the CT scan

Author	Inclusion criteria	Exclusion criteria	mean age (years)	mean BMI	mean or median CA-125 level	CT scan	reviewer CT scan
Chesnais	epithelial fallopian tube, peritoneal or ovarian cancer	non-epithelial or bordeline tumors, IDS	62.5	23.8 kg/m2	914 U/mL	not reported	2 radiologist, blinded for surgical outcome
Fuso	epithelial, fallopian tube or peritoneal cancer	FIGO stage I-II ovarian cancer, CT scan not available for re-evaluation, recurrence ovarian cancer, surgical radicality not traceable	62.5	not reported	not reported	64-slice CT, administration of oral and iv contrast	not reported
Janco	PDS and pre-operative CT scan 90 days prior to surgery	Recurrence ovarian cancer, IDS	64.4	28,7 kg/m2	Complete CRS: 518 U/mL	8 to 128 multi-detector rows, section thickness of 3-5mm. CT exams were reviewed digitally on axial and coronal planes using QREADS	1 radiologist
Rema	IDS	Age >75 years, previous suboptimal surgeries, borderline ovarian tumor	52	not reported	not reported	16-slice MDCT, administration of oral and iv contrast	1 radiologist, expert in the field
Stachs	epithelial, fallopian tube or peritoneal cancer, PDS	borderline ovarian tumor	63	28 kg/m2	not reported	not reported	1 radiologist, expert in the field, blinded for surgical outcome
Suidan	Age >18 years, epithelial, fallopian tube or peritoneal cancer	IDS, significant delay in surgery after CT scan or serum CA-125, CT scan was not of sufficient quality	61	not reported	860 U/mL	contiguous slices were acquired, slice thickness 5-7.5mm. Administration of oral and iv contrast	1 radiologist, expert in the field

CRS= cytoreductive surgery; IDS= interval CRS; PDS= primary CRS

Quality assessment

Table 3 demonstrates the results of the quality assessment according to the Newcastle-Ottowa Quality Assessment Scale. All included studies were found to be of moderate to high quality.

Table 3 Results of the Newcastle-Ottowa Quality Assessment Scale

	Newcastle-Ottowa Quality Assessment Scale		
	Selection Maximum score: • • • •	Comparability Maximum score: • •	Outcome Maximum score: • • •
Chesnais et al (2017)	• • •	•	• • •
Fuso et al (2018)	• • •	• •	• •
Janco et al (2015)	• • •	•	• • •
Stachs et al (2019)	• • •	• •	• • •
Suidan et al (2017)	• • •	•	• • •
Rema et al (2018)	• • •	•	• • •

Data analysis

Table 4 demonstrates the radiological features in the articles which were evaluated. The only parameter investigated in all the articles was the presence of ascites. In four papers, ascites was significantly associated with the inability to perform cytoreductive surgery. Omental lesions were reported as a significant predictor for residual tumor after cytoreductive surgery in three of the six reviewed studies(15,19,20) peritoneal disease was reported as a significant predictor in two of four reviewed studies(15,19) and diaphragmatic lesions(15,20) were reported as a significant predictor in two of five reviewed studies. The following parameters were associated with residual tumor after cytoreductive surgery in one of the reviewed studies: peritoneal implants(15), tumor invading pelvic side wall/ hydroureter(21), diffuse small bowel adhesions / thickening(22), involvement of mesocolon(15), lesions in splenic hilum/ ligaments(22), gastrohepatic ligament/ porta hepatis lesion(22), gallbladder fossa/ liver intersegmental fissure lesion(22), lesser sac(22), retroperitoneal lymph nodes above the renal hilu(22) and lesions in the root of the superior mesenteric artery(22). Fuso et al. evaluated different radiologic features according to a point scale(18). The scale includes the following scores: 0.5, 1 and 2. A score of 1 point was assigned when a variable had a specificity of ≥75%, positive predictive value ≥50% and negative predictive value ≥50%. In addition, a score of 2 points is given when accuracy is greater than 60%. The radiologic features assigned with 2 points are presented as X2 in Table 4.

Table 4 Radiologic parameters incorporated in the prediction models of the studies

CT Parameters	Chesnais (2017)	Fuso (2018)	Janco (2015)	Stachs (2019)	Suidan (2017)	Rema (2018)
Peritoneal thickening	-	**X²**	**X***	**X***	-	NS
Peritoneal implants	-	NS	-	**X***	-	NS
Presacral extraperitoneal disease	-	-	-	-	NS	-
Ascites	NS	**X²**	**X***	**X***	**X***	NS
Tumor invading anterior abdominal wall	-	-	-	-	NS	-
Tumor invading pelvic side wall / hydroureter		NS				**X***
Omental lesion	**X***	**X²**	**X***	**X***	NS	NS
Bowel invasion	-	-	NS	-	NS	-
Small intestine	NS	-	-	-	-	-
Colon	NS	**X²**	-	-	-	-
Sigmoid / rectum	-	**X²**	-	-	-	-
Diffuse small bowel adhesions / thickening	-	-	-	-	**X***	-
Involvement of small bowel mesentery	-	-	-	-	NS	NS
Involvement of large bowel mesentery	-	-	-	-	-	NS
Involvement of mesocolon	NS	NS	-	**X***	-	-
Metastases	NS	-	-	-	-	-
Diaphragm	**X***	**X²**	NS	**X***	-	NS
Pulmonary metastases	-	-	-	-	NS	-
Pleural metastases	-	-	-	-	NS	-
Pleural effusion	NS	NS	NS	NS	-	-
Liver lesion	-	-	NS	NS	NS	NS
Liver intraparenchymal lesion	-	**X²**	NS	NS	NS	-
Subscapular liver lesion	-	-	-	-	NS	-
Perihepatic lesion	-	-	-	-	NS	-
Spleen intraparenchymal lesion	-	NS	NS	-	NS	-
Lesion in splenic hilum / ligaments	-	NS	-	-	**X***	-
Gastrohepatic ligament / porta hepatis lesion	-	**X²**	-	-	**X***	-
Galbladder fossa / liver intersegmental fissure lesion	-	-	-	-	**X***	NS
Lesser sac	-	-	-	-	**X***	-
Lymphadenopathy	-	-	NS	-	-	-
Pathological enlargement of cardiophrenic lymph nodes	-	-	-	-	-	-
Abdominal / pelvic nodes	NS	-	-	-	-	-

Table 4 *(Continued)*

CT Parameters	Chesnais (2017)	Fuso (2018)	Janco (2015)	Stachs (2019)	Suidan (2017)	Rema (2018)
Mediastinic lymph nodes	-	NS	-	-	-	-
Retroperitoneal lymph nodes above the renal hilum	-	-	-	-	X*	-
Suprarenal lymph nodes	-	NS	-	NS	-	NS
Infrarenal lymph nodes	-	NS	-	NS	-	NS
Involvement inguinal canal	-	-	-	NS	-	NS
Extensive inguinal disease or involvement of inguinal lymph node	-	-	-	-	-	NS
Root of the superior mesenteric artery lesion	-	-	-	-	X*	-

NS: Variable used in prediction model but not significantly associated with the inability for a complete cytoreductive surgery

X*: Variable found to have a significant association with residual disease after performing cytoreductive surgery

-: Variable was not investigated in the study

X²: Variable was assigned two points by Fuso et al

Discussion

This systematic review identified diagnostic features in the literature on CT scans in preoperative staging associated with the inability to complete cytoreductive surgery for patients with advanced epithelial ovarian cancer. Six articles of moderate to high quality were included. The most common factor associated with residual tumor after cytoreductive surgery was ascites followed by omental and diaphragm lesions and peritoneal disease.

Guidelines for ovarian cancer staging and follow-up were defined by the female imaging subcommittee of the European Society of Urogenital Radiology based on the expert consensus of imaging protocols of 12 leading institutions and a critical review of the literature(1). According to the findings in literature and compared to all items in the guidelines of the European Society of Urogenital Radiology, the following items are indispensable in a structured CT report for predicting surgical outcome: Ascites; omental metastases, including the lesser sac; site of peritoneal thickening and implants outside the pelvis and on the diaphragm; involvement of the small bowel and roots of the mesenteric artery; lesions in the splenic hilum- gastrohepatic- and gastrosplenic ligament, hepatic portal vein, gallbladder fossa, liver; hydronephrosis; retroperitoneal lymph nodes above the renal hilum; invasion of the abdominal

wall; presence of pleural effusion and cardiophrenic lymph nodes with a short-axis diameter of >5mm.

The reviewed studies indicated under which circumstances the CT scan was performed. CT imaging with coverage of the base of the lungs to the inguinal region has been validated as an accurate imaging method in ovarian cancer and is regarded as the imaging technique of choice for preoperative staging. This was performed in all reviewed studies. The study of Janco et al. used a slice thickness of 3 to 5 mm(19). All other studies did not report the slice thickness in their manuscript or used a slice thickness of 5 to 7.5 mm(22) (Table 4). The guideline of the European Society of Urogenital Radiology recommends taking images up to a slice thickness of 3 to 5 mm at 3 to 4 mm intervals in transaxial, coronal and sagittal planes(1).

CT imaging demonstrated a moderate predictive value for complete cytoreduction(9, 23). Several studies tried to develop prediction models to predict outcome of surgery for advanced ovarian cancer. Rutten et al. described in a systematic review the lack of an externally validation with good predictive value for residual disease(9). One validation study of two radiological prediction models was found which demonstrated that most prediction models have limitations after external validation(24). The author stated that most prediction models will succeed or fail based on the underlying rates of surgical outcome used for the test cohort. When a model was tested in centers with different rates of surgical outcome, the model performed unlike.

It is difficult to correlate the findings of this review with clinical practice. For example, ascites can be easily removed but it correlates with the peritoneal spread of ovarian cancer which is more difficult to remove(20). Another example, an extensive omental involvement usually allows for a complete cytoreductive surgery. Other factors that will influence the surgical outcome in daily practice are medical condition, patient and surgeon factors(25). It is important to realize that is impossible to focus on a single CT feature to predict surgical outcome. When it would be possible to come to a multivariate model to predict surgical outcome, factors such as the patient's medical condition, patient's preference regarding the extent of surgery and surgical facilities should be taken into account as well.

This is the first study in which CT features were associated with complete cytoreductive surgery. Our study had several limitations. Firstly, the majority of the included studies were retrospective studies. The risk of recall bias, misclassification bias and selection bias cannot be excluded. The data of the reviewed manuscripts were diverse and complicated by a shift in time from accepting residual disease as a proper surgical

outcome (residual disease < 1cm), to achieve a complete cytoreductive surgery (no residual disease). Furthermore, different CT features used in the studies hinder the process of making a clear comparison between study outcomes. Additionally, not all CT features were analyzed for significance. Fuso et al. worked with an assignment of different points, dependent on the sensitivity, specificity, positive predictive value and negative predictive value(18). As a consequence of the above, a meta-analysis could not be carried out and the impact of each characteristic on residual disease could not be determined.

Implications for Practice and Future Research

This is the first systematic review about CT features associated with complete cytoreductive surgery. The following CT features have been associated with the inability to achieve a complete cytoreductive surgery: ascites and tumor deposits at the omentum, peritoneum and diaphragm. In daily practice, these CT features are often present in patients with advanced ovarian cancer. In spite of this, a complete cytoreductive surgery can be achieved regularly. The use of other techniques, such as magnetic resonance imaging, could provide better precision and should be explored(26).

Conclusions

In this systematic review, the most commonly reported features associated with the inability to complete cytoreductive surgery were ascites and tumor deposits at the omentum, peritoneum and diaphragm. In clinical daily practice, these CT features are often present in patients with advanced epithelial ovarian cancer. Nevertheless, a complete cytoreductive surgery can be achieved regularly. Further research should focus on the predictive value of these CT features. Even, other factors that influence the surgical outcome must be taken into account, such as patients factors and surgical facilities.

Supplementary

Table S1 The searching strings

Database	
Embase.com	('x-ray computed tomography'/exp OR 'computer assisted tomography'/exp OR 'multidetector computed tomography'/de OR (radiolog* OR ct OR ((ct OR computed*) NEAR/3 (scan* OR tomograph*))):ab,ti) AND (('reporting'/de OR 'outcome assessment'/de OR 'interpretation'/de OR (guideline* OR interpret* OR structural* OR ((systemat*) NEAR/3 (review*)) OR report*):ab,ti) OR ('prediction and forecasting'/exp OR 'predictive value'/de OR (((predict*) NEAR/3 (value*))):ab,ti) AND ('preoperative evaluation'/de OR 'surgical outcome'/de OR (((surg*) NEAR/3 (outcome* OR approach*)) OR ((preoperative*) NEAR/3 (evaluation* OR assessment* OR staging*))):ab,ti)) AND ('gynecologic surgery'/exp OR 'ovary cancer'/exp OR 'ovary tumor'/de OR ('cytoreductive surgery'/de AND 'ovary cancer'/exp) OR (debulk* OR ((gynaecol* OR gynecol*) NEAR/3 (surg* OR operat* OR procedure*)) OR ((ovar* OR adnex*) NEAR/3 (cancer OR tumor* OR tumour* OR carcinoma* OR mass* OR neoplasm*)) OR ((cytoreduc*) NEAR/6 (surg* OR ovar* OR adnex*))):ab,ti)
Medline Ovid	(exp "Multidetector Computed Tomography"/ OR exp "Tomography, X-Ray Computed"/ OR exp "Positron Emission Tomography Computed Tomography"/ OR (radiolog* OR ct OR ((ct OR computed*) ADJ3 (scan* OR tomograph*))).ab,ti.) AND (("Outcome Assessment (Health Care)"/ OR (guideline* OR interpret* OR structural* OR ((systemat*) ADJ3 (review*)) OR report*).ab,ti.) OR ("prediction and forecasting"/ OR "predictive value"/ OR (((predict*) ADJ3 (value*))).ab,ti.)) AND ((((surg*) ADJ3 (outcome* OR approach*)) OR ((preoperative*) ADJ3 (evaluation* OR assessment* OR staging*))).ab,ti.) AND (exp "Gynecologic Surgical Procedures"/ OR exp "Ovarian Neoplasms"/ OR ("Cytoreduction Surgical Procedures"/ AND exp "Ovarian Neoplasms"/) OR (debulk* OR ((gynaecol* OR gynecol*) ADJ3 (surg* OR operat* OR procedure*)) OR ((ovar* OR adnex*) ADJ3 (cancer OR tumor* OR tumour* OR carcinoma* OR mass* OR neoplasm*)) OR ((cytoreduc*) ADJ6 (surg* OR ovar* OR adnex*))).ab,ti.)
Web of science	(TI=(((radiolog* OR ((ct OR computed*) NEAR/2 (scan* OR tomograph*))))) OR AB=(((radiolog* OR ((ct OR computed*) NEAR/2 (scan* OR tomograph*)))))) AND (TI=(guideline* OR interpret* OR report* OR ((((predict*) NEAR/2 (value*)))))) OR AB=(guideline* OR interpret* OR report* OR ((((predict*) NEAR/2 (value*)))))) AND (TI=(debulk* OR ((gynaecol* OR gynecol*) NEAR/3 (surg* OR operat* OR procedure*)) OR ((ovar* OR adnex*) NEAR/2 (cancer OR tumor* OR tumour* OR carcinoma* OR mass* OR neoplasm*)) OR ((cytoreduc*) NEAR/5 (surg* OR ovar* OR adnex*))) OR AB=(debulk* OR ((gynaecol* OR gynecol*) NEAR/3 (surg* OR operat* OR procedure*)) OR ((ovar* OR adnex*) NEAR/2 (cancer OR tumor* OR tumour* OR carcinoma* OR mass* OR neoplasm*)) OR ((cytoreduc*) NEAR/5 (surg* OR ovar* OR adnex*))))
Cochrane Central	(((CT NEXT/4 scan) OR (computed NEXT/1 tomography)):ab,ti) AND ((guideline* OR interpret* OR structural* OR report* OR prediction* OR (predict* NEAR/3 value*) OR (systemat* NEAR/3 review*)):ab,ti) AND ((debulk* OR ((gynaecol* OR gynecol*) NEAR/3 (surg* OR operat* OR procedure*)) OR ((ovar* OR adnex*) NEAR/3 (cancer OR tumor* OR tumour* OR carcinoma* OR mass* OR neoplasm*)) OR ((cytoreduc*) NEAR/6 (surg* OR ovar* OR adnex*))):ab,ti)
Google Scholar	"computed tomography"|"CT scan" "ovarian cancer"|"adnex cancer" prediction|interpretation 'computed tomography'|'CT scan' 'ovarian cancer'|'adnex cancer' prediction|interpretation

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10

Unresectable Ovarian Cancer Requires a Structured Plan of Action: A Prospective Cohort Study

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Abstract

Background

Patients with unresectable disease during cytoreductive surgery (CRS) for advanced-stage ovarian cancer are underreported. Knowledge of treatment and survival after surgery is limited. The aim of this study is to address the knowledge gap about postoperative treatment and survival of patients whose surgery was abandoned due to unresectability after abdominal exploration.

Methods

Women with FIGO stage IIIB-IV epithelial ovarian cancer whose disease was considered to be unresectable during surgery were included in this prospective study, a post hoc analysis of the PlaComOv study. The unresectable disease was defined as the inability to achieve at least suboptimal CRS without attempted CRS after careful inspection of the entire abdomen. Preoperative clinical data, perioperative findings, postoperative treatment and survival data were analyzed.

Results

From 2018 to 2020, 27 patients were included in this analysis. Treatment ranged from the cessation of treatment to one or several lines of chemotherapy with or without maintenance therapy. The median overall survival was 16 (IQR 5–21) months (95%CI 14–18). At 24 months of follow-up, four patients (15%) were alive.

Conclusions

This study indicated a two-year survival of 15%. Optimal treatment strategies in terms of survival benefits are still ill-defined. Further study of this specific group of patients is warranted. We advocate an (inter)national registry of patients with unresectable cancer and comprehensive follow-up.

Introduction

Despite extensive preoperative examinations, during abdominal exploration, it may be found that cytoreductive surgery (CRS) is impossible because of extensive disease in patients with advanced-stage epithelial ovarian cancer (AEOC). In those patients, surgery has to be abandoned because of unresectable disease. Patients with unresectable ovarian cancer are typically underreported or included in a suboptimal CRS (>1 cm residual tumor) group(1).

Ovarian cancer is the eighth most occurring cancer in women, with almost 314,000 new cases and more than 207,000 deaths worldwide within 2020(2). At present, the standard treatment of advanced-stage epithelial ovarian cancer (AEOC) consists of cytoreductive surgery (CRS) and platinum-based chemotherapy (mainly six courses, three weekly: neoadjuvant carboplatin (AUC6) with paclitaxel (175 mg/m2), followed by maintenance therapy with poly adenosine diphosphate-ribose polymerase (PARP) inhibitor in selected patients(3,4). The timing of surgery may be as primary CRS or as interval CRS after three cycles of neoadjuvant chemotherapy(5). Complete resection of all macroscopic diseases (at primary or interval surgery) is the strongest independent variable in predicting overall survival(6).

In the case of unresectable disease for patients with AEOC, knowledge of further postoperative treatment and survival is limited.

To address this knowledge gap, we analyzed data from patients whose surgery was abandoned due to unresectability after abdominal exploration(7,8). The aim of this study was to establish a detailed account of individual patients' treatment along with a report on overall survival.

Materials and Methods

Study Design and Patients

From 2018 to 2020, 327 patients with AEOC International Federation of Gynecology and Obstetrics (FIGO) stage IIIB-IV who were suitable for CRS and chemotherapy were eligible for inclusion in the PlaComOv study. The PlaComOv study was a multicenter randomized controlled trial to investigate the use of the PlasmaJet Surgical device during CRS (Figure 1)(8). The study was approved by the Medical Ethics Review Board of the Erasmus University Medical Center Rotterdam, the Netherlands

(NL62035.078.17). Details of the PlaComOv study and main study outcomes were published previously(7).

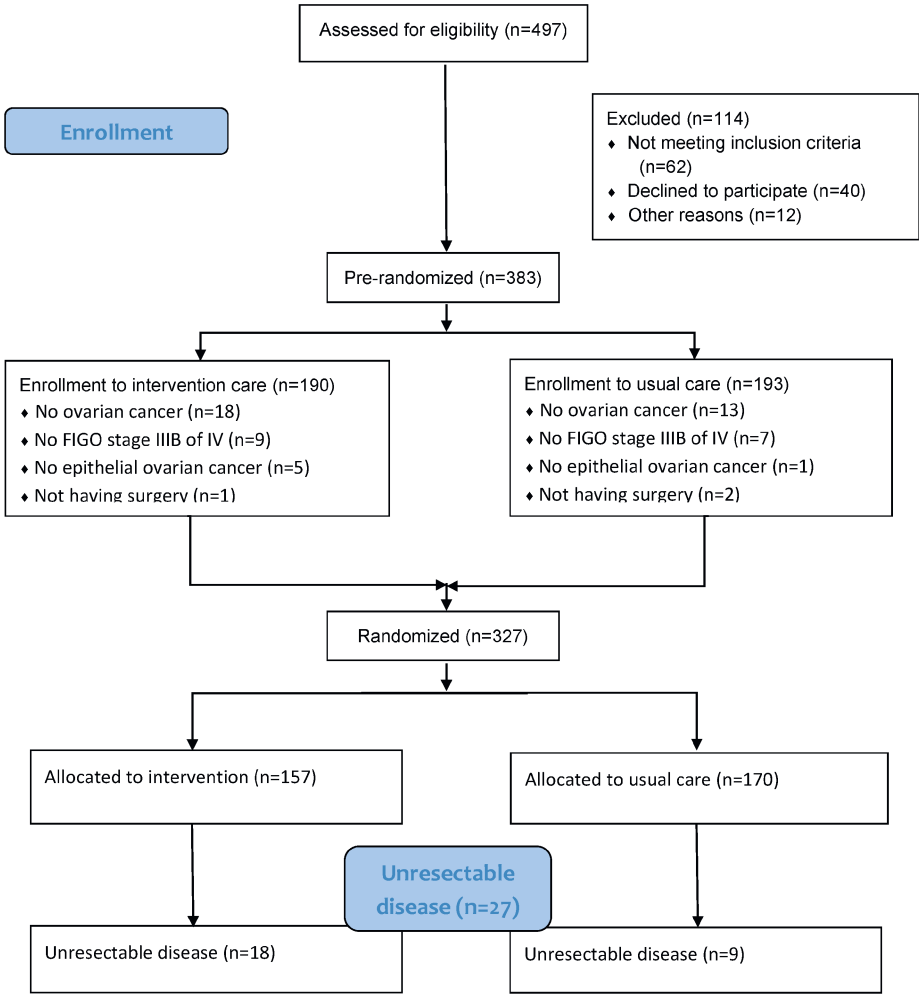

Figure 1 Consort flow diagram PlaComOv study

In this prospective cohort study, we included patients in whom the disease was considered unresectable during surgery. 'Unresectable' was defined as the inability to achieve at least suboptimal CRS (tumor lesions >1 cm) without attempted CRS after careful inspection of the entire abdomen and after intra-operative consultation with the anesthesiologist and the gynecologic oncologic surgeon.

At diagnosis, a laboratory test of the CA-125 level and a computerized tomography (CT) scan was performed, followed by discussion in a multidisciplinary tumor board meeting to determine whether primary CRS or neoadjuvant chemotherapy (NACT) followed by interval CRS was appropriate(5,9).

The NACT regimen consisted of three cycles of intravenous paclitaxel (175 mg per square meter of body-surface area) and carboplatin (area under the curve of 6 mg per milliliter per minute) with an interval of three weeks for each cycle(4,5). A CT scan after three cycles of NACT was performed to evaluate the degree of tumor response. In the subsequent tumor board meeting, patients with (partial) response or at least stable disease were considered eligible and planned for interval CRS unless strict criteria for the unresectable disease were present(10).

All surgical procedures were performed by well-trained gynecological oncologists and by an oncological surgeon when indicated. Postoperatively, the possibility of continuing first-line chemotherapy was discussed with the patient.

In the current study, preoperative clinical data, perioperative findings and postoperative treatment and survival data were analyzed. The pre-operative data which were analyzed were age, BMI, histology, FIGO stage, somatic mutation status of BRCA1 and BRCA2, level of Cancer antigen 125 at diagnosis and after NACT, WHO performance status, comorbidity and polypharmacy.

Normal CA-125 level was defined as <35 kU/L(11). The reduction of CA-125 level after NAC was calculated.

Multimorbidity was defined as morbidity in three or more organ systems. Polypharmacy was defined as the use of five or more medicines for at least 90 days(12).

Statistical Analysis

Categorical variables were presented as numbers, and continuous variables were presented as mean ± standard deviation (SD) or median with interquartile range (IQR) as appropriate. Overall survival (OS) was calculated from date of surgery to time of death or last follow-up. The survival analysis was performed using Kaplan–Meier method. Statistical significance was considered when p-value $p < 0.05$. The analysis was performed using IBM SPSS statistics for Windows, version 22.0 (Armonk, NY, USA: IBM Corp).

Results

Of 327 patients in the PlaComOv study, 27 patients (8.3%) had the unresectable disease and were included in this analysis (Figure 1). The baseline characteristics are presented in Table 1. The mean age was 70 (SD 10.5, IQR 29–82) years. The mean body mass index was 25 (SD 6.4, IQR 17.2–47.9) kg/m2. Nine patients (35%) were classified as World Health Organization (WHO) performance status 0, 13 patients (50%) as WHO 1, and 4 patients (15%) as WHO 2. There were eight patients (30%) with multimorbidity (morbidity affecting three or more organ systems), and six patients (22%) had polypharmacy (using five or more medicines for at least 90 days at diagnosis). The median CA-125 at diagnosis was 660 kU/L (IQR 120–16,054). After three cycles of NACT, the median CA-125 was 81 kU/L (IQR 13–2695). The mean percentage of CA-125 reduction after NACT was 76% ± 25 (IQR 19.4–98.6). Seven patients (26%) had a drop of ≥95%.

All but one patient had high-grade serous adenocarcinomas; one patient had low-grade serous adenocarcinomas. Sixteen (59%) patients were FIGO stage III and nine (41%) were FIGO stage IV. The somatic mutation status of BRCA1 and BRCA2 was tested in twenty patients, and all were negative.

Table 1 Patient characteristics

Patient	Age (Year)	BMI (kg/m²)	FIGO Stage	CA-125 (Diagnosis) (kU/L)	CA-125 (NACT) (kU/L)	WHO[1]	Dose Modification in NACT	Co-Morbidity[2]	Polypharmarcy[3]
1	67	47.9	IIIC	1715	98	2	No	–	+
2	65	20.7	IIIC	1681	599	2	No	–	+
3	72	24.5	IIIC	16,054	700 *	0	No	–	–
4	60	21.8	IIIC	586	41	2	No	–	–
5	62	31.6	IIIC	581	377	1	No	–	–
6	81	22.5	IIIC	2703	180	1	No	+	+
7	80	17.2	IIIC	5198	1873	1	No	–	–
8	73	31.6	IIIC	1300	79 *	1	No	–	–
9	76	22.9	IV	869	34 *	0	No	+	–
10	64	21	IV	2688	37 *	0	No	–	–
11	64	23.1	IIIC	220	98	1	No	–	–
12	76	19.8	IIIC	760	170	-	No	–	–
13	77	22	IV	130	81	0	No	–	–
14	75	19.5	IV	241	146	1	Yes	+	+
15	78	20.4	IV	1331	51 *	0	No	–	–
16	76	18.8	IV	11,239	3695	2	No	+	–
17	74	22.3	IV	2532	40 *	1	No	+	–
18	69	20.1	IV	237	27	1	No	+	–
19	61	22.5	IIIC	11,000	220 *	0	No	+	–
20	76	30.7	IV	290	64	0	Yes	–	–
21	78	22.3	IIIB	526	13.3 *	1	No	–	–
22	71	26.7	IV	550	38	0	No	–	–
23 †	28	20	IIIC	120	74.9	1	No	–	–
24	58	29.4	IIIC	470	270	0	No	–	+
25	72	27.7	IIIC	310	250	1	No	+	+
26	68	33.6	IV	660	51	1	No	–	–
27	68	28.3	IIIC	649	77	1	No	–	–

† low-grade serous cancer; * = ≥95% decrease; + = yes; – = no; NACT = neoadjuvant chemotherapy; 1 WHO = performance status (see method); 2 Comorbidity: + = or more systems; 3 Polypharmacy: + = five or more medicines for at least 90 days.

Surgical Findings

Table 2 reported the intraoperative findings and reasons for abandoning surgery. One patient was eligible for interval CRS after a diagnostic laparoscopy, but an optimal CRS was not feasible with laparotomy. All patients had ascites and extensive peritoneal carcinomatosis (defined as >200 tumor spots on the peritoneal surface and at the small bowel mesentery). Twenty-five patients (93%) had extensive tumors involving the small intestine, colon, sigmoid and/or rectum. Extensive liver, spleen or stomach involvement was seen in 11 (41%) patients. Five (19%) patients were diagnosed with frozen pelvis. Three patients (10%) were reported with tumor involvement at the renal vein, inferior vena cava or truncus coeliacus.

Table 2 Description of surgical findings

Patient	Description of Surgical Findings
1	extensive peritoneal carcinomatosis, extensive tumor lesions entire bowel, mesentery and liver
2	extensive peritoneal carcinomatosis, extensive tumor lesions entire bowel and mesentery
3	extensive peritoneal carcinomatosis, tumor lesions up to 10 cm entire bowel, bladder, liver, spleen, diaphragm. Involvement renal vein by enlarged para aortic lymph nodes.
4	extensive peritoneal carcinomatosis, tumor lesions entire colon and small bowel, mesentery, liver, diaphragm, spleen, truncus coeliacus
5	extensive peritoneal carcinomatosis, extensive tumor lesions entire bowel and mesentery, no access to pelvis after adhesiolysis
6	extensive peritoneal carcinomatosis, extensive tumor lesions entire bowel, mesentery and liver
7	extensive peritoneal carcinomatosis, extensive tumor lesions entire bowel and mesentery, no access to pelvis after adhesiolysis
8	extensive peritoneal carcinomatosis, extensive tumor lesions entire bowel and mesentery
9	extensive peritoneal carcinomatosis, extensive tumor lesions entire bowel and mesentery, extensive tumor lesions in liver and spleen
10	extensive peritoneal carcinomatosis, extensive tumor lesions entire bowel, mesentery and mesocolon
11	extensive peritoneal carcinomatosis, extensive tumor lesions entire bowel and mesentery
12	extensive peritoneal carcinomatosis, extensive tumor lesions entire bowel and mesentery
13	extensive peritoneal carcinomatosis, extensive tumor lesions entire bowel and mesentery
14	extensive peritoneal carcinomatosis, extensive tumor lesions entire bowel and mesentery
15	extensive peritoneal carcinomatosis, extensive tumor lesions entire bowel and mesentery, all organs and block by adhesions
16	extensive peritoneal carcinomatosis, extensive tumor lesions entire bowel, mesentery and mesocolon
17	extensive peritoneal carcinomatosis, extensive tumor lesions entire bowel, mesentery, mesocolon and stomach
18	extensive peritoneal carcinomatosis, extensive tumor lesions entire bowel and mesentery
19 *	extensive peritoneal carcinomatosis, extensive tumor lesions entire bowel and mesentery
20	extensive peritoneal carcinomatosis, extensive tumor lesions entire bowel, mesentery, liver and stomach

Table 2 *(Continued)*

Patient	Description of Surgical Findings
21	extensive peritoneal carcinomatosis, extensive tumor lesions entire bowel, mesentery and liver, no access to pelvis after adhesiolysis
22	extensive peritoneal carcinomatosis, extensive tumor lesions entire bowel and mesentery, extensive tumor lesions in spleen
23 †	extensive peritoneal carcinomatosis, extensive tumor lesions in colon and mesocolon, spleen, pancreas, vessels liver, vena cava inferior
24	extensive peritoneal carcinomatosis, extensive tumor lesions entire bowel and mesentery
25	extensive peritoneal carcinomatosis, extensive tumor lesions entire bowel, mesentery and liver
26	extensive tumor in peritoneum, mesentery and liver
27 *	extensive peritoneal carcinomatosis, extensive tumor lesions entire bowel and mesentery, all organs and block by adhesions, mass in mesentery extending to the superior mesenterial artery

† low-grade serous cancer; * a diagnostic laparoscopy was performed prior to interval cytoreductive surgery.

Postoperative Treatment

Table 3 reported the postoperative treatments. There were four of 27 patients (15%) who did not continue chemotherapy. One patient had a poor performance status after surgery. She was ineligible for chemotherapy and died three months after surgery. The patient with low-grade serous adenocarcinoma received maintenance letrozole without continuing chemotherapy (died after 32 months). Two patients declined further chemotherapy after surgery: one patient died 15 months after surgery, and the other started paclitaxel/carboplatin chemotherapy at further progression 8 months after surgery but stopped after two cycles because of the side effects and died 17 months after surgery.

Table 3 Postoperative treatment and overall survival

Patient	Postoperative treatment	progression of disease (months)	2nd and subsequent treatment lines	Overall survival (months)
1	-		-	2,9
2	TC		-	3,8
3	TC		-	3,9
4	TC		-	4,5
5	TC		-	5,1
6	TC		-	5,4
7	TC		-	5,7
8	TC maint bev	6	TC q3w (1 cycle)	8,1
9	TC	3	Wee1 kinase inhibitor and carbo (8 cycles)	9,3

Table 3 *(Continued)*

Patient	Postoperative treatment	progression of disease (months)	2nd and subsequent treatment lines	Overall survival (months)
10	TC	7	TC q3w	10,2
11	TC	4	PLD q4w- bev	10,3
12	-	3	-	15,3
13	TC	7 15	TC q3w TC (1 cycle)	16,2
14	TC	8	PLD q4w (1 cycle)	16,9
15	TC	9	TC, maint niraparib (3 weeks)	17,1
16	TC	7	paclitaxel weekly + bev, maint bev	17,7
17	-	8	TC weekly (2 cycles)	17,7
18	TC	8	paclitaxel weekly + bev, maint bev	18,1
19	TC	13	PLD/carboplatin q4w, maint olaparib	19,0
20	TC	10	PLD q4w	22,4
21	TC	9 20	TC weekly PLD q4w	22,9
22	cyclophosphamide/bev	19	carb q3w (3 cycles)	23,1
23 †	Letrozole	18	continuing letrozole	31,5
24	TC	1	letrozole	alive with disease >24 months
25	TC	13 28	Cyclofosfamide + bev, maint bev PLD/ carb q4w	alive with disease >36 months
26	TC	15	TC, maint olaparib	alive with disease >33 months
27	TC	8 17 21	gemcitabine PLD q4w TC q3w	alive with disease >28 months

† low-grade serous cancer; Q3w = every three weeks; TC = paclitaxel/carboplatin; PLD = pegylated liposomal doxorubicin; carb = carboplatin; bev = bevacizumab; maint = maintenance.

Most patients (n = 22, 81%) received postoperative chemotherapy with paclitaxel/carboplatin; in one patient, this was combined with bevacizumab. One patient received postoperative chemotherapy with cyclophosphamide/bevacizumab. Among the 23 patients who received further chemotherapy, five died within six months after surgery. Three patients had progressive disease within six months after surgery, and all of them received second-line chemotherapy.

Within 6–12 months after surgery, 11 patients (37%) had progressive disease. Platinum-based doublets were administered to six patients with the platinum-sensitive disease, of whom one received maintenance niraparib. Two patients received pegylated liposomal doxorubicin (PLD), two patients received paclitaxel weekly with bevacizumab, and one patient received gemcitabine for platinum-resistant disease.

In four patients with progressive disease > 12 months after first-line treatment, four different second-line regimens were given, i.e., single agent carboplatin, cyclophosphamide/bevacizumab, paclitaxel/carboplatin/bevacizumab and PLD/carboplatin followed by maintenance therapy the PARP inhibitor olaparib.

As part of the second-line treatment, six patients were treated with maintenance treatments after chemotherapy: three with bevacizumab and three with PARP inhibitors. One patient started with letrozole (Table 3).

Overall Survival

The median overall survival after surgery was 16 (IQR 5–21) months (95%CI 14–18) (Figure 2). At 24 months of follow-up, four patients (15%) were alive with the disease.

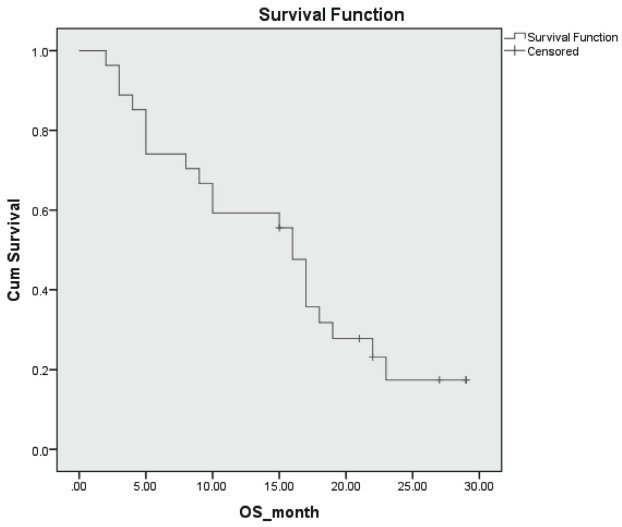

Figure 2 Kaplan–Meier curve of overall survival (n = 27)

Discussion

The purpose of this study was to establish a detailed description of the treatment of individual patients and a report on overall survival. In this post hoc analysis of a large RCT, 27 patients with AEOC were included with the unresectable disease during abdominal exploration. We described in detail the subsequent treatments in our patients. Treatment after attempted surgery was divers, ranging from the cessation of treatment to, predominantly, one or several lines of chemotherapy with or without maintenance treatment with bevacizumab and/or PARP inhibitors.

In our study, the median overall survival after surgery was 16 months (IQR 5–21). It is remarkable that 15% of the patients are still alive after two years. This is quite comparable with the study of Kaban et al., who reported a median OS of 22 months from the first treatment to death in patients with suboptimal cytoreduction(13), and Bland et al., who reported a median OS of 23 months for AEOC patients with suboptimal interval cytoreduction(14). Both studies calculated the OS from the day chemotherapy started, while we calculated OS from the day of surgery.

CA-125

Every patient underwent interval CRS. The median CA-125 after NACT was 81 kU/L. Although previous studies demonstrated a correlation between the percentage of decrease in CA-125 after NACT and surgical outcome, we neither found an association between the preoperative value of CA-125 nor the reduction rate of CA-125 level after NACT and unresectable disease. One study reported a significant relation between CA-125 level and complete CRS in multivariable analysis, while all other studies did not perform a multivariable analysis [15,16,17]. Although the study by Gupta et al. found a significant correlation between a >95% decrease in preoperative CA-125 level and complete CRS, our study showed that this does not guarantee complete CRS. In our study, seven patients (26%) had a decrease of ≥95%(16).

Overall Survival

It must be noted that the survival of patients with unresectable disease is much worse than in patients in which a complete or optimal CRS is possible(5). There is a paucity of data on survival outcomes comparing delayed CRS with no surgery (neoadjuvant chemotherapy only). To fill this knowledge gap, the GO SOAR2 study was designed(18).

In the PlaComOv study, both mandatory criteria of a proper selection of patients for CRS (via preoperative imaging) and a skilled surgical team to achieve complete

cytoreduction were met. However, our results showed that in 8% of the cases, it was impossible to perform CRS due to extensive tumor lesions at the bowel and mesentery [8]. Unfortunately, from other studies, nothing is known about the number of patients with unresectable diseases. Only the study by Fagotti et al. described two out of 171 patients (1.1%) as unresectable due to retroperitoneal disease(19). We believe that most studies included patients with unresectable diseases in the same group as those with suboptimal CRS.

At present, there are no clear international treatment recommendations concerning further postoperative treatment strategies in the case of unresectable ovarian cancer(20). In current practice, physicians discuss with their patients whether to continue their chemotherapy based on previous responses and toxicity. We described in detail the subsequent treatments in our patients. Treatment after attempted surgery was diverse. Most patients continued paclitaxel/carboplatin as part of the first-line treatment. The second-line treatment ranged from chemotherapy with or without maintenance treatment with bevacizumab and/or PARP inhibitors. Due to the small number and diverse treatments, we cannot comment on the treatment decisions or the best options. However, a number of patients who received second-line treatment and maintenance therapy survived for more than two years in our study. Therefore, maintenance therapy might be valuable for selected patients.

Strength and Limitations

This study is a post hoc analysis in a prospective cohort of data from a multicenter randomized controlled trial. Patient characteristics and intra-operative and postoperative information were uniformly collected in an electronic database management platform which reduced the risk of missing data. Before any treatment was administered, a multidisciplinary tumor board was convened. All patients were centralized to the registered cancer hospitals and underwent CRS by experienced gynecologic oncologists, which ensured the maximal effort of the surgery. Despite some data limitations and bias due to the study's nature, this study shed light on a subgroup of patients who are often overlooked.

Conclusions

This study indicates that patients with unresectable AEOC have poor survival rates. Currently, optimal treatment strategies in terms of survival benefits are still ill-defined. Further study of this specific group of patients is warranted. In order to provide a recommendation for these women, we advocate an (inter)national registry

with a biobank of patients with unresectable cancer and comprehensive follow-up. Subsequently, an international multidisciplinary group of experts should write a clinical guideline with their treatment advice and evaluate this through prospective data collection of comparable patients.

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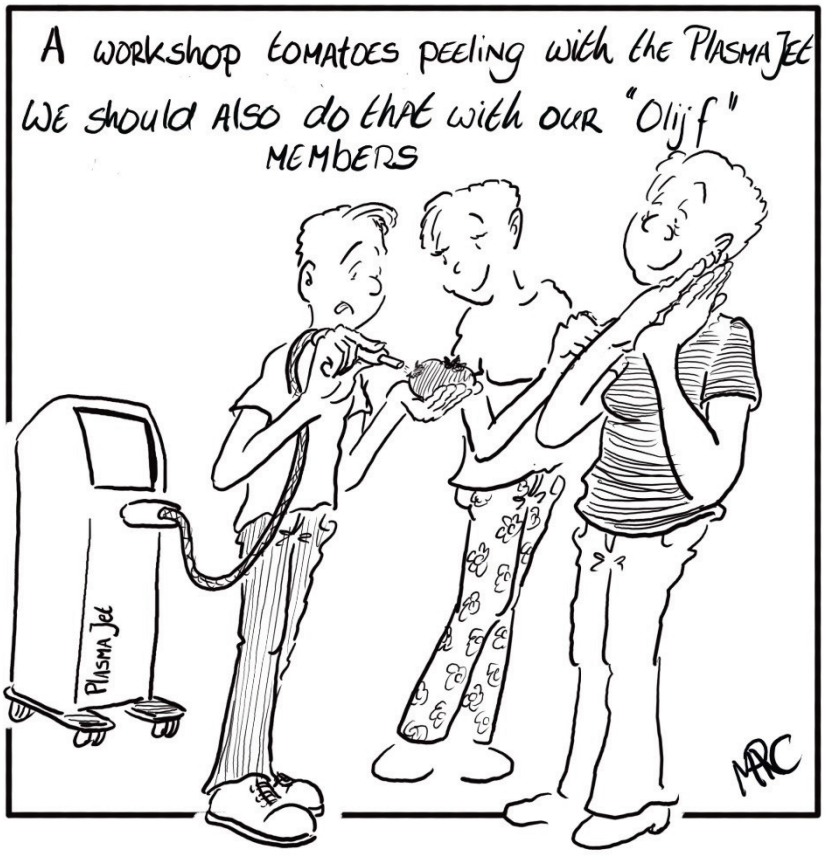
Discussion



PlasmaJet Surgical device during CRS

The main aim of this thesis was to answer the question whether the likelihood of complete cytoreductive surgery (CRS) for advanced stage ovarian cancer can be safely increased by the use of the PlasmaJet as a new surgical device. The second part of this thesis focused on the predictive value of the tumor marker CA-125 and the assessment of the CT scan for achieving a complete CRS.

In our multicenter randomized controlled PlaComOv study, the intention-to-treat analysis demonstrated an increase of the percentage of complete CRS for patients in the intervention group(1). In this study, 75.8% of the patients in the intervention group underwent complete CRS compared to 67.6% of the patients in the control group (p=0.131). A per-protocol analysis was performed to demonstrate the surgical outcome of the patients who actually underwent CRS. In addition to excluding 27 patients who did not undergo CRS, 3 patients were excluded because of protocol violation: those patients underwent surgery in which the PlasmaJet was used while they were included in the control group. In the per-protocol analysis, complete CRS was achieved in 85.6% of the patients in the intervention group compared to 71.5% of the patients in the control group (p=0.005). No differences were found between the two groups in terms of surgical time or blood loss. Postoperatively, the number of complications, re-laparotomies or readmissions did not appear to be significantly different between the two groups.

De main outcome of the study was the percentage complete CRS in the intervention group and in the control group(2). A factor that can partly explain the non-significant outcome of the intention-to-treat analysis was that the percentage of complete CRS in the control group (67.6%) was higher than the percentage of complete CRS used for the power analysis (62%)(2-4). In retrospect, the PlaComOv study was underpowered, and this was made worse by 3 cross-over patients and a number of inoperable patients. The data of those patients were analyzed in the intention-to-treat analysis because ‘unresectable disease’ was not defined as an exclusion criterion in the study protocol. For this intervention study it would be more realistic to look at the outcomes of the per-protocol analysis, in which the percentage complete CRS was significant higher in the intervention group than in the control group. Ultimately, it is about whether patients in the intervention group have a longer progression-free and overall survival. We will get an answer to this question in the coming years.

Safety

Part of the main aim of the study was to assess safety and efficiency. First, our clinical data demonstrated that the complication rates of the two groups did not differ(1). A relaparotomy was performed in eight patients of the intervention group and in three patients of the control group. No relaparotomy was related to the use of the PlasmaJet. Apart from a higher rate of postoperative pneumonia in the control group (6.3% versus 1.4%, p=0.072), there were no significant differences between the two groups in postoperative complications within 30 days following surgery. Nevertheless, caution is still advised. If the plasma is introduced directly into a blood vessel, a gas embolism may occur. This complication was not observed in our study, possibly due to the fact that in most cases small amounts of air are broken down directly in the capillary bed and are absorbed into the systemic circulation without consequence.

Secondly, we looked into the effect of the PlasmaJet on tissue damage in relation to electrocoagulation. In a series of 106 histological slides of patients with advanced stage ovarian cancer, the average thermal tissue damage depth was 0.15 mm (range 0.03–0.60 mm) after use of neutral argon plasma and 0.33 mm (range 0.08–1.80 mm) after use of electrocoagulation ($p<0.001$)(5). A greater disruption of the tissue surface was often observed after electrocoagulation. In line with other studies, our case study demonstrated that the use of neutral argon plasma during CRS produced significantly less thermal tissue damage than electrocoagulation treatment(6,7).

We conclude that the PlasmaJet is considered a clinically and thermally safe instrument for CRS. It should be noted that safety for the surgeon has not been studied. In our opinion, research should be done into the amount of smoke generated when using the PlasmaJet, as well as possible particulate matter due to incomplete combustion.

Efficiency and costs

Although the operation time was 32 minutes longer (p=0.084) in the intervention group, a higher percentage of complete CRS could be reached(1). Especially within the intervention group, more patients with peritoneal carcinomatosis underwent a complete CRS (72.2% versus 51.5%, p=0.034). Therefore, it is plausible that this explained the largest difference in operation time. Possibly, future procedures may be performed faster than during the study period because the surgeons using the PlasmaJet may not have reached their learning curve yet. In daily practice it is seen -not officially investigated- that when surgeons use the PlasmaJet more often, more steps of the procedure are performed by the PlasmaJet and instruments are changed less often.

The PlasmaJet was efficiently used to remove small tumor lesions on the intestines. Bowel surgery was performed in about 50% of the patients in both groups. Patients in the intervention group had more frequent disease involvement of the surface of rectum and rectosigmoid(1). Rectal involvement was found in 52 of the 139 patients (37.5%) in the intervention group versus 45 of the 158 patients (28.5%) in the control group (p=0.033). In the intervention group, disease at this site was removed more often without the need for bowel resection compared with the control group . Besides a lower proportion of bowel resections in the intervention group, the number of colostomies was smaller in the intervention group (6.5% versus 12.7%, p=0.169)(1).

The mean total health care costs of the use of the PlasmaJet in CRS were significantly higher than those of conventional CRS(8). In the PlaComOv study, this difference is fully explained by the additional surgery costs of the use of the PlasmaJet. All equipment costs included costs of depreciation and maintenance costs of the PlasmaJet device were fully taxed among patients in the intervention group. The cost of a PlasmaJet handpiece was only included if the PlasmaJet has been used during CRS. If the use of the PlasmaJet is no longer limited to patients randomly assigned to the intervention arm, we suspect that surgeons are likely to use the PlasmaJet in more patients. Therefore, fixed costs of using the PlasmaJet can then be divided among more patients. This will reduce the additional costs per person of surgery using the PlasmaJet. Also, if the PlasmaJet will be used for other indications, this will reduce the fixed costs per procedure, and the handpieces can probably be ordered for a decreased price.

Finally, if the extra costs per procedure with the PlasmaJet are weighed against the savings due to fewer stomas, the difference in costs may not be financially significant. Most importantly, a cost-effectiveness will be calculated after obtaining the 5-year survival data to establish the number of gained disability-adjusted life years.

Quality of life

In our single blinded randomized PlaComOv study, patients with advanced stage ovarian cancer were requested to complete QoL questionnaires until 4 years after CRS(2). In general, 4 weeks after CRS, all patients reported a lower QoL than before surgery. During follow-up, however, patients indicated that their QoL was equal to or higher than the QoL at diagnosis(9-11). The QoL outcomes until 2 years after CRS are analyzed and demonstrated the positive effect of the PlasmaJet on QoL. Patients who underwent CRS with the PlasmaJet mainly reported better physical and role functioning, less fatigue and pain.

The difference in QoL between the study groups was clinically small but statistically significant(12,13). Besides, in patients with a high risk of recurrence of ovarian cancer within two years, any improvement in QoL is relevant. A possible explanation for the differences in QoL in both study groups could be related to the differences in tissue damage due to the use of different equipment during surgery. The PlasmaJet infiltrates the tissue less deeply than electrosurgery(5). With less tissue damage, the process of tissue repair (inflammation, proliferation by fibrogenesis and angiogenesis and remodeling) will proceed better than when there is more tissue damage. Especially in surgery involving extensive peritoneal stripping, the surgeon must be aware of the effect of the instrument used.

Peritoneal carcinomatosis

A sub-analysis was performed for patients with peritoneal carcinomatosis, defined as more than 50 tumor lesions on the peritoneal surface(1). The rate of complete CRS of these patients was 72.2% in the intervention group versus 51.5% in the control group (p=0.034). Hypothetically, those are the patients in which the PlasmaJet can make the greatest difference in surgical outcome. It is easier to perform a diaphragm stripping if there are no muscle contractions thanks to the use of an electrically neutral device. Also, when the correct tissue plane is reached, it is easy to perform a stripping of the peritoneum. And if many small tumor lesions are located at the site of the intestine and mesentery, these lesions can be vaporized without destroying the underlying tissue.

In the study on the depth of tissue infiltration, the PlasmaJet was found to infiltrate the tissue less than the use of electrocoagulation(5). Additional histological examination of residual microscopic tumor lesions was performed on a number of tissues on which macroscopic tumor lesions were vaporized. If these tumor lesions were macroscopically removed, it was found that microscopic tumor was no longer present. Because this was only a small study, these results have not been published

It would have been interesting to perform a sub-analysis on the surgical outcome in all patients in whom surgery was actually performed with the PlasmaJet compared to all patients in whom the PlasmaJet was not used. However, there would be selection bias because this group would include more patients with peritoneal carcinomatosis and more extensive disease. The patients in the intervention group in which the PlasmaJet was not used generally had less extensive disease and no peritoneal carcinomatosis.

Unresectable disease

Even though all patients had been discussed in a multidisciplinary consultation, 27 patients were found to have unresectable disease during surgery(14). In addition to determining the value of the preoperative examinations, this determines the fact that optimal treatment strategies in terms of survival benefit are still poorly defined. All patients with unresectable disease were offered different treatment. Survival ranged from 2.9 to currently more than 31.5 months. For those patients, optimal treatment strategies in terms of survival benefit are still poorly defined in our guidelines. Further study of this specific group of patients would be highly desirable to make recommendations for the treatment of these women. We advocate national and international registration of these patients and extensive follow-up. Subsequently, an international multidisciplinary group of experts should write a clinical guideline for their treatment advice and evaluate this advice through prospective data collection of comparable patients.

Implementation of the PlasmaJet during cytoreductive surgery

Users' perspective

During the PlaComOv study, the PlasmaJet device was used in 75% of all procedures in the intervention group(1). The gynecological oncologist assessed whether the use of the PlasmaJet was necessary (12%) or very useful (29%) to achieve complete CRS. At the end of the PlaComOv study, a user survey was conducted, which was completed by 27 gynecologic oncologists. The outcomes of this user survey were not published. The respondents, who were representative for all users, were most positive about the device because it was considered easy to use, reliable in the fact that tissue damage is visible, and very accurate in removing tumor from the peritoneum and diaphragm and disease on the bowel or lymph nodes while leaving the underlying tissue intact. The kinetic energy released in the process was believed to be helpful for separating the tissues. Of the 27 respondents, seven (26%) indicated that the PlasmaJet could sometimes prevent the placing of a colostomy. Disadvantages, mentioned by the same responders, were the relative heaviness of the hand piece and the generation of smoke. Some users indicated that this smoke caused headaches in case of prolonged use of the PlasmaJet.

Almost half of the respondents (41%) indicated that they would like to use the PlasmaJet in the future, and 33% of the respondents preferred to wait for the results of the PlaComOv study to evaluate the results for surgical outcome, percentage of colostomies and complications. A few respondents preferred to wait for the

assessment of the long-term results of overall survival before considering the implementation of the PlasmaJet during CRS.

During the PlaComOv study, surgical outcome was not affected by increased expertise in using the PlasmaJet (surgical procedures 1-10 versus >10)(1). The majority of the respondents indicated that about 5 to 10 procedures per year would be needed to continue optimal use of the device.

No insurmountable issues were mentioned that would prevent implementation, although 33% of the respondents indicated that the extra costs could be an issue. This reservation addresses a realistic problem. In the Netherlands, the additional costs are surgical costs and are therefore paid by the department of Gynecologic Oncology. A cost-effectiveness analysis can only be performed when the long-term data are known (5-year survival). The results of this analysis will possibly show that the use of the PlasmaJet is cost-effective because of a longer survival, a higher quality of life and fewer colostomies. However, these cost savings will not be earned back by the department of Gynecologic Oncology. We suggest that the extra costs of the use of the PlasmaJet should be discussed during the process of implementation and should not constitute a financial loss for the departments of Gynecologic Oncology.

Patients' perspective

In the close relationship we maintained with members of patient association 'Olijf', we understood that they preferred to implement the PlasmaJet in all hospitals as soon as possible, based on the results of the PlaComOv study and the QoL outcomes. During the PlaComOv study, no increase in complication rate was found. Besides, a decrease in the percentage of colostomies and an increase in QoL are important results of the implementation of the PlasmaJet, even though these differences were not statistically significant. Even if the PlasmaJet eventually does not lead to a longer progression-free and overall survival, the implementation of the PlasmaJet is viewed positively from the perspective of patients.

Lessons learned from the PlaComOv study

Surgical outcome

Thanks to a grant from ZonMw, we were able to design and conduct a multicenter randomized controlled trial to determine the value of the PlasmaJet Surgical device during a CRS(2). When we formulated the research question, we had to take into account ZonMw's requirement to have an answer to the primary research question

within four years. This time constraint led to the primary research question whether the use of the PlasmaJet could improve the number of patients with complete CRS by 15%. During the development of the study, there were extensive discussions on how the surgical outcome had to be measured as objectively as possible.

Although all the previous studies on CRS described surgical outcome in terms of complete CRS (no gross residual disease), optimal CRS (residual disease ≤ 1 cm in maximum tumor diameter) and suboptimal CRS (residual disease > 1 cm tumor diameter), these descriptions do not solve the issue of objectivity(15,16). Preferably the surgical outcome would be determined by an independent observer, but it was deemed impossible to organize this. During the PlaComOv study, each patient was operated by two gynecologic oncologists, and both were present when the surgical outcome was assessed(2). At the end of each surgical procedure, photographs were requested and taken of different quadrants of the abdomen and, in case of an optimal or suboptimal CRS, also of the largest residual tumor mass. During the review of these photographs by two other gynecologic oncologists who did not know the surgical outcome, it became apparent that it was very difficult to assess the surgical outcome based on a photograph, particularly due to the glare of the light and the lack of the ability of palpation. Nevertheless, the opinion of the gynecologists who reviewed the photographs concurred, and no discrepancies were found between their opinion and the surgical outcome in the reports of the treating surgeons. So, given the fact that the surgical outcome was decided by two oncologic gynecologists and the fact that no discrepancy between the judgment of the surgeons and the reviewers of the photographs could be demonstrated, we concluded that the surgical outcome given by the surgical team represented a reliable measurement. It is notable that this issue remains unaddressed in the literature on surgical outcomes.

Currently, there are no objective assessment methods for the surgical outcome available that are deployable. Neither the tumor marker CA-125 nor a CT scan is sensitive and specific enough to detect residual tumor lesions(17-20).

A possible intra-operative visualization technique for the detection of residual metastases may be immunofluorescence. In immunofluorescence, patients could receive intravenous injections of agents such as folate-FITC, 5-aminolevulinic acid, indocyanine green and OTL38(21-23). These fluorescent agents accumulate in malignant tumor cells and can be detected intraoperatively by an imaging system. However, this technique is time consuming and due to the administration of a contrast medium it can cause side effects such as gastrointestinal distress and abdominal pain(21).

An alternative option for visualizing residual tumor after CRS may be hyperspectral imaging (HSI)(24). HSI is a noninvasive imaging technique that can detect malignant tissue. In HSI, multiple images of the underlying tissue are taken in contiguous spectral bands(25). These data can be used to build a 3D hyperspectral cube, which contains spatial information in two dimensions and spectral information in one dimension. The measured reflectance is related to the absorption and scattering properties of the tissue. This spectral signature of the underlying tissue can be used to classify tumor and non-tumor tissue. HSI has already shown promising results in other oncological fields(26,27). Currently, this technique has only been investigated ex vivo in ovarian cancer patients(24).

Finally, in a future perspective, treatment response might be predicted by means of postoperative analysis of circulating cell-free DNA (cfDNA)(28-31). Cell-free tumor DNA is released into the blood by apoptosis and necrosis of tumor cells and has already been shown to be a more specific marker of tumor burden than CA-125. cfDNA provides a real-time reflection of tumor burden because it has a relatively short half-life. Currently, this technique has not been sufficiently investigated to correlate outcomes with residual tumor volume. It should be noted that analysis of cfDNA will be a postoperative evaluation and not a peroperative method to measure residual tumor.

Multicenter study

A second consideration I would like to deliberate is the lessons we have learned from conducting a multicenter study. Multicenter studies offer many advantages over single-center studies, including a larger sample size for more generalizable findings and fostering networking. Well-conducted multicenter studies are more likely to have objective and reproducible results(32). During the PlaComOv study, we also encountered the challenges of a multicenter study. We would like to describe the challenges we experienced during the four phases of the study.

1. Planning phase. The idea to investigate the PlasmaJet in a randomized controlled trial was put forward by an academic and peripheral gynecologist. The research question and secondary outcome measures were mainly formulated at Erasmus MC. The systematic literature review was also conducted without the involvement of colleagues from other centers. By keeping this process within the center that initiated the study, collaboration was optimal. However, to create greater support during the study, our advice is to already involve the other centers that will participate in the multicenter study at this stage.

2. Project development phase. The principal investigator developed the study protocol and identified local investigators. The study protocol was developed in consultation with members of the patient association. After that, the study protocol was submitted to the local investigators. For better implementation, it would have been desirable to have requested more substantive input from the local investigators. In addition to an increase in substantive input, this would have created an opportunity to estimate the involvement and willingness of the local investigators to participate in the study. It may have been possible at this stage to clarify which centers would be better off not to participate in the study. Other aspects within this phase of the study went well, such as the submission of the protocol for local ethical approval and the participation in the PlasmaJet training.
3. Implementation phase. In this phase, patients should be informed, randomized and included in a uniform manner, and the same holds for data analysis. In a multicenter study, uniform implementation is a challenge and requires good collaboration between the principal investigator and the local investigators. During the PlaComOv study, it was noticeable that some hospitals had many more inclusions while other hospitals lagged behind in the number of inclusions. Although we spoke about this discrepancy with the local investigators, we did not take any action against it. For quality assurance of the study, it would have been better if we had made clear agreements about the number of inclusion per period in advance. Although the learning curve in using the PlasmaJet is steep, it seems obvious that a surgeon who has performed more procedures with the PlasmaJet should be able to use it more effectively. We advise hospitals that set up a multicenter study to specify the quality requirements to be met by the participating hospitals as well as the minimum number of inclusions to be achieved. If these requirements are not met, there should be consequences for participation in order to obtain comparable study populations in all the participating hospitals.
4. Dissemination phase. In this study phase, the discussion about the results and their implications for clinical practice should be held with balanced contributions from all the participating centers to avoid bias as much as possible and to create support for possible implementation.

Involvement of patient association 'Olijf'

Members of patient association 'Olijf' were closely involved in the design and implementation of the study as well as during the inclusion period. Halfway through the study, the principal investigator and a delegation of 'Olijf' members reviewed the preliminary results of the QoL questionnaires. The purpose of this evaluation was

to adjust the care if the results of the questionnaires would demonstrate that there was a need for this.

Besides, we regularly reported on the progress of the study in the newsletters of Olijf. Participants of the PlaComOv study were aware of these reports and knew that they could obtain information about the study progress during the inclusion period and about the results of the study. In retrospect, we had a useful collaboration, which ensured that we always evaluated the importance of the results from a patient perspective.

Preoperative prognostic value of CA-125 and CT scan

Complete CRS is an important prognostic predictor in patients with advanced epithelial ovarian cancer(33, 34). Also, a CRS is a complex treatment and severe 30-day postoperative complications occurred in 15% of the patients(35). Therefore, preoperative prediction of surgical outcome is clinically essential to guide treatment decisions such as primary CRS or neoadjuvant chemotherapy followed by interval CRS or to decide not to perform surgery(36). To predict surgical outcome, we studied the prognostic value of tumor marker CA-125 and the results of features on the computerized tomography (CT) scan in literature.

CA-125

Numerous biomarkers have been proposed for the detection, prognostic value and follow-up of ovarian cancer. Even though the serum CA-125 has a poor sensitivity and limited specificity, it is the most frequently used tumor marker in ovarian cancer(17, 37).

We described patients included in the PlaComOv study who underwent interval CRS with preoperative CA-125 levels ≤ 35 kU/L had higher odds of achieving complete CRS than patients with CA-125 levels >35 kU/L (85% vs. 67%, p=0.002)(17). In multivariable analysis with presence of ascites and peritoneal carcinomatosis, normalized preoperative CA-125 did not appear to be a significant predictor for complete CRS. The results of some studies in the systematic review were remarkably inconsistent, which is likely due to selection bias or missing data due to the retrospective nature of most of the included studies. It is quite possible that other studies that determined the value of CA-125 on surgical outcome have not been published.

During our systematic review, we approached all authors of the included articles to share their data to perform a meta-analysis. With the data available in the literature, this was impossible because CA-125 units were not described and different cutoff values were used. None of the authors were willing to share their data. The main reason given was that their data was no longer available or that the data did not belong to the corresponding author. This emphasizes the limitations of retrospective studies.

For primary CRS, the value of CA-125 as a preoperative predicting factor for surgical outcome is inconclusive. For interval CRS, the normalization of CA-125 after NACT (≤35 kU/L) was significantly associated with a higher percentage of complete CRS. However, in some patients, the value of CA-125 was normalized but a CRS was impossible(14). Consequently, CA-125 level for the prediction of surgical outcome should be used with caution and preoperative CA-125 level should not be used as an isolated predictive parameter.

CT scan

To determine whether surgical outcome can be predicted based on CT scan features, we performed another systematic review. During this systematics review, we found that the data was very diverse and complicated by a shift in time from acceptance of residual disease <1cm as a proper surgical outcome to the achievement of a complete CRS. Other factors at stake are the surgical team, the number of procedures performed and patient related factors.

Based on our systematic review we concluded that CT scan features associated with the inability to achieve a complete CRS were ascites, omental lesions, diaphragm lesions and liver lesions. It seems difficult to correlate these findings with our clinical practice. For example, if there is an extensive omental involvement, it is usually possible to achieve a complete CRS. This also applies to ascites. It is very likely that the preoperative CT scan findings are important but cannot be isolated unless, for example, there is a very obvious tumor in growth in the mesenteric vessels. For the gynecologic oncologist, it seems most likely that a combination of factors will inhibit performing a complete CRS. Therefore, it is important to optimize the surgical conditions such as the composition of the surgical team and surgical equipment and devices.

We believe that the data of the PlaComOv study should be sufficient to study the relationship between CT findings and surgical findings in more detail, and we are currently working on this. Unfortunately, for the patients included in our study, no

surgical and radiologic peritoneal cancer index (PCI) had been determined, nor could we determine this index retrospectively. In future research we will focus on the value of preoperative CT scan features according to a structured report as recommended by the European Society of Urogenital Radiology (ESUR) guidelines and compare this with surgical findings.

Future implications for research

In the introduction of this thesis, we outlined an overview of factors that influence the selection of patients who will benefit from a CRS. Factors such as prehabilitation and the role of MRI are currently being investigated by other research groups(38-40).

In order to predict a patient's response to treatment and to determine which patient actually benefits from surgery, we have to identify reliable predictive biomarkers that are easily obtainable. A biomarker has to be highly sensitive and specific to make the discriminative value as high as possible. More recently, liquid biopsies containing circulating cell-free DNA (cfDNA) show promising results in predicting treatment response and prognosis in ovarian cancer(28-31). cfDNA is released in blood by apoptosis and necrosis of tumor cells and has already been shown to be a more specific marker for tumor load than CA-125. It is a real-time reflection of tumor load since it has a relatively short half-life(28). Most cfDNA studies in cancer either use polymerase chain reaction (PCR) or next-generation sequencing (NGS) techniques to focus on the identification of gene mutations in oncogenes or tumor suppressor genes. These PCR and NGS approaches can also be used to target the epigenome, such as DNA methylation. Hypermethylation of the promotor region of tumor suppressor genes is an early event in carcinogenesis(41-45). Although the majority of DNA methylation changes during carcinogenesis are secondary, these changes can be useful for detecting cancer and monitoring therapy outcome.

Genome-wide methods to detect DNA methylation are used to find new biomarkers, but also to establish a genome-wide DNA methylation signature associated with a specific type of cancer. By finding a large number of differentially methylated regions (DMRs) and focusing on genome-wide methylation profiles, a more sensitive analysis can be performed. However, genome-wide DNA methylation analysis on cfDNA samples is technically challenging and expensive.

A new DNA methylation sequencing technique has been developed: MeD-seq. Using this technique, highly reproducible CpG methylation profiles can be reached for >50%

of all potentially methylated CpGs(46). A study on patients with colorectal cancer showed that the use of MeD-seq revealed a clearly different signature in patients with colorectal cancer compared to healthy controls(47).

The hypothesis of our study group for future research on the DNA methylation sequencing technique is that we can use MeD-seq for genome-wide cfDNA methylation profiling in patients with AEOC and for monitoring cfDNA methylation profiles during the course of the disease. If the cfDNA methylation profile is able to distinguish healthy women from women with AEOC and if it differs pre- and postoperatively, it may be a good reflection of tumor load and may be used in real-time disease monitoring. This would be promising in predicting treatment response and prognosis. If we will find a cfDNA methylation profile to be a reliable and easily available predictive biomarker for patients' response to therapy, it will bring us closer to an answer to the question how useful surgery will be in each individual patient.

Final note and general conclusion

It is Christmas Day again, exactly 213 years after Ephraim McDowell made the important decision to perform the first oophorectomy. The Dutch King Willem-Alexander of Orange said in his Christmas speech of the year 2022 that the time has passed to avoid important decisions or to postpone those decisions to a later date(48). Despite the king was not referring to the health care related to ovarian cancer, there are far-reaching plans to continue the centralization of surgery for ovarian cancer. Except for the logistical challenge to operate all patients in a timely manner, the PlaComOv study did not show a difference in the percentage complete CRS between procedures performed in an academic or peripheral center.

The question arises whether centralization contributes to an improvement of gynecologic care in general. If knowledge is lost in the hospitals where patients present with an abdominal mass, these patients may be undertreated due to incorrect or missing diagnoses. Also, in various hospitals some surgical expertise in the gynecological teams will be lost. In the management of obstetric emergencies, this can have a negative effect for patient outcomes. Therefore, I advocate keeping all care in perspective and not to focus on a particular group of obstetric and gynecologic patients. Let us have learned our lessons from the COVID period, when regular care was postponed in order to treat one specific group of patients(49).

In conclusion, this thesis highlights various aspects of the deployment of the PlasmaJet Surgical device during CRS, which were examined in the PlaComOv study. We concluded that the use of the PlasmaJet increased the probability of a complete CRS in patients with advanced stage ovarian cancer without a higher complication rate, especially in patients with a large number of peritoneal lesions.

One of the effects of the results of the PlaComOv study was an awareness of patients who underwent surgery but in whom it was impossible to remove the tumor. We advocate a registry of those patients with unresectable cancer and to study a comprehensive follow-up in order to provide recommendations for the optimal treatment strategies in terms of survival benefit.

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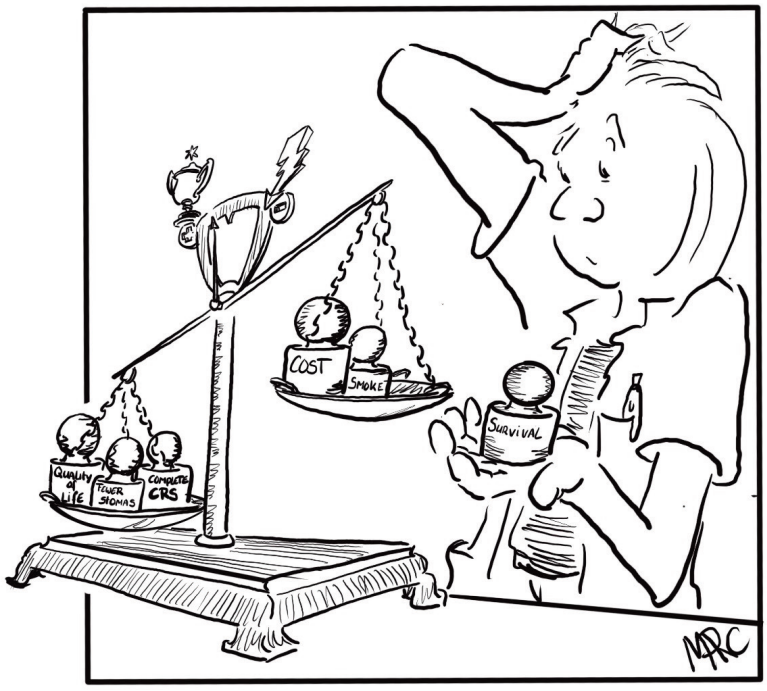
Summary


COST
SMOKE
SURVIVAL
QUALITY OF LIFE
TUMOR STONIAS
COMPLETE CRS
MRC

In 2021, 1238 Dutch women were diagnosed with ovarian cancer. More than 75% of these women were diagnosed with an advanced stage disease: metastases were found throughout the whole abdominal cavity (FIGO stage III) or even outside the abdominal cavity (FIGO stage IV). In FIGO stage III-IV ovarian cancer, the 1-year survival rate is 74% and the 5-year survival rate is 38%. Of all Dutch women, 1% die of ovarian cancer. This makes ovarian cancer the deadliest gynecologic malignancy in the Netherlands (https://iknl.nl/kankersoorten/eierstokkanker/registratie/).

The survival gain for women with advanced stage ovarian cancer (≥FIGO stage IIB) is mainly found in women in whom complete cytoreductive surgery (CRS) can be achieved. This means that all visible tumor in the abdomen is removed. In recent years, it became increasingly clear that there are large differences in overall survival between those women in whom all disease could be removed and those in whom minimal disease (less than 1 cm) remained after surgery. Therefore, surgical teams are committed to removing all disease in every woman, even from difficult sites and precarious surfaces such as the bowel, the small bowel and the diaphragm.

This thesis first aims to answer the question whether the likelihood of complete cytoreductive surgery (CRS) can be safely increased by using the PlasmaJet as a new surgical device. The second part of this thesis focuses on the predictive value of the tumor marker CA-125 and the assessment of the CT scan for achieving a CRS.

Part I: The effectiveness and safety of the PlasmaJet during cytoreductive surgery

Chapter 1 of this thesis is the introduction and demonstrates an overview of the factors that influence the outcome of CRS. A careful preoperative analysis is required to select the patients who will benefit from CRS and identify those who will not benefit from surgery.

The question is raised whether the surgical outcome can be improved by the use of new devices, such as the PlasmaJet® Surgical device. The PlasmaJet converts argon gas into plasma, which has several advantages. Firstly, very small superficial metastases for example on the intestine can be removed due to the vaporizing effect of plasma. In addition, the ablation effect of plasma makes it easy to find the right tissue plane between tissues. This correct plane is sometimes more difficult to find because of adhesions created by the tumor. Finally, since the PlasmaJet is an

electrically neutral device, its use will not lead to any muscle contractions during the removal near to the diaphragm.

To know in which types of surgery the PlasmaJet could be used and whether the use of the PlasmaJet would be safe and effective during CRS for ovarian cancer patients, a literature review was conducted. **Chapter 2** summarizes the limited evidence that was available in 2019. The main finding of this literature review is that a randomized controlled trial is lacking. No evidence is available on the long-term effects for the progression-free period and overall survival nor on the effects on complication rates, quality of life and cost-effectiveness.

As a result, a multicenter randomized trial was designed, the PlaComOv study. 'PlaComOv' is an acronym for 'Will the use of the PLAsmaJet® device improve the rate of COMplete cytoreductive surgery for advanced-stage OVarian cancer?' **Chapter 3** describes the study protocol of this study. The primary objective of the PlaComOv study was to assess the efficacy and safety of the PlasmaJet. Our hypothesis was that the PlasmaJet would be effective and safe if it could be demonstrated that the use of this device leads to a 15% increase in the number of complete cytoreductive surgeries without an increase in the complication rate.

Chapter 4 presents a detailed description of the surgical outcomes of 327 women with advanced stage epithelial ovarian cancer who were included for the PlaComOv study between February 2018 and September 2020. Of these women, 157 were randomized into the intervention group and 170 into the control group. Randomization involved stratification for suspected ovarian cancer versus proven ovarian cancer, primary versus interval CRS, presence versus absence of peritoneal carcinomatosis on CT scan, and whether or not hyperthermic intraperitoneal chemotherapy (HIPEC) was administered. For patients in the intervention group, the surgeon could decide whether or not to use the PlasmaJet during surgery. This device was used in 75% of all procedures in the intervention group.

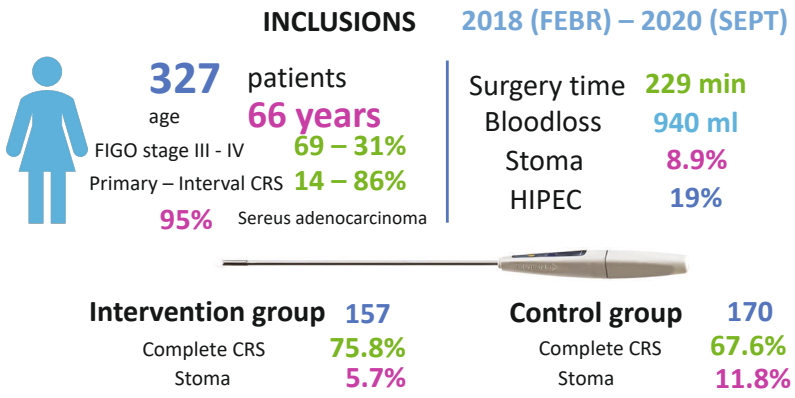


Figure 1 Results of the PlaComOv study. CRS=cytoreductive surgery, HIPEC= hyperthermic intraperitoneal chemotherapy.

The intention-to-treat analysis showed that 75.8% of the patients in the intervention group underwent complete CRS compared to 67.6% of the patients in the control group (p=0.131).

Even though all patients had been discussed in a multidisciplinary consultation, 27 patients were found to have unresectable disease during surgery. This group, although randomized, was unevenly distributed between the two study arms, with 18 patients in the intervention group and 9 in the control group. Since we did not specify “unresectable disease” as an exclusion criterion in the study protocol, these patients were included in the intention-to-treat analysis.

The per-protocol analysis showed the surgical outcome of the patients who actually underwent CRS. In addition to excluding 27 patients who did not undergo CRS, 3 patients were excluded because of protocol violation: those patients underwent surgery in which the PlasmaJet was used while they were included in the control group. In the per-protocol analysis, complete cytoreductive surgery was achieved in 85.6% of the intervention group compared to 71.5% in the control group (p=0.005).

A sub-analysis for patients with peritoneal carcinomatosis (≥50 lesions on the diaphragm, peritoneum and/or mesentery) showed that the use of the PlasmaJet improved the surgical outcome: complete CRS was achieved in 72.2% in the intervention group versus 51.5% in the control group (p=0.034).

Secondarily, no differences were found between the two groups in terms of surgical time or blood loss. Postoperatively, the number of complications, re-laparotomies or readmissions did not appear to be significantly different between the two groups.

We concluded that the use of the PlasmaJet increased the probability of complete CRS, especially in patients with a large number of peritoneal lesions. Also, the use of the PlasmaJet did not lead to a higher complication rate.

Chapter 5 describes the depth of tissue damage using the PlasmaJet compared to using electrocoagulation devices. In a series of 106 histological samples from 17 patients who underwent interval CRS, the mean depth of tissue damage was found to be smaller in tissue treated with the PlasmaJet (0.15 mm) than in tissue treated with electrocoagulation (0.33 mm) ($p<0.001$). When the PlasmaJet had been used, the tissue often showed superficial damage that was evenly distributed over the surface. After electrocoagulation, the tissue more often showed a rough, irregular damage, as if the sparks had disproportionately damaged the tissue.

Before the implementation of a new device, the additional costs must be calculated. **Chapter 6** summarizes all healthcare costs for the patients included in the PlaComOv study. These costs comprised the healthcare costs from diagnosis and treatment until six weeks after the last cycle of chemotherapy. The mean total health care costs for patients treated with the PlasmaJet were significantly higher than those for patients treated with conventional CRS (€19,414 versus €18,165, $p=0.017$). This difference is fully explained by the additional costs of the use of the PlasmaJet and not by an increase in complications or a longer hospitalization.

Table 1 The average cost of care per patient in euros (2020)

	Diagnostics	Surgery – inpatient care	Chemo therapy	TOTAL COSTS
CRS with PlasmaJet (n=157)	2.034	10.956	6.417	19.414
CRS without PlasmaJet (n=170)	1.974	9.556	6.628	18.165

It should be noted that the difference in cost will be slightly lower in clinical practice since this was a study. During our study, both the fixed and variable costs (handpiece) associated with the use of the PlasmaJet were shared among patients in the intervention group. Since the number of participating hospitals was expanded at

the end of the study, two extra devices were included in the costs, even though the number of inclusions in those hospitals (retrospectively) was low.

The discussion in Chapter 6 refers to the fact that a cost-effectiveness analysis would provide a better overview of all costs because long-term costs and savings will be included. For example, the reduced number of colostomies in the intervention group would be included in the calculation.

Patients who participated in the PlaComOv study were asked to complete questionnaires regarding their quality of life (QoL). They did not know into which study arm they were randomized: with or without the PlasmaJet. Three validated questionnaires were used for this part of the study, two questionnaires of the European Organization for Research and Treatment of Cancer (EORTC) and a general questionnaire in which patients rated their QoL. **Chapter 7** describes the QoL outcomes of patients in the intervention group compared with those of patients in the control group. The high response rate was remarkable: preoperatively, 285 patients (87%) completed the questionnaires, and two years postoperatively, 172 patients (77%) out of 224 living patients completed the questionnaires.

QoL decreased postoperatively but increased after six months to the same QoL level as before surgery. Higher QoL was reported in several domains by patients treated in the intervention group. Twelve months after surgery, patients in the intervention group rated their QoL higher than patients in the control group ($p=0.005$). Two years after surgery, this difference in QoL was no longer significant.

The higher QoL in the intervention group might be partially explained by the surgery outcome. Patients with complete cytoreductive surgery rated their QoL higher than patients without complete cytoreductive surgery.

Part II: The predictive value of CA-125 and CT scan on surgical outcome

The second part of this thesis focused on the predictive value of the tumor marker Cancer Antigen 125 (CA-125) and computed tomography (CT) scan assessment for surgical outcome. In contrast to previous studies that aimed to achieve optimal CRS, we focused on achieving complete CRS.

Chapter 8 presents a systematic literature review as well as an analysis of our own data regarding the predictive value of tumor marker CA-125 for complete CRS. While the literature review showed that normalization of the tumor marker CA-125 after induction chemotherapy was significantly associated with complete CRS, this association was not confirmed by the multivariate analysis of our own data. Therefore, we concluded that the tumor marker CA-125 can be included in the decision whether or not to perform surgery, but only in a multivariate analysis.

Chapter 9 presents a systematic review of CT scan features that are predictive of the inability to achieve complete CRS. Unfortunately, the available literature is very heterogeneous. Several research groups have attempted to develop prediction models, but most models have not been validated in independent cohorts. A validation study is needed to establish the predictive value of CT scan for surgical outcome.

One of the effects of the results of the PlaComOv study was an awareness of a "forgotten group" of patients. This group consists of patients who underwent surgery but in whom it was impossible to remove the tumor. **Chapter 10** describes 27 cases in which surgery was abandoned due to unresectability after abdominal exploration. The treatment of these patients varied, ranging from cessation of treatment to, predominantly, one or several lines of chemotherapy with or without maintenance treatment with bevacizumab or poly adenosine diphosphate-ribose polymerase (PARP) inhibitors. The survival ranged from 2.9 to more than 31.5 months.

Currently, optimal treatment strategies in terms of survival benefit are still ill defined. Further study of this specific group of patients is warranted. In order to provide recommendations for the treatment of these women, we advocate a national or international registry of patients with unresectable cancer and comprehensive follow-up. Subsequently, an international multidisciplinary group of experts should write a clinical guideline with their treatment advice and evaluate this advice through prospective collection of data of comparable patients.

The discussion of this thesis, **Chapter 11**, highlights the key findings and implications for practice. Future research should focus on the long-term outcomes of using the PlasmaJet during CRS.

Appendices

Nederlandse samenvatting

In 2021 kregen 1238 Nederlandse vrouwen de diagnose ovariumcarcinoom. Meer dan 75% van de vrouwen werd gediagnosticeerd in een hoog stadium: er was sprake van metastasen in de gehele buikholte (FIGO stadium III) of zelfs buiten de buikholte (FIGO stadium IV). Bij een FIGO stadium III-IV ovariumcarcinoom is de 1-jaars overleving 74% en de 5-jaars overleving 38%. Van alle Nederlandse vrouwen overlijdt 1% aan een ovariumcarcinoom. Daarmee is het ovariumcarcinoom de dodelijkste gynaecologische maligniteit in Nederland (https://iknl.nl/kankersoorten/eierstokkanker/registratie).

De overlevingswinst voor de vrouwen met een hoog-stadium ovariumcarcinoom (≥FIGO stadium IIB) wordt vooral gevonden in de groep waarbij een complete cytoreductie tijdens chirurgie wordt bereikt. Hiermee wordt bedoeld dat alle zichtbare tumor in de buik is weggehaald. In de afgelopen jaren is steeds duidelijker geworden dat er grote overlevingsverschillen zijn tussen de vrouwen waarbij alle ziekte werd weggehaald en de vrouwen bij wie minimale ziekte (minder dan 1 cm) achterbleef na de ingreep. Chirurgische teams zetten zich daarom in om bij iedere vrouw alle ziekte weg te halen, ook van lastig te bereiken plaatsen en van precaire oppervlakten, zoals de (dunne) darm en het diafragma. Dit proefschrift richt zich daarop en wil in het eerste deel de vraag beantwoorden of de inzet van een nieuw chirurgisch apparaat tijdens de operatie, de PlasmaJet®, de kans op een complete cytoreductie veilig kan vergroten.

Het tweede deel van dit proefschrift richt zich op de voorspellende waarde van de tumormarker CA-125 en de CT scan op een complete cytoreductie. De thesis sluit af met een beschrijving van een cohort patiënten waarbij een cytoreductie niet mogelijk was.

Deel I: Het effect en de veiligheid van de PlasmaJet tijdens cytoreductieve chirurgie

In de introductie van dit proefschrift, in **hoofdstuk 1**, wordt een overzicht van de factoren gegeven die de chirurgische uitkomst beïnvloeden. Het is belangrijk om de patiënte preoperatief zo goed mogelijk in kaart te brengen. Hierdoor worden de patiënten geselecteerd die baat hebben bij een cytoreductie en worden de patiënten die hier geen baat bij hebben een operatie bespaard. Een operatie kan plaatsvinden voorafgaand aan de chemotherapie (primaire cytoreductie) of na drie kuren chemotherapie (interval cytoreductie).

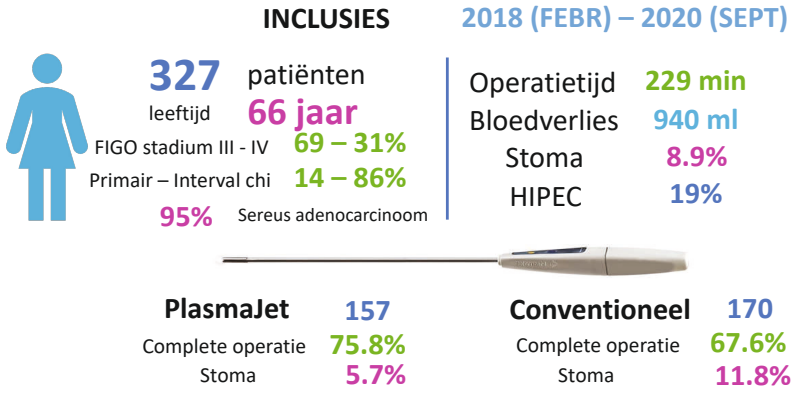
De vraag rijst of de inzet van nieuwe apparaten tijdens de operatie, zoals de PlasmaJet®, de uitkomst van de operatie kan verbeteren. De PlasmaJet zet argongas om in plasma en heeft een aantal voordelen ten opzichte van andere apparatuur. Door het vaporiserende effect van plasma kunnen zeer kleine oppervlakkige uitzaaiingen op bijvoorbeeld de darm worden verdampt. Daarnaast kan door het ablatie-effect van plasma op een eenvoudiger manier het juiste weefselvlak tussen de weefsels worden gevonden. Dit juiste vlak is soms moeilijker zichtbaar door de verklevingen die ontstaan zijn door de tumor. Tenslotte is de PlasmaJet een elektrisch neutraal apparaat waardoor er geen spiercontracties optreden tijdens het verwijderen van tumor op bijvoorbeeld het diafragma.

Om meer inzicht te krijgen bij welke operaties de PlasmaJet kan worden ingezet en of het gebruik van de PlasmaJet veilig en effectief is tijdens een operatie voor een ovariumcarcinoom, is een literatuurstudie verricht. **Hoofdstuk 2** bevat een overzicht van het beperkte bewijs dat in 2019 bekend was. De belangrijkste bevinding van deze literatuurstudie is dat een gerandomiseerd onderzoek ontbreekt. Zowel effecten van het gebruik op het gebied van complicaties en kwaliteit van leven als langetermijneffecten zoals de progressievrije periode, de totale overleving en de kosteneffectiviteit zijn onbekend.

Hieruit voortvloeiend is een multicentrische gerandomiseerde studie opgezet, de PlaComOv-studie. 'PlaComOv' is een acroniem voor 'Will the use of the PLAsmaJet® device improve the rate of COMplete cytoreductive surgery for advanced-stage OVarian cancer'. In **hoofdstuk 3** wordt het onderzoeksprotocol van deze studie beschreven. De PlaComOv-studie had als primair doel de effectiviteit en de veiligheid van de PlasmaJet te onderzoeken. Onze hypothese was dat de PlasmaJet effectief en veilig genoemd kon worden indien er door de inzet van dit apparaat een toename van 15% in het aantal complete cytoreducties kon worden aangetoond zonder dat het gebruik zou leiden tot een toename van complicaties.

Hoofdstuk 4 toont een gedetailleerde beschrijving van de operatieuitkomst van 327 vrouwen met een hoog-stadium epitheliaal ovariumcarcinoom. Tussen februari 2018 en september 2020 zijn in totaal 327 patiënten voor de PlaComOv-studie geïncludeerd: 157 in de interventiegroep en 170 in de controlegroep. Bij de randomisatie is gestratificeerd voor een verdenking op ovariumcarcinoom versus een bewezen ovariumcarinoom, een primaire versus interval cytoreductie, de aanwezigheid versus afwezigheid van een peritonitis carcinomatosa op de CT scan en het wel of niet aanvullend toedienen van hyperthermische intraperitoneale chemotherapie (HIPEC).

Bij de patiënten in de interventiegroep kon de chirurg ervoor kiezen om tijdens de operatie de PlasmaJet te gebruiken. Dit werd in 75% van de operaties gedaan.



Figuur 1 Resultaten uit de PlaComOv studie. Chi =chirurgie

Uit de intention-to-treat analyse blijkt dat 75.8% van de patiënten in de interventiegroep een complete cytoreductie onderging ten opzichte van 67.6% van de patiënten in de controlegroep (p=0.131).

Ondanks het feit dat alle patiënten in een multidisciplinair overleg waren besproken, bleek bij 27 patiënten sprake van niet-resectabele ziekte tijdens de operatie. Deze groep was, hoewel gerandomiseerd, ongelijk verdeeld over beide studiearmen met 18 patiënten in de interventie- en 9 patiënten in de controlegroep. Omdat in het studieprotocol een 'niet-resectabele ziekte' niet als exclusiecriterium stond vermeld, zijn deze patiënten meegenomen in de intention-to-treat analyse.

De per-protocol analyse toonde de resultaten van de operatieuitkomst van de patiënten die daadwerkelijk een cytoreductie ondergingen. Behalve dat de patiënten die geen cytoreductie ondergingen zijn geëxcludeerd, zijn ook patiënten waarbij sprake was van protocolschending geëxcludeerd: drie patiënten zijn geopereerd met behulp van de PlasmaJet terwijl zij geïncludeerd waren in de controlegroep. In de per-protocol analyse werd een complete cytoreductie bereikt in 85.6% in de interventiegroep ten opzicht van 71.5% in de controlegroep (p=0.005).

Bij een sub-analyse voor patiënten met een peritonitis carcinomatosa (≥50 laesies op het diafragma, het peritoneum en/of mesenterium) bleek dat inzet van de PlasmaJet van invloed was op de operatieuitkomst: een complete cytoreductie werd bereikt in 72.2% in de interventiegroep versus in 51.5% in de controlegroep (p=0.034).

Er werd geen significant verschil tussen beide groepen gevonden wat betreft operatieduur en bloedverlies. Postoperatief bleek het aantal complicaties, re-laparotomieën en heropnames niet significant verschillend tussen beide groepen.

Wij hebben geconcludeerd dat bij het gebruik van de PlasmaJet de kans op een complete cytoreductie toeneemt, vooral wanneer er sprake was van een groot aantal peritoneale laesies. Tevens leidde het gebruik van de PlasmaJet niet tot meer complicaties waaruit we concludeerden dat het apparaat voor de patiënte veilig is om te gebruiken.

In **hoofdstuk 5** wordt een beschrijving gegeven van de weefselschade na het gebruik van de PlasmaJet. In een serie van 106 histologische samples van 17 patiënten die een interval cytoreductie ondergingen, bleek de gemiddelde diepte van weefselschade lager in het weefsel dat behandeld was met de PlasmaJet (0.15 mm) dan in het weefsel dat behandeld was met elektrocoagulatie (0.33 mm) (p<0.001). Indien de PlasmaJet was gebruikt liet het weefsel vaak een oppervlakkige schade zien die evenredig over het oppervlak was verspreid. Indien elektrocoagulatie was gebruik liet het weefsel vaker een ruwe, irregulaire beschadiging zien alsof vonkjes het weefsel onevenredig hadden beschadigd.

Indien sprake is van de implementatie van een nieuw apparaat, moet duidelijk zijn welke extra kosten dit met zich mee brengt. **Hoofdstuk 6** toont een overzicht van alle kosten van de geïncludeerde patiënten van de PlaComOv-studie. Dit waren de zorgkosten in het traject van diagnose en behandeling tot zes weken na de laatste chemotherapie. De kosten rondom de operatie zijn hierin apart weergegeven. De gemiddelde totale gezondheidskosten bij het gebruik van de PlasmaJet waren €19.414. Indien de PlasmaJet niet werd gebruikt bedroegen de kosten €18.165.

Tabel 1 De gemiddelde kosten van zorg per patiënt in euro's (2020). Chi = chirurgie.

	Diagnostiek	Operatie - opname	Chemotherapie	TOTALE KOSTEN
Chi met PlasmaJet (n=157)	2.034	10.956	6.417	19.414
Chi zonder PlasmaJet (n=170)	1.974	9.556	6.628	18.165

De studie toonde aan dat het verschil in kosten alleen veroorzaakt werd door het gebruik van het extra apparaat en niet door een toename in complicaties of langere opnameduur. Er moet worden opgemerkt dat het verschil in kosten in werkelijkheid iets kleiner zal zijn omdat dit een onderzoek in studieverband betrof. Zowel de vaste als variabele kosten (handstuk) die de mogelijkheid van het gebruik van de PlasmaJet met zich mee brengt waren nu alleen verdeeld over de patiënten in de interventiegroep. Ook werd het aantal includerende ziekenhuizen aan het einde van de studie uitgebreid waardoor er twee extra apparaten in de kosten zijn meegenomen terwijl het aantal inclusies in die ziekenhuizen (achteraf) laag was. In de discussie van hoofdstuk 6 wordt verwezen naar het belang van een kosten-effectiviteitsanalyse. Deze analyse kan worden verricht als de lange termijn resultaten van kosten en besparingen bekend zijn en dan zal het verminderde aantal stoma's in de groep waarbij de PlasmaJet kon worden gebruikt in de analyse worden meegenomen.

Patiënten die deelnamen aan de PlaComOv-studie werden gevraagd om vragenlijsten in te vullen ten aanzien van hun kwaliteit van leven. Zij wisten niet in welke studiearm zij waren behandeld: met of zonder de PlasmaJet. Hiervoor zijn drie gevalideerde vragenlijsten gebruikt: twee vragenlijsten van de Europese Organisatie voor Onderzoek en behandeling van kanker (EORTC) en een algemene vragenlijst waarin patiënten hun kwaliteit van leven kunnen beoordelen. In **hoofdstuk 7** worden de uitkomsten van kwaliteit van leven van de patiënten in de interventiegroep vergeleken met de kwaliteit van leven van de patiënten in de controlegroep.

Opvallend is de hoge respons: Preoperatief hadden 285 patiënten (87%) de vragenlijsten ingevuld. Twee jaar na de operatie vulden 172 patiënten (77%) van de 224 nog levende patiënten de vragenlijst in. De kwaliteit van leven daalde postoperatief, maar steeg na zes maanden tot de kwaliteit van leven zoals voor de operatie. Op verschillende domeinen wordt een hogere kwaliteit van leven gerapporteerd door mensen die behandeld zijn in de interventiegroep. Twaalf maanden na de operatie gaven de patiënten in de interventiegroep een hoger cijfer

voor hun gezondheid dan patiënten in de controlegroep (P=0.005). Twee jaar na de operatie was dit effect niet meer zichtbaar. Een hogere kwaliteit van leven in de interventiegroep leek ten dele verklaard te worden door de operatieuitkomst. Patiënten bij wie sprake was van een complete cytoreductie beoordeelden hun kwaliteit van leven hoger dan patiënten waarbij geen sprake was van een complete cytoreductie. Een andere verklaring kan de diepte van de weefselschade zijn. Bij het gebruik van de PlasmaJet is de infiltratie in het weefsel minder diep dan bij het gebruik van elektrocoagulatie, wat een andere reactie van herstel van het weefsel kan geven.

Deel II: De voorspellende waarde van CA-125 en CT scan op de operatieuitkomst

Het tweede deel van dit proefschrift heeft zich gericht op de voorspellende waarde van de tumormarker CA-125 en de beoordeling van de CT scan op de uitkomst van de operatie. Hierbij lag de focus op het behalen van een complete cytoreductie. Eerdere publicaties handelden veelal over het behalen van een optimale cytoreductie (restziekte tot 1 cm) en daarom hebben we opnieuw een systematisch literatuuronderzoek verricht.

In **hoofdstuk 8** wordt een overzicht van de bestaande studies uit de literatuur gegeven evenals een analyse van onze eigen data met betrekking tot de voorspellende waarde van tumormarker CA-125 op een complete cytoreductie. Ondanks dat het literatuuronderzoek aantoonde dat een normalisatie van de tumormarker CA-125 na inductiechemotherapie significant geassocieerd is met een complete cytoreductie, werd dit in de multivariate analyse van onze eigen data niet gezien. De tumormarker CA-125 kan daarom meegenomen worden in de beslissing om een patiënt wel of niet te opereren, maar niet als een op zichzelf staande parameter.

Hoofdstuk 9 toont een overzicht van CT scan parameters die in de literatuur genoemd worden en een voorspellende waarde lijken te hebben op de operatieuitkomst. Helaas is de beschikbare literatuur zeer divers. Verschillende onderzoeksgroepen hebben gepoogd om een predictiemodel te maken, waarbij de meeste modellen niet zijn gevalideerd in onafhankelijke cohorten. Er is duidelijk behoefte aan een validatiestudie om een antwoord te krijgen op de voorspellende waarde van de CT scan op de operatieuitkomst en of de CT scan het beste onderzoek is om de juiste patiënte te selecteren die baat heeft bij een cytoreductie.

Een van de effecten van de PlaComOv-studie was dat we ons bewust zijn geworden van een 'vergeten groep'. Deze groep betreft de patiënten die wel worden geopereerd, maar bij wie de tumor niet kan worden weggenomen. In **hoofdstuk 10** worden 27 patiënten beschreven die na inclusie voor de PlaComOv-studie gepland werden voor een cytoreductie maar waarbij dit tijdens de operatie niet mogelijk bleek. Er blijkt geen rode lijn zichtbaar in de patiëntenkarakteristieken of de uitkomst van preoperatieve onderzoeken. De behandeling na de operatie bleek zeer verschillend te zijn en varieerde van het volledig staken van de behandeling tot het continueren met meerdere lijnen chemotherapie. De levensverwachting varieerde van 2.9 tot langer dan 31.5 maanden. Dit hoofdstuk is een oproep om gegevens van deze patiënten te bundelen om in de toekomst te komen tot een (inter)nationaal advies ten aanzien van een zinvol na-traject voor deze inoperabele patiënten.

In de discussie van dit proefschrift, **hoofdstuk 11**, wordt de nadruk gelegd op de belangrijkste bevindingen van de PlaComOv-studie en de implicaties voor de praktijk. Toekomstig onderzoek moet zich onder andere richten op de langetermijnuitkomsten van de inzet van de PlasmaJet tijdens een cytoreductie.

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List of abbreviations

ASEOC	Advanced stage epithelial ovarian cancer
ASOC	Advanced stage ovarian cancer
CA-125	Cancer Antigen 125
CCS	Complete Cytoreductive Surgery
CEA	Carcinoembryonic Antigen
CRS	Cytoreductive Surgery
cfDNA	cell-free tumor DNA
CI	Confidence Interval
CRS	Cytoreductive surgery
CT	Computed Tomography
DMR	Differentially Methylated Regions
EC	Electrocoagulation
ESGO	European Society of Gynaecological Oncology
ESUR	European Society of Urogenital Radiology
EOC	Epithelial Ovarian Cancer
EORTC	European Organization for Research and Treatment of Cancer
FIGO	International Federation of Gynecology and Obstetrics
HBD	Healthy Blood Donor
HIPEC	Hyperthermic intraperitoneal chemotherapy
HIS	Hyperspectral Imaging
iCRS	interval Cytoreductive Surgery
IQR	Interquartile Range
ITT	Intention-to-treat
NACT	Neoadjuvant Chemotherapy
NGS	Next-generation sequencing
OS	Overall Survival
PARP	Poly Adenosine Diphosphate-Ribose Polymerase
PCI	Peritoneal Cancer Index
PCR	Polymerase Chain Reaction
pCRS	primary Cytoreductive Surgery
PFS	Progression Free Survival
PJ	PlasmaJet
PlaComOv	Acronym: Will the use of the PlasmaJet surgical device the percentage of Complete cytoreductive surgery for patients with Ovarian cancer
QoL	Quality-of-life
RCT	Randomized Controlled Trial
RD	Risk Difference

SD	Standard Deviation
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TNM	Tumor-Node-Metastasis
VAS	Visual Analog Scale
WHO	World Health Organization

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1. Van de Berg NJ, **Nieuwenhuyzen-de Boer GM**, Gao XS, Rijstenberg L, van Beekhuizen HJ. Plasma Device Functions and Tissue Effects in the Female Pelvis: a systematic review. Cancers (Basel). 2023, 15, 2386. doi. org/10.3390/cancers15082386.

2. **Nieuwenhuyzen-de Boer GM**, van de Berg NJ, Gao XS, Ewing-Graham PC, van Beekhuizen HJ. The effects of neutral argon plasma versus electrocoagulation on tissue in advanced-stage ovarian cancer: a case series. J Ovarian Res. 2022; Dec 15(1), 140. doi.org/10.1186/s13048-022-01070-5.

3. **Nieuwenhuyzen-de Boer GM**, Kengsakul M, Boere IA, van Doorn HC, van Beekhuizen HJ. Unresectable Ovarian Cancer Requires a Structured Plan of Action: A Prospective Cohort Study. Cancers (Basel). 2022 Dec 22;15(1):72. doi: 10.3390/cancers15010072. PMID: 36612068; PMCID: PMC9817808.

4. Kengsakul M, **Nieuwenhuyzen-de Boer GM**, Udomkarnjananun S, Kerr SJ, van Doorn HC, van Beekhuizen HJ. Clinical validation and comparison of the Comprehensive Complication Index and Clavien-Dindo classification in predicting post-operative outcomes after cytoreductive surgery in advanced ovarian cancer. Int J Gynecol Cancer. 2022 Dec 8:ijgc-2022-003998. doi: 10.1136/ijgc-2022-003998. PMID: 36600504.

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6. **Nieuwenhuyzen-de Boer GM**, Geraerds AJLM, van der Linden MH, van Doorn HC, Polinder S, van Beekhuizen HJ. Cost Study of the PlasmaJet Surgical Device Versus Conventional Cytoreductive Surgery in Patients With Advanced-Stage Ovarian Cancer. JCO Clin Cancer Inform. 2022 Sep;6:e2200076. doi: 10.1200/CCI.22.00076. PMID: 36198130.

7. Kengsakul M*, **Nieuwenhuyzen-de Boer GM***, Udomkarnjananun S, Kerr SJ, van Doorn HC, van Beekhuizen HJ. Factors Predicting 30-Day Grade IIIa–V Clavien–Dindo Classification Complications and Delayed Chemotherapy

Initiation after Cytoreductive Surgery for Advanced-Stage Ovarian Cancer: A Prospective Cohort Study. Cancers 2022, 14, 4181. doi.org/10.3390/cancers14174181.

8. Kengsakul M, **Nieuwenhuyzen-de Boer GM**, Udomkarnjananun S, Kerr SJ, Niehot CD, van Beekhuizen HJ. Factors predicting postoperative morbidity after cytoreductive surgery for ovarian cancer: a systematic review and meta-analysis. J Gynecol Oncol. 2022 Jun 7. doi: 10.3802/jgo.2022.33.e53.

9. **Nieuwenhuyzen-de Boer GM**, Hofhuis W, Reesink-Peters N, Willemsen S, Boere IA, Schoots IG, Piek JMJ, Hofman LN, Beltman JJ, van Driel WJ, Werner HMJ, Baalbergen A, van Haaften-de Jong AMLD, Dorman M, Haans L, Nedelcu I, Ewing-Graham PC, van Beekhuizen. Adjuvant Use of PlasmaJet Device During Cytoreductive Surgery for Advanced-Stage Ovarian Cancer: Results of the PlaComOv-study, a Randomized Controlled Trial in The Netherlands. Ann Surg Oncol. 2022 May 13. doi: 10.1245/s10434-022-11763-2.

10. **Nieuwenhuyzen-de Boer GM**, van Beekhuizen HJ. ASO Author Reflections: The PlasmaJet® Device Contributes to an Increase in the Number of Complete Cytoreductive Surgeries for Ovarian Cancer Patients. Ann Surg Oncol. 2022 Apr 28. doi: 10.1245/s10434-022-11827-3.

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12. Kengsakul M, **Nieuwenhuyzen-de Boer GM**, Bijleveld AHJ, Udomkarnjananun S, Kerr SJ, Niehot CD, van Beekhuizen HJ. Survival in Advanced-Stage Epithelial Ovarian Cancer Patients with Cardiophrenic Lymphadenopathy Who Underwent Cytoreductive Surgery: A Systematic Review and Meta-Analysis. Cancers (Basel). 2021 Oct 7;13(19):5017. doi: 10.3390/cancers13195017.

13. **Nieuwenhuyzen-de Boer GM**, Dasgupta S, Ewing-Graham PC, Van Bockstal MR. Adenoid cystic carcinoma of the Bartholin gland is not HPV-related: A case report and review of literature. Pathol Res Pract. 2020 Jun;216(6):152968. doi: 10.1016/j.prp.2020.152968.

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15. **Nieuwenhuyzen-de Boer GM**, Hofhuis W, Reesink-Peters N, Ewing-Graham PC, Schoots IG, Beltman JJ, Piek JMJ, Baalbergen A, Kooi GS, Haaften A van, Huisseling H van, Haans L, Dorman M, Beekhuizen JJ van. Evaluation of effectiveness of the PlasmaJet surgical device in the treatment of advanced stage ovarian cancer (PlaComOv-study): study protocol of a randomized controlled trial in the Netherlands. BMC Cancer 19, 58 (2019). doi. org/10.1186/s12885-019-5275-3.

16. **Nieuwenhuyzen-de Boer GM**, Kamping MA, Kersting S, Dijkman A. Anemia and Thrombocytopenia after delivery: a case study of Thrombotic Thrombocytopenic Purpura (TTP). Clin Case Rep Rev 2016(1): doi: 10 15761/CCRR 1000233.

17. **Nieuwenhuyzen-de Boer GM**, Gerestein CG, Eijkemans MJC, Burger CW, Kooi GS. Nomogram for 30-day morbidity after primary cytoreductive surgery for advanced stage ovarian cancer. Eur J Gynecol Oncol. 2016;37(1):63-8.

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19. Dijkstra MG, Heideman DAM, Kemenade FJ van, Hogewoning JA, Hesselink AT, Verkuijten CGT, Baal, WM van, **Nieuwenhuyzen-de Boer GM**, Snijders PJF, Meijer JLM, Brush-based self-sampling in combination with GP5+/6+-PCR-based hrHPV testing: High concordance with physician-taken cervical scrapes for HPV genotyping and detection of high-grade CIN, Journal of Clinical Virology. 2012;54:147-51.

20. Gerestein CG, **Nieuwenhuyzen-de Boer GM**, Eijkemans MJ, Kooi GS, Burger CW. Prediction of 30-day morbidity after primary cytoreductive surgery for advanced stage ovarian cancer. Eur J Cancer. 2010;46(1):102-9.

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PhD Portfolio

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PhD period	January 2018 – March 2023
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Copromotor	Dr. H.J. van Beekhuizen

Summary of PhD training and teaching activities		*ECTS*
General courses		
2017	Basiscursus Regelgeving en Organisatie voor Klinisch Onderzoekers (BROK)	1.5
2018	Gemstracker	0.1
2020	Clinical Epidemiology (Schiermonnikoog)	2.0
2020	BROK refresher course	0.5
2022	Scientific Integrity	0.3
2022	Medical scientific writing	1.0
Oral presentations		
2018	Refereer Rotterdamse Gynaecogen Opleidings Cluster (RGOC) 'PlaComOv study: ongoing research'	0.3
2019	Nederlandse Vereniging voor Obstetrie en Gynaecologie (NVOG) 55th Gynaecongress, 'PlaComOv study: ongoing research'	0.3
2021	NVOG, 58th Gynaecongress, 'PlaComOv study: preliminary results'	0.3
2022	Refereer RGOC, Albert Schweitzer hospital, Dordrecht 'State of the art, endometrial cancer'	0.3
2022	Science Day Albert Schweitzer hospital, Dordrecht 'Quality-of-life outcomes after cytoreductive surgery for advanced stage ovarian cancer' (First price)	0.5
2022	International Gynecologic Cancer Society Congress (IGCS), New York City -Cost study of PlasmaJet Surgical device versus conventional cytoreductive surgery in advanced stage ovarian cancer patients -Role of genome-wide methylation profiling of circulating cell-free DNA by methylated DNA sequencing (Med-SEQ) in advanced stage ovarian cancer	1.0

Poster presentations

2021	European Society of Gynaecological Oncology (ESGO), Prague (2 posters)	0.6
2022	Science Day Albert Schweitzer hospital, Dordrecht (3 posters)	0.3
2022	International Gynecologic Cancer Society Congress (IGCS), New York City (2 posters)	

(Inter)national conferences, symposia and courses

2018	Radiation protection course 5B, Diffusion of radioactive substances	1.5
2018	COBRAdagen 2018	0.3
2018	Teach the Teacher III	0.2
2018	International Ovarian Tumor Analysis (IOTA) course	1.0
2018	NVOG, 53st Gynaecongress, Pijlerdagen	0.3
2019	NVOG, 55th Gynaecongress Pijlerdagen	0.3
2019	22nd Doelen Congress, Rotterdam	0.3
2019	Congress, ESGO, Athens	0.5
2020	Symposium Dutch Gynaecology Oncology Group (DGOG)	0.1
2020	Course VvAA 'Onderhandelen', Utrecht	0.1
2020	NVOG, 57th Gynaecongress	0.3
2021	Symposium trophoblasttumor, NVOG	0.1
2021	Advanced techniques in laparoscopic gynecologic surgery, Straatsburg	0.5
2021	Congress, ESGO, Prague	0.5
2021	NVOG, 58th Gynaecongress	0.3
2022	Symposium Dutch Gynaecology Oncology Group (DGOG)	0.1
2022	Training Shared Decision Making	0.1
2022	Refresher course Managing Obstetric Emergencies and Trauma (MOET)	1.0
2022	Science Day Albert Schweitzer hospital, Dordrecht	-
2022	Congress, IGCS, New York City	0.5
2022	NVOG, 59th Gynaecongress	0.3
2022	Congress, Modernisering Medische Vervolgopleidingen (MMV)	0.2
2018-2022	Refereer RGOC	1.0
2018-2022	Working Group Oncological Gynaecology	1.0
2018-2022	Symposium BRCAdemy	1.0
2018-2023	Multidisciplinary Tumor Board, Gynecological Oncology	1.0

Teaching activities

2017	Training sessions PlasmaJet for medical specialists, skillslab	1.5

2017-present	Teaching activities bachelor students 'Geneeskunde', Erasmus University	2.0
2019	Development e-learning 'HPV- Cervixpathologie' master students 'Geneeskunde', Erasmus University	1.0
2023	Training sessions PlasmaJet for medical specialists, skillslab	0.5
Supervision		
2019-2023	Supervising master thesis: Medical students Erasmus MC and students TU Delft *Anna Bijleveld, Puck Brons, Sharline Perez, Laurie de Weerd, Hanane Aamran, Dominique Plak*	6.0
Miscellaneous		
2018-2022	Patient Organization Olijf: contact, newsletters, website information	2.0
2018-2019	Fellowship Gynecological Oncology, Erasmus MC, Rotterdam	6.0
2019-present	NVOG Committee 'Patient communication'	0.5
2020-2022	Federation of Medical Specialists (FMS): committee 'Development information films'	1.0
	TOTAL	**42**

Dankwoord

Inmiddels is het alweer zes jaar geleden dat Heleen en ik onze nieuwsgierigheid niet meer konden bedwingen. Het was eind juni 2017 en we zouden die dag uitsluitsel krijgen over een ingediende subsidieaanvraag. We zaten samen in onze werkkamer in de voormalige Daniel den Hoedkliniek op Rotterdam-Zuid. Om half 5 hadden we nog geen bericht ontvangen. Hoewel ik ook wel begrijp dat als mensen hard aan het werk zijn een telefoontje juist vertragend werkt, pakte ik toch de telefoon. Het antwoord stelde ons enigszins gerust. De medewerkers hadden het pand nog niet verlaten en waren bezig met het versturen van de definitieve besluiten. Even later kwam het bericht dat onze aanvraag positief was beoordeeld en het ingediende onderzoeksvoorstel een subsidie kreeg toegekend. We waren ontzettend blij en dankbaar. Op dat moment dachten we niet aan de hobbels en obstakels die we de komende jaren zouden moeten trotseren. En nu, zes jaar later, lijkt het opnieuw alsof die obstakels er nauwelijks geweest zijn. Alsof de handtekeningen die voor een multicenter studie nodig zijn er zo waren. Alsof er geen inclusie-dip was tijdens de Coronapandemie, alle CRF's op tijd waren ingevuld, nooit een PlasmaJet device buiten de studie is gebruikt en er nooit tot 's avonds laat en hele zaterdagen aan het onderzoek is gewerkt. We zijn over al die hobbels heen en u heeft de antwoorden op de onderzoeksvragen in handen. Alle reden om iedereen die een bijdrage heeft geleverd aan het tot stand komen van dit proefschrift te bedanken.

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laatste twee jaar werd elk vrij moment besteed aan het onderzoek en door jouw hulp was dat drie uur per week extra! Ik hoop dat je nog vele jaren bij ons blijft komen.

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Allerliefste Linco, Christian, Thomas en Maurits, jullie hebben mij ongetwijfeld het meest gesteund tijdens dit traject. Ik bewonder jullie geduld, optimisme, kookkunsten en solidariteit tijdens onze sportactiviteiten. Dank voor jullie onvoorwaardelijke liefde en dat we met elkaar mogen zeggen: ‘Soli Deo Gloria’.

Curriculum Vitae

Gatske Maaike Nieuwenhuyzen- de Boer, oudste dochter van Thomas de Boer en Trijntje Venema, werd op 18 april 1979 geboren in Smallingerland. In 1997 slaagde zij voor het atheneum aan de Jacobus Fruytier scholengemeenschap te Apeldoorn. Zij volgde haar opleiding geneeskunde aan de Universiteit van Utrecht. Tijdens deze studie was zij actief bij de studentenvereniging CSFR, waarvan een jaar als landelijk fiscus. Na het afronden van haar bachelor verbleef zij zes maanden in Guinee. Hier werd duidelijk dat als ze terug zou komen, ze vooral meer gynaecologische kennis wilde overdragen.

In 2004 behaalde zij haar artsexamen en in 2007 rondde zij de opleiding tot tropenarts af aan het Koninklijke Instituut voor de Tropen in Amsterdam. Gatske was werkzaam als anios Gynaecologie en Verloskunde in het Albert Schweitzer ziekenhuis in Dordrecht (dr. G.S. Kooi). Nadat zij in 2010 was aangenomen voor de opleiding tot gynaecoloog werkte zij tot en met 2016 als aios in het Reinier de Graaf Gasthuis in Delft (dr. W.A. ter Harmsel), het Erasmus MC in Rotterdam (Prof. Dr. C.W. Burger en dr. M.J. Ten Kate-Booij) en het Albert Schweitzer ziekenhuis in Dordrecht (drs. L.N. Hofman). Tijdens de opleiding tot gynaecoloog haalde zij haar basiskwalificatie onderwijs (BKO). In 2018 en 2019 deed zij een fellowship Gynaecologische Oncologie in het Erasmus MC (Dr. H.C. van Doorn).

In 2017 schreef zij een subsidieaanvraag voor een doelmatigheidsonderzoek naar de inzet van de PlasmaJet tijdens cytoreductieve chirurgie voor het hoogstadium ovariumcarcinoom, welke werd gehonoreerd door ZonMw (dr. H.J. van Beekhuizen). Voor dit onderzoek werkte zij samen met mensen uit diverse ziekenhuizen in Nederland. De resultaten van dit onderzoek zijn beschreven in dit proefschrift. Ze zijn gepresenteerd op zowel nationale als internationale congressen en gepubliceerd in diverse internationale tijdschriften.

Sinds 1 januari 2020 is Gatske werkzaam in het Erasmus MC en het Albert Schweitzer ziekenhuis. Zij werkt als gynaecoloog-oncoloog, doet onderzoek en is sinds juni 2023 lokaal opleider binnen het Rotterdamse Gynaecologen Opleidings Cluster (RGOC).

Op 29 september 2005 trouwde zij met Linco Nieuwenhuyzen. Zij hebben drie kinderen, Christian, Thomas en Maurits.