FACULTY OF MEDICINE AND HEALTH SCIENCES

Secondary Debulking Surgery of Ovarian Cancer: A Critical Appraisal

Ottilie Derycke
Student number: 01606885

Supervisors: Prof. Dr. Hannelore Denys, Dr. Emiel De Jaeghere

A dissertation submitted to Ghent University in partial fulfilment of the requirements for the degree of Master of Medicine in Medicine

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Ottilie Derycke (student)

Prof. Dr. Hannelore Denys (promotor)

Preface

First of all, I would like to thank my supervisor, Prof. Dr. Denys, and co-supervisor, Dr. De Jaeghere, for the guidance in the learning process of which this master's thesis is the result. Constructive feedback was provided and I was motivated to always get the most out of this assignment.

I would also like to thank Jasper, my parents, family, and friends, as I found myself always welcome to get any concerns off my chest. Your spare time also made this thesis what it is, either by your help in reviewing it or by supporting me at all times.

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Abbreviations

95%CI	95% confidence interval
AGO	Arbeitsgemeinschaft Gynäkologische Onkologie
AJCC	American Joint Committee on Cancer
AOC	Advanced ovarian cancer
BER	Base excision repair
*BRCA*m	*BRCA* mutated cells
*BRCA*wt	*BRCI* wild type
CA-125	Cancer antigen 125
CT	Computed tomography
DESKTOP	Descriptive Evaluation of perioperative Selection KriTeria for OPerability in recurrent OVARian cancer
DFI	Disease free interval
ECOG	Eastern Cooperative Oncology Group
EOC	Epithelial ovarian cancer
FDA	Food and Drug Administration
FIGO	Fédération Internationale de Gynécologie et d'Obstétrique
GCIG	Gynecological Cancer InterGroup
GOG	Gynaecologic Oncology Group
HGSOC	High-grade serous ovarian cancer
HIPEC	Hyperthermic intraperitoneal chemotherapy
HNPCC	Hereditary Non-Polyposis Colorectal Cancer
HR	Homologous repair
HRD	Homologous repair deficiency
IDS	Interval debulking surgery
IP	Intraperitoneal
IV	Intravenous
LGSOC	Low-grade serous ovarian cancer
LOROCSON	Late onset Recurrent Ovarian Cancer: Surgery or Not
MOC	Mucinous ovarian cancer
MRI	Magnetic resonance imaging
MSKCC	Memorial Sloan Kettering Cancer Centre
NPV	Negative predictive value
OC	Ovarian cancer
OCCC	Ovarian clear cell cancer
OS	Overall survival
PARP	Poly ADP ribose polyperase
PARPi	Poly ADP ribose polyperase inhibitor
PCT	Primary chemotherapy
PDS	Primary debulking surgery
PET	Positron Emission Tomography
PFI	Platinum-free interval
PFS	Progression free survival
Post-OP	Post-operative
PPV	Positive predictive value
QOL	Quality of life
R0	No macroscopic disease
RD	Residual disease
ROC	Recurrent ovarian cancer
RT	Residual tumour
SC	Cytoreductive surgery
SOC	Surgery or Chemotherapy in Recurrent Ovarian Cancer
SOCcer	Surgery Ovarian Cancer Recurrence
TFI	Treatment free interval

TFIb	Treatment free interval from last biologic agent
TFInp	Treatment free interval from last non-platinum
TFIp	Treatment free interval from last platinum
TME	Tumour microenvironment
TNM	Tumour, lymph nodes, metastasis
ULN	Upper limit of normal
VEGF	Vascular endothelial growth factor
WHO	World Health Organisation

1. Abstract (English)

Purpose: About 80% of women with primary ovarian cancer will eventually be diagnosed with recurrent ovarian cancer. Therefore, questions on the treatment of this patient population need to be answered. As the first level of evidence I data from recent randomised studies is available, surgery in treatment of patients with relapsed ovarian cancer has become a topic of interest. In this thesis, we will discuss the role of secondary cytoreductive surgery.

Methods: The search engines PubMed and Embase were consulted. Key words included 'ovarian cancer', 'debulking surgery', 'recurrence', and 'intraperitoneal chemotherapy' and their combinations. All articles found (3189 articles after removing duplicates) were first screened on title and abstract (2745 studies excluded), and thereafter articles were selected based on their full text (365 studies excluded). Reference lists of all eligible articles were checked for other relevant studies. Conference presentations were included. In total, 79 sources were withheld.

Results: GOG213 demonstrated no overall survival benefit with a difference in median OS of 50.6 months and 64.7 months for surgery versus no surgery respectively (HR 1.29, 95%CI 0.97-1.72, p=0.08), and no PFS benefit was seen, with a difference of 18.9 months versus 16.2 months for surgery versus no surgery respectively (HR 0.82, 95%CI 0.66-1.01) (2). DESKTOP III showed a benefit for surgery compared to no surgery, both in OS (53.7 months versus 46.0 months respectively, HR 0.75, 95%CI 0.58-0.96, p=0.02), and in PFS (18.4 months versus 14.0 months respectively, HR 0.66, 95%CI 0.54-0.82, p<0.001) (3). A third randomised trial, SOC1, is still ongoing and its results are highly anticipated (4).

Conclusion: There is no consensus on survival benefit comparing surgery and no surgery, as GOG213 and DESKTOP III show different conclusions. However, both studies showed an overall survival benefit in women receiving complete macroscopic debulking, compared to women left with residual disease after surgery. Selection of the right patients and execution by a well-trained surgeon are key.

2. Abstract (Nederlands)

Doel: Gezien ongeveer 80% van de vrouwen met ovariumkanker uiteindelijk zal hervallen, is het belangrijk ook vragen over de behandeling van deze patiëntengroep te beantwoorden. Recent zijn de eerste level of evidence I data verschenen uit gerandomiseerde studies. De rol van chirurgie in de behandeling van patiënten met ovariumkanker die hervallen, is een hot topic in de gynaecologische oncologie. In deze thesis bespreken we de rol die secundaire debulking chirurgie hierin speelt.

Methodologie: Er werd gebruik gemaakt van de online databases PubMed en Embase. Er werd gezocht via de concepten 'ovarian cancer', 'debulking surgery', 'recurrence', 'intraperitoneal chemotherapy' en combinaties van concepten. De bekomen artikels (3189 na het verwijderen van duplicaten) werden eerst geselecteerd op basis van titel en abstract (2745 artikels verwijderd), en nadien verder uitgefilterd op de volledige inhoud en tekst (365 artikels verwijderd). De referentielijsten van artikels werden gescreend op relevante artikels en ook conferentiepresentaties werden gebruikt. In totaal werden 79 bronnen weerhouden.

Resultaten: GOG213 toonde geen overall survival benefit aan, met een verschil in OS van 50.6 maanden tegenover 64.7 maanden voor respectievelijk chirurgie en geen chirurgie (HR 1.29, 95%CI 0.97-1.72, p=0.08) en toonde ook geen PFS voordeel, met een verschil van 18.9 maanden tegenover 16.2 maanden voor respectievelijk chirurgie versus geen chirurgie (HR 0.82, 95%CI 0.66-1.01) (2). DESKTOP III toonde wel een overlevingsvoordeel voor patiënten die chirurgie ondergingen tegenover patiënten die geen chirurgie ondergingen, zowel wat betreft OS (53.7 maanden versus 46.0 maanden respectievelijk, HR 0.75, 95%CI 0.58-0.96, p=0.02) als PFS (18.4 maanden versus 14.0 maanden respectievelijk, HR 0.66, 95%CI 0.54-0.82, p<0.001) (3). Een derde gerandomiseerde studie, SOC1, loopt momenteel nog en naar de resultaten wordt met grote interesse uitgekeken (4).

Conclusie: Er is geen consensus wat betreft een overlevingsvoordeel van chirurgie ten opzichte van geen chirurgie, gezien de verschillende conclusies uit GOG213 en DESKTOP III. Wel is het zeker dat vrouwen die na chirurgie geen residuele ziekte meer hebben, een langere overleving tonen dan vrouwen die wel nog residuele ziekte overhouden na een operatie. Daarom is de selectie van de juiste patiënten en het uitvoeren van de ingreep door een getrainde en gespecialiseerde chirurg essentieel.

3. Introduction

3.1 Cancer as a disease

3.1.1 Orientation and background

The World Health Organisation (WHO) describes cancer as a large and heterogeneous group of diseases, consisting of many different histological and molecular types of neoplasms, marked by the uncontrollable growth of abnormal cells, beyond their usual boundaries, invading neighbouring tissues and sometimes spreading to distant parts of the body, thus affecting multiple organs (5). This last process, called metastasizing, is the main cause of death from cancer.

Annually, about nine and a half million people die from cancer, making it the second leading cause of death worldwide, following cardiovascular diseases. About eighteen million people are newly diagnosed each year. Among the most prevalent cancers are lung, breast, colorectal, and prostate cancer, whereas the most lethal cancers are lung, colorectal, stomach, and liver cancer (see figure 1). In Belgium, 67 087 new patients were reported in 2015, with the same four types noted as most prevalent (5-8).

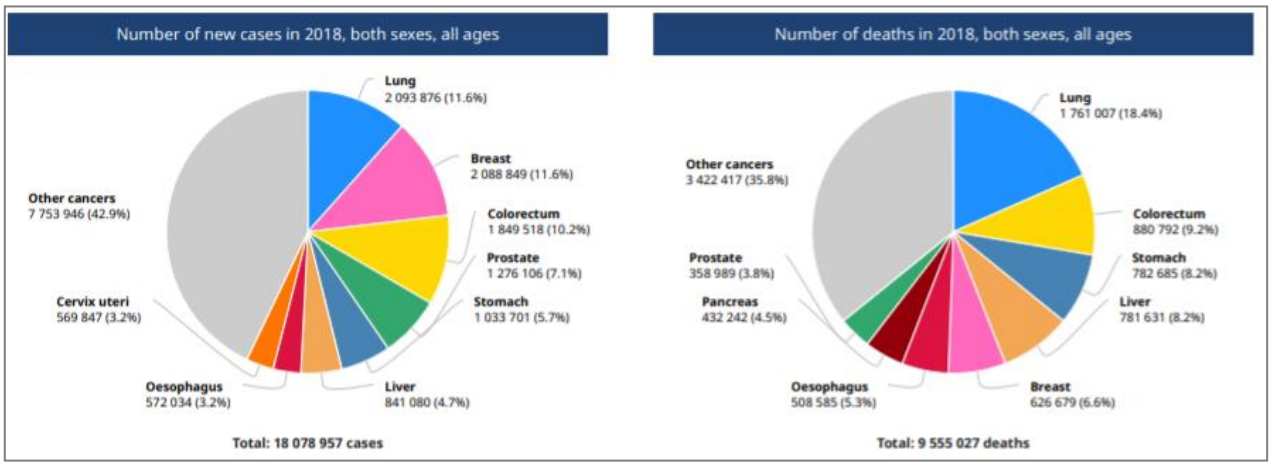


Figure 1 Numbers of new cases and cancer deaths in 2018, from Cancer Today: GLOBOCAN 2018 (6)

It has been established that the majority of the cancer deaths occur in low- and middle-income countries, mainly because they do not have access to qualified healthcare, nor the possibility to be diagnosed early and correctly, or to receive the necessary treatments (6-9). This demonstrates the importance of early detection and quality of treatment.

3.1.2 Development of a cancer

3.1.2.1 Oncogenesis

The development of cancer starts with non-lethal mutations and/or epigenetic changes in the DNA of somatic cells, often induced by carcinogenic agents (1, 10). Mutations leading to adaptations and reprogramming the normal pathways as found in non-malignant cells, are essential to the proliferation, dissemination and survival of neoplastic tumour cells, as well as for achieving resistance against the human defence system and generating angiogenesis and immortality. In a 'survival of the fittest'-like evolution, the cells with the most valuable mutations, that have acquired the most effective tumour capabilities, will establish heterogeneous subpopulations in the tumour (1, 11).

These subpopulations compete amongst each other, which results in clonal expansion, and accumulation of additional mutations. These complex interactions influence the tumorigenesis, the disease progression, and further neoplastic transformation, as well as the therapeutic outcomes, often resulting in poor prognosis as the metastatic potential of the tumour evolves (10). Alongside these mutations, there are other factors that allow the tumour to thrive, adding another dimension of complexity to the understanding of the tumour: the tumour microenvironment (TME) (1, 11).

3.1.2.2 Hallmarks of cancer

In 'Hallmarks of Cancer: The Next Generation', Hanahan and Weinberg list ten hallmarks: biological capabilities acquired by cells during the development of a tumour. As mentioned above, these changes and acquired capacities are crucial for tumour cells to thrive and survive. The hallmarks of cancer establish a rational framework for organizing and understanding the diversity of human tumours. The ten hallmarks are: evading growth suppressors; avoiding immune destruction; enabling replicative immortality; tumour-promoting inflammation; activating invasion and metastasis; inducing angiogenesis; genome instability and mutation; resisting cell death; deregulating cellular energetics; and sustaining proliferative signalling (see figure 2) (1, 11, 12).

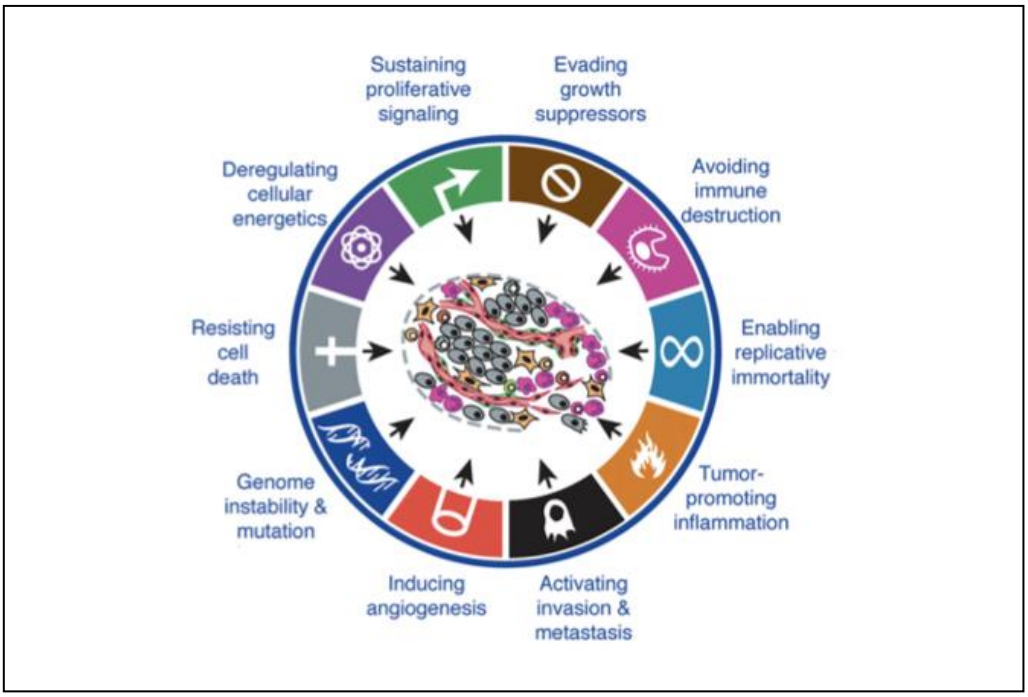


Figure 2 The ten hallmarks of cancer, after Hallmarks of Cancer: the next generation – Hanahan and Weinberg (1)

As neoplastic cells evolve gradually, through a multistep process, they acquire those capabilities, and as such become more tumorigenic and malignant (1, 11). A tumour's most important capability is its resistance to cell death, and the ability to grow and proliferate uncontrollably. Apoptosis is the natural defence system against cancer development as regulating circuits trigger apoptosis when abnormalities in the DNA of cells are detected (1, 10, 11). One of the most prominent regulators in this process is the p53 tumour suppressor protein: a sequence-specific DNA-binding transcription factor, which reacts to accumulating DNA damage and chromosomal abnormalities (1). When the gene *TP53* is affected by mutations, the protein loses its function and cells gain increased susceptibility to diverse types of cancer, seeing as no response to stress stimuli (hypoxia, DNA damage, and oncogenic stress) is induced (10).

Another crucial tumour suppressor gene is *BRCA.* Two types of *BRCA*genes occur; *BRCA1* and *BRCA2,* both associated with hereditary cancers such as breast cancer and ovarian cancer. Its principal function is to regulate the DNA damage repair system called 'homologous repair' (HR). If affected by mutations, DNA repair mechanisms are troubled, resulting in homologous repair deficiency (HRD) and accumulation of DNA damage, thus promoting genome instability and mutations, which has another key role in the development of neoplasms (10). HRD itself does not

lead directly to apoptosis, as other repair mechanisms compensate for the loss of the *BRCA1/BRCA2* genes. In normal functioning cells, p53 induces apoptosis when too much DNA damage is detected. However, if alongside *BRCA, TP53* is mutated, accumulation of DNA damage does not lead to apoptosis and mutated cells can proliferate and grow further. Tumours with mutated *TP53* are generally known to have a poor prognosis and an increased therapeutic resistance compared to non-mutant ones (10, 13). The recognition and understanding of the above-mentioned concepts offers new possibilities for the development of therapeutic options, better screening tools and cancer treatment (1, 11).

3.2 Ovarian cancer

3.2.1 Ovarian cancer: facts and figures

Ovarian cancer is the seventh most common female cancer worldwide and the eighth most common cause of cancer death in women, accounting for approximately 150 000 deaths annually, which amounts to about 5% of all cancer deaths. Each year, 230 000 women are newly diagnosed with this type of cancer (14-16). In Belgium, there were 766 new diagnoses and 678 deaths in 2013. When comparing gynaecological tumours, it is the second most common cause of gynaecological cancer death, after cancer of the cervix uteri, but it is still the most lethal gynaecological cancer (17, 18). The high morbidity and mortality can be explained by the lack of specific early warning symptoms, delayed diagnosis and presentation in advanced disease, the lack of screening options, and limited effective therapy. ‘The silent killer’ is the ominous nickname given to ovarian cancer since 80% of patients are diagnosed in an advanced stage of disease (FIGO stage III-IV). The majority of the patients presents months before diagnosis with non-specific symptoms, but the seriousness is often not recognised, neither by patients, nor by doctors, which leads to delayed diagnosis in an advanced and lethal stage. Possible symptoms include bloating, urinary urgency, pelvic pain, nausea, change in bowel function, back pain, fatigue, and loss of weight (16, 19). The five-year survival is only 46%, whereas breast cancer has a five-year survival rate of 85% (16). The stage in which a patient presents is the most important prognostic factor, as late stage presentation (FIGO stage III-IV) has a five-year relative survival rate of only 29%, compared to 92% for early-stage (FIGO stage I-II) disease (15).

Investigations include bimanual clinical evaluation, elevated CA-125 tumour marker analysis, and a pelvic ultrasound. However, there are no adequate or approved screening options to detect

ovarian cancer at an early stage as of yet. When diagnosed, staging procedures include imaging of chest, abdomen, and pelvis by CT scan and/or MRI (14-16, 19).

Risk factors of developing ovarian cancer include nulliparity, history of infertility, early menarche or late menopause, endometriosis, obesity, age, Lynch syndrome (HNPCC), and a family history of breast cancer or ovarian cancer. In both breast and ovarian cancer, *BRCA1* and *BRCA2* mutations can be found, and are known to be inheritable. If a woman has a first-degree relative diagnosed with ovarian cancer, her lifetime risk is tripled (14). Conversely, gravidity, oral contraceptive use, and breastfeeding are risk reducing factors (14-16).

Table 1: FIGO staging classification for cancer of the ovary, fallopian tube and peritoneum. Adapted from Cancer of the ovary, fallopian tube, and peritoneum- J. S. Berek (20)

Stage I: Tumour confined to ovaries of fallopian tube(s)		T1-N0-M0
IA	Tumour limited to 1 ovary (capsule intact) or fallopian tube surface; no malignant cells in the ascites or peritoneal washings	T1a-N0-M0
IB	Tumour limited to both ovaries (capsules intact) or fallopian tubes; no tumour on ovarian or fallopian tube surface; no malignant cells in the ascites or peritoneal washings	T1b-N0-M0
IC	Tumour limited to 1 or both ovaries or fallopian tubes, with any of the following:	
IC1	Surgical spill	T1c1-N0-M0
IC2	Capsule ruptured before surgery or tumour on ovarian or fallopian tube surface	T1c2-N0-M0
IC3	Malignant cells in the ascites or peritoneal washings	T1c3-N0-M0
Stage II: Tumour involves 1 or both ovaries or fallopian tubes with pelvic extension (below pelvic brim) or peritoneal cancer		T2-N0-M0
IIA	Extension and/or implants on uterus and/or fallopian tubes and/or ovaries	T2a-N0-M0
IIB	Extension to other pelvic intraperitoneal tissues	T2b-N0-M0
Stage III: Tumour involves 1 or both ovaries or fallopian tubes, or peritoneal cancer, with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes		T1/T2-N1-M0
IIIA1	Positive retroperitoneal lymph nodes only (cytologically or histologically proven):	T3a2-N0/N1-M0
IIIA1(i)	Metastasis up to 10 mm in greatest dimension	
IIIA1(ii)	Metastasis more than 10 mm in greatest dimension	
IIIA2	Microscopic extra pelvic (above the pelvic brim) peritoneal involvement with or without positive retroperitoneal lymph nodes	
IIIB	Macroscopic peritoneal metastasis beyond the pelvis up to 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes	T3b-N0/N1-M0

IIIC	Macroscopic peritoneal metastasis beyond the pelvis more than 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes (includes extension of tumour to capsule of liver and spleen without parenchymal involvement of either organ)	T3c-N0/N1-M0
Stage IV		Any T, any N, M1
IVA	Pleural effusion with positive cytology	
IVB	Parenchymal metastases and metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)	

As mentioned before, prognosis and outcome are highly dependent on the stage of the disease. The Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) and the American Joint Committee on Cancer (AJCC) have designed a system to stage ovarian cancer (FIGO stages). In ovarian cancer, TNM (describing Tumour, lymph Nodes and Metastasis) staging is hardly used, whereas the FIGO stage is the nowadays universally used method (15, 20, 21). FIGO stages range from stage I to stage IV and are often even divided in substages, each well defined, in order to utilise a universally used characterisation system of ovarian cancer (see table 1) (20).

3.2.2 Epithelial ovarian cancer heterogeneity

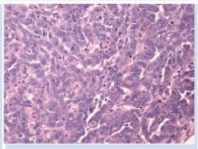
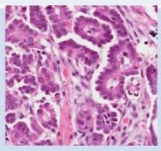
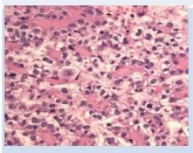
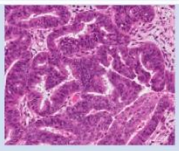
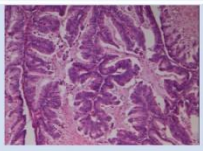
Ovarian cancer (OC) is not just a unitary disease but can be roughly divided into two groups: the epithelial ovarian cancers (EOC) (95% of the OC's), and the non-epithelial ovarian cancers (5% of the OC's), which originate from germ cells and sex-cord stromal tissues. Epithelial ovarian cancer includes five different histological subtypes: high-grade serous ovarian cancer (70% of the OC's), low-grade serous ovarian cancer (10% of the OC's), ovarian clear cell carcinoma (5% of the OC's), endometrioid ovarian cancer (10% of the OC's), and mucinous ovarian cancer (2.4% of the OC's). This means that EOC is a heterogenic disease, that varies in biologic behaviour, chemotherapy response, and prognosis (see table 2) (15, 16, 20, 22).

3.2.2.1 High-grade serous ovarian cancer

High-grade serous ovarian cancer (HGSOC) is the prototype of ovarian cancer (15). Mutations in the *TP53* gene are found in 97% of the cases of HGSOC. This gene functions as a tumour suppressor gene and is important for the DNA repair and apoptosis in case of irreparable DNA damage. *TP53* mutations lead to loss of tumour suppression and to a higher risk of uncontrolled cell division (10, 15, 16).

Inherited predisposition is found in 15-25% of the patients with HGSOC. These tumours are characterised by *BRCA1/BRCA2* mutations. The *BRCA* mutations make HGSOC highly sensitive to platinum chemotherapy, which in fact damages the DNA of the tumour. Moreover, there is an accumulation of excessive DNA damage due to the homologous repair deficiency, which leads to apoptosis (13, 15).

Table 2 Histological subtypes of Epithelial Ovarian Cancer (EOC), adapted from Evolution of management in the era of precision medicine, S. Lheureux (16)

	HGSOC	LGSOC	Clear Cell	Endometrioid	Mucinous
Clinical information	Age, heredity, clinical examination, imaging, staging				
Subtype-specific clinical information	Inherited predisposition in 15-25%	Evolution from borderline tumor	Associated with endometriosis	Synchronous primary ~10% in endometriosis	Exclude GI primary
Pathology					
Molecular features	CNA high *TP53* *BRCA1/2* HRD	CNA low MAPK act. *KRAS* *BRAF*	*ARID1A* PI3K/AKT act. RTK/Ras act. MMR	*PI3KCA* *ARID1A* *KRAS* Wnt/β-catenin act. *PTEN*	*KRAS* *HER2* amplif.
Platinum Chemotherapy	Sensitive	Relatively Resistant	Relatively Resistant	Sensitive	Relatively Resistant

3.2.2.2 Low-grade serous ovarian cancer

About ten percent of the EOC's are low-grade serous ovarian cancers (LGSOC). Low-grade serous ovarian cancers present at an earlier age (55.5 years) compared to HGSOC (62.6 years). More than 90% of the cases present at an advanced stage III or stage IV disease (23). LGSOC does not seem related to *BRCA1/BRCA2* mutations but to mutations in *BRAF* and *KRAS* (15, 16, 23).

LGSOC has intermediate to low sensitivity to platinum chemotherapy but is treated the same way as HGSOC. Compared to HGSOC, the prognosis is better for LGSOC, despite its relative resistance to chemotherapy. This may be related to the slow growth of low-grade serous carcinomas and the higher likelihood of achieving no residual disease after primary debulking (15, 23).

3.2.2.3 Ovarian clear cell cancer

Ovarian clear cell cancer (OCCC) is a rare histological type of EOC. It accounts for only five percent of the EOC's in Europe and North America whereas it is much more prevalent in Japan (25% of the EOC's). In 50-75% of the cases, it is associated with endometriosis. The high incidence of endometriosis in Japan is a possible explanation for the high rates of OCCC (24-26).

Mutations in *TP53*, *BRCA1* or *BRCA2* genes are rarely found in OCCC and the biology, morphology and origin of OCCC are still unclear (15, 24).

3.2.2.4 Endometrioid ovarian cancer

Endometrioid ovarian cancer presents at an earlier age than other EOC's and is often diagnosed at an early stage of disease. This earlier presentation and diagnosis results in better five- and ten-year overall survival rates. It is, like OCCC, associated with endometriosis and the transformation of atypical endometriosis cells to malignant cells (15, 16).

The most important mutations are mutations in *PIK3CA*, *ARID1A* and *KRAS*. Endometrioid ovarian cancer is sensitive to platinum chemotherapy and has the best prognosis out of the five subtypes of epithelial ovarian cancer (15, 16).

3.2.2.5 Mucinous ovarian cancer

Mucinous ovarian cancer represents only 2.4% of the EOC's. It is characterised by the presence of multilocular cysts filled with an opaque, mucoid substance. Mucinous ovarian cancer does not seem associated with TP53 or BRCA mutations but is related to *KRAS* mutations and *HER2* amplifications (14-16).

MOC has a better prognosis because the majority of the patients is diagnosed at an earlier stage compared to other OC's. However, if detected at an advanced stage (stage III or IV), the prognosis is worse because of the higher resistance to chemotherapy (15, 16).

3.2.3 Treatment of primary ovarian cancer

3.2.3.1 Primary debulking surgery (PDS)

The standard treatment of ovarian cancer consists of primary debulking surgery (PDS) followed by six courses of chemotherapy, which include carboplatin and paclitaxel. The surgery involves

laparotomy through a midline incision, followed by hysterectomy, bilateral salpingo-oophorectomy and omentectomy (15, 20, 27). The aim of this surgery is to have no residual macroscopic tumour left after surgery (R0). In retrospective studies, an overall survival (OS) benefit from PDS has been shown, however no level of evidence I is available (16, 28, 29).

The success of the surgery depends on the patient's performance status, the tumour location and the surgeon's expertise (30-32). This surgery has to be performed by a skilled gynaecological oncologist, since this benefits the quality of treatment and the patient outcome. The difficulty of the procedure is proportional to the stage of the disease because the many and widespread metastatic foci make it hard to achieve complete cytoreduction (33).

3.2.3.2 Interval debulking surgery

Interval debulking surgery (IDS) means that the debulking surgery is performed after three to four courses of primary chemotherapy (PCT) and followed by two to three postoperative courses of chemotherapy. Studies comparing PDS and IDS are e.g., the EORTC 55971 and the CHORUS trial. Both are non-inferiority studies that were positive, but many criticisms were noted: selection bias, older patients with poor performance status, and short operation times (33-35). In both studies, a benefit was seen in women with advanced disease (stage IIIC-IV) (15, 33-36).

Although IDS could be seen as an alternative for an unqualified surgeon, it is not. Primary chemotherapy followed by interval debulking surgery should be reserved either for patients who are inoperable, meaning that they are too medically ill to undergo aggressive surgery, due to comorbidities or extent of disease (e.g. lung embolism, or heart failure,…); or for patients who have disease that is unresectable (e.g. disease near large veins and/or arteries, multiple disseminated metastasises in e.g. brain, liver, lungs,…) (15, 27, 33, 37). Interval debulking surgery can be considered for patients in FIGO stage IIIC or more and if the disease meets the above-mentioned criteria (37-40).

3.2.3.3 Chemotherapy

The standard chemotherapy consists of the combination of platinum-based drugs and non-platins. Typically, carboplatin or cisplatin is combined with paclitaxel (20). In general, there is a higher tolerance for carboplatin than for cisplatin because the former has fewer adverse side effects. The decrease of nephrotoxic effects in particular is the greatest benefit, next to nausea and vomiting, which are also less severe with carboplatin (41). Eighty percent of the patients with advanced EOC,

especially with HGSOC, with BRCA mutations, or other homologous recombination deficiencies, respond well to chemotherapy (16). Chemotherapy can be given intravenously (IV) or can be directly instilled in the peritoneal cavity (intraperitoneal chemotherapy, IP). When the IP is heated, it is called hyperthermic intraperitoneal chemotherapy (HIPEC) (42).

Intraperitoneal (IP) chemotherapy is a procedure in which chemotherapeutic fluid is infused and circulates directly in the abdominal cavity through a catheter. IP has been introduced in the treatment of ovarian cancer because this cancer has typically spread all over the intra-abdominal cavity. The direct exposure of IP chemotherapy to the cancer cells improves the lethality of the chemotherapy on cancer cells. Because the chemotherapy is mostly isolated in the peritoneal cavity, much higher doses can be used, less side-effects occur, and lower toxicity is registered than when using systemic chemotherapy (43, 44). The rationale behind HIPEC is that hyperthermia makes the IP chemotherapy more effective since the heat improves the penetration of the chemotherapy in the cancer cells at the peritoneal surface and amplifies the sensitivity of the cancer cells to chemotherapy by debilitating the DNA repair. The hyperthermia also induces apoptosis, promotes the denaturation of proteins, and inhibits angiogenesis (40, 45). In primary therapy, IP and HIPEC have been studied in randomised trials (GOG104, GOG114, GOG172, GOG252 and the phase III trial by Van Driel et al) (43, 46-49).

3.2.4 Treatment of relapsed ovarian cancer

Roughly 80% of the women diagnosed with ovarian cancer will relapse after primary treatment. In most of these patients, disease is uncurable and the main goals of management are palliation, prevention of complications, symptom control, and pain relief.

3.2.4.1 Timing of therapy

After primary therapy, follow-up consists of a consultation every three months with anamnesis, clinical evaluation, and, depending on therapeutic choices, measurement of CA-125. After two years, follow-up consultations are planned every six months for about five years or until relapse occurs. Signs of relapse are an increase in the CA-125 level, more than twice the upper limit of normal (i.e. biochemical relapse); the appearance of abnormalities on (PET-)CT or other imaging techniques (CT graphical or radiological relapse); or finding anomalies in a physical examination and the appearance of clinical symptoms (clinical and symptomatic relapse) (14, 27, 50, 51).

Rising levels of CA-125 often present months before clinical findings or symptoms. The EORTC 55955, a randomised phase III trial (2005), aimed to establish the benefit of early treatment in women with recurrent ovarian cancer, compared to women receiving treatment based on the appearance of clinical symptoms. 529 patients with complete remission after first-line platinum-based therapy and normal CA-125 levels were randomly assigned to the early treatment-arm (265 patients), or a delayed treatment-arm (264 patients). In the group receiving early treatment, treatment was started within 28 days after increasing CA-125 levels (exceeding twice the upper limit of normal [ULN]), whereas women in the delayed treatment-arm received treatment upon appearance of clinical or symptomatic relapse. The primary endpoint in this study was overall survival (52).

No benefit in overall survival was seen in those women receiving early treatment compared to women who had regular CA-125 monitoring (HR 0.98, 95%CI 0.80-1.20, p=0.85), with a difference of 1.4 months in median overall survival between the two groups in favour of the delayed treatment group. In the delayed treatment-arm, a delay of 4.8 months in therapy was seen, and a better quality of life (QOL) was noted as they were less exposed to chemotherapy (52). The practice on CA-125 based follow-up depends therefore on local practice, as well as on patient and clinician wishes, as the results from EORTC55955 could be interpreted as so to delay secondary treatment for recurrent ovarian cancer (ROC) until the appearance of clinical symptoms (50-52).

3.2.4.2 Surgery

In clinical practice, secondary cytoreductive surgery is offered to patients that have platinum-sensitive disease, longer disease-free interval, no extensive recurrent disease, and no ascites (14, 50, 51). As is the case in primary debulking surgery, the aim of the surgical procedure is to leave a patient with no macroscopic residual disease, even though in most patients this is not possible due to the extent of the disease (2, 14, 53-55).

Despite the ongoing research on which patients would benefit from secondary surgery, there are still questions that need to be answered. As mentioned before, many women relapse and if they do, it is established that OC is not curable. Many of them will receive secondary, tertiary, sometimes even quaternary surgery. In this paper, a full review of the literature is conducted, in order to answer the question whether secondary debulking has a role in the treatment of relapsed ovarian cancer and if so, which patients should be selected for this procedure.

3.2.4.3 Chemotherapy

The cornerstone of treatment for relapsed ovarian cancer is (platinum-based) chemotherapy. A rigid paradigm, based on the platinum-free interval (PFI: the time from last dose of platinum-based therapy until documented disease progression), was used to (arbitrarily) define whether women were platinum-sensitive or platinum-resistant (PFI>6 months vs PFI<6 months). Recently, these classifications were updated by the The Gynecological Cancer InterGroup's (GCIG) 4th Ovarian Cancer Consensus Meeting, taking into account PFI, histology (some types are more sensitive to platinum than others), *BRCA* status (*BRCA*mut is more sensitive than *BRCA*wt), use of PARPi (overlap in sensitivity to platinum), etc. A nomenclature based on the treatment free interval (TFI) was proposed, i.e. the time since the last administration of platinum-based chemotherapy (TFIp), non-platinum agents (TFInp), biologicals (TFIb), or other agents such as PARPi's (poly-ADP ribose polymerase inhibitors). As recurrent ovarian cancer is considered incurable, management of disease should take a more individual approach. Aforementioned therapeutic options should be taken into account, as well as BRCA-status, platinum allergies and toxicity, etc. Moreover, the main goals should be palliation, prevention of complications, and symptom control (14, 27, 50, 51, 56).

As discussed in primary ovarian cancer, chemotherapy administration can be done in different ways. In recurrent ovarian cancer, there is no sufficient evidence on the use of neoadjuvant chemotherapy, nor about (hyperthermic) intraperitoneal administration (42, 57).

3.2.5 Targeted therapy in ovarian cancer

The philosophy behind targeted therapy is to only target the pathways known to be abnormally activated in cancer cells and to spare the normal cells from the cytotoxicity.

3.2.5.1 Bevacizumab

Bevacizumab or *Avastin* is an anti-angiogenic agent. It is a humanised monoclonal antibody against vascular endothelial growth factor (VEGF). Angiogenesis, a negative prognostic factor in ovarian cancer, is the consequence of excessive VEGF. Bevacizumab decreases the VEGF expression, which leads to reduced tumour vascularisation and less angiogenesis, both necessary for the tumour cells to survive, and consequentially leads to a prolonged survival (41, 58). It was first used in colon, lung and renal cancers and has been approved by the FDA to use in combination with chemotherapy for advanced ovarian cancer since 2018 (15, 41, 53, 59, 60). Bevacizumab was studied in recurrent ovarian cancer in OCEANS, a randomised phase III trial concluding that women

with platinum-sensitive recurrent ovarian cancer receiving gemcitabine and carboplatinum (i.e. chemotherapy) plus bevacizumab, followed by bevacizumab maintenance therapy had a progression-free survival (PFS) benefit compared to women receiving gemcitabine and carboplatinum plus placebo (61). A similar result was concluded out of AURELIA, another randomised phase III trial. Addition of bevacizumab to chemotherapy for women with platinum-sensitive recurrent ovarian cancer improved the PFS in comparison to chemotherapy without bevacizumab (62).

3.2.5.2 PARP inhibitors

Poly ADP ribose polyperase (PARP) enzymes of the base excision repair (BER) mechanism play a critical role in the repair of DNA single-strand breaks. Patients with *BRCA* mutations, or other homologous recombination deficiencies (HRD), have impaired repair mechanisms for DNA double-strand breaks. Unrepaired DNA damage results in accumulation of mutations and uncontrolled cell division, which makes HRD related to cancer susceptibility. However, HRD by itself does not always lead to excessive DNA damage and apoptosis because the mutated cells rely now more on the PARP enzymes to resolve DNA damage. With PARP inhibitors, the remaining repair mechanisms are also inhibited, which leads to accumulation of DNA damage and lethality. PARP inhibitors are mainly interesting as treatment for HGSOC because *BRCA1/BRCA2* mutations are the most common in this subtype (13, 63, 64).

The three PARP inhibitors approved by the FDA for use in relapsed ovarian cancer after response to platinum chemotherapy are olaparib, rucaparib and niraparib (64).

3.2.5.3 Immunotherapy

The aim of immunotherapy is twofold: on the one hand to upregulate the immune system and on the other hand to restrain the local immune suppression to defend itself against the evolvements of the cancer. Currently, no immunotherapies have been approved for the treatment of (relapsed) ovarian cancer (24, 65).

4. Problem statement

Ovarian cancer (OC) is the second most common cause of gynaecological cancer death, accounting for 230.000 new patients each year and about 150.000 women die due to the disease every year (14-16). In addition, ovarian cancer is known as a 'silent killer', as most women are diagnosed in advanced stage disease (FIGO III-IV), after a long time of non-specific symptoms including bloating, urinary urgency, pelvic pain, nausea, change in bowel function, back pain, fatigue and loss of weight (14, 15).

Prognosis and outcome are highly dependent on initial stage of disease as a difference in five year survival rates of 60% is seen between women in stage I and II disease (92%) on the one hand and women with stage III or IV disease (29%) on the other hand (15). Furthermore, complete debulking with no residual disease is the aim of primary surgery, as different studies have shown an increase in overall survival in women who got complete gross resection (28, 29).

Despite improving therapeutic options in primary ovarian cancer, about 80% of patients experience relapse of disease and will need secondary (or even tertiary, quaternary, and so on) therapy (14, 27). When women with recurrent ovarian cancer are offered secondary debulking surgery (in combination with chemotherapy), the goal of this surgery should be the same as in primary cytoreductive surgery: no residual disease after debulking (54, 55, 66).

As we know, full cure is impossible once a woman relapses in ovarian cancer. She will relapse again eventually, even after debulking surgery with no macroscopic residual disease. There is an urging need to investigate if and which patients should be offered cytoreductive surgery in recurrent ovarian cancer, as morbidity and mortality in this patient population is often high (14, 54, 55, 66). Main trials focussing on these two questions are DESKTOP (I/II/III) and the recently published GOG213, as well as the still ongoing SOC1 (2-4, 54, 55).

Given the fact that many women will relapse, other questions about debulking surgery are arising, and criticisms are being formulated on this hot topic.

5. Methods

5.1 Search strategy

The search engines PubMed and Embase were used in our search, as these databases are the most appropriate sources for the relevant subject matter from major medical and nursing literature. They were consulted using the network provided by the Faculty of Medicine and Health Sciences, Ghent University as well as by searching the Ghent University library. In both databases, we used the following concepts to look for papers, using no filter on time of publication: (“ovarian cancer” AND “surgery” AND “recurrence”) OR (“ovarian cancer” AND “recurrence” AND “intraperitoneal chemotherapy”). A detailed search strategy is shown in table 3.

We also included studies and their results as presented at international meetings. In addition to PubMed and Embase searches, we searched the references of selected papers, conducted a search for critics on the found articles, and consulted experts in the field to help identify additional studies.

5.2 Selection criteria

Articles were deemed not eligible if they met any of the following exclusion criteria: (1) they discussed either primary ovarian cancer, non-high grade serous ovarian cancer only, or non-ovarian cancer, (2) they described and discussed the technicity of surgical procedures and techniques, (3) the population investigated was paediatric or juvenile, (4) they discussed radiotherapy or chemotherapy without any surgical aspect, or (5) they discussed genetics.

Study formats included comparative studies, meta-analyses, conference abstracts, conference presentations, clinical studies, commentaries and critiques on publications. Reviews, both narrative and systematic, as well as case reports were not deemed eligible for inclusion. Only one investigator (OD) independently sorted the articles into the categories “excluded” and “included” on the basis of the title, abstract, and full text. If no abstract was available, inclusion or exclusion was based on title alone. If no full text was available, papers were excluded. The citation manager EndNote was used to organise all articles, as well as for referencing in the written review.

5.3 Findings

The search yielded 3337 articles (3318 from database search, 19 from other sources as mentioned above), but this number was reduced to 3189 after duplicates were removed. On the basis of title or abstract, 2745 articles were removed. 444 articles were then screened on full text. Out of those, a total of 79 articles were withheld for the paper. The study selection is shown in figure 3. The final reference list was generated on the basis of originality and relevance to the broad scope of this review.

Table 3 Search Strategy

Concept	**Search strategy (including index terms, free text words and probably a search filter; including Boolean, Proximity [when appropriate], Truncation operators [when appropriate] and field codes)**
NAME OF DATABASE: PubMed	
Concept 1: OVARIAN CANCER	"Carcinoma, Ovarian Epithelial" [Mesh] OR Carcinoma, Ovarian Epithelial[TIAB] OR "Ovarian Neoplasms"[Mesh] OR ovarian neoplas*[TIAB] OR "ovary tumor"[TIAB] OR "ovary tumour"[TIAB] OR "ovarian cancer"[TIAB] OR "cancer of the ovary"[TIAB] OR "ovary cancer"[TIAB] OR "ovary carcinoma"[TIAB] OR "carcinoma of the ovary"[TIAB] OR "Fallopian Tube Neoplasms"[Mesh] OR fallopian tube neoplas*[TIAB] OR "fallopian tube tumor"[TIAB] OR "fallopian tube tumour"[TIAB] OR "fallopian tube cancer"[TIAB] OR "cancer of the fallopian tube"[TIAB] OR "fallopian tube carcinoma"[TIAB] OR "carcinoma of the fallopian tube"[TIAB] OR primary peritoneal neoplas*[TIAB] OR "primary peritoneal tumor"[TIAB] OR "primary peritoneal tumour"[TIAB] OR "primary peritoneal cancer"[TIAB] OR "primary cancer of the peritoneum"[TIAB] OR "primary peritoneum carcinoma"[TIAB] OR "primary carcinoma of the peritoneum"[TIAB]
Concept 2: DEBULKING SURGERY	"cytoreduction surgical procedures"[Mesh] OR cytoreduction surgical procedure*[TIAB] OR debulking surgical procedure*[TIAB] OR cytoreductive surger*[TIAB] OR cytoreductive surgical procedure*[TIAB] OR resection[TIAB] OR "primary debulking"[TIAB] OR "primary debulking surgery"[tiab] OR "secondary debulking"[TIAB] OR "secondary debulking surgery"[TIAB] OR "secondary cytoreductive surgery"[TIAB] OR "tertiary debulking"[TIAB] OR "tertiary debulking surgery"[TIAB] OR "tertiary cytoreductive surgery"[TIAB] OR "quaternary debulking"[TIAB] OR "quaternary debulking surgery"[TIAB] OR "quaternary cytoreductive surgery"[TIAB] OR "interval debulking surgery"[TIAB] OR "interval debulking"[TIAB] OR "interval cytoreductive surgery"[TIAB] OR "debulked"[TIAB] OR "second-look surgery"[TIAB] OR "second look surgery"[TIAB]
Concept 3: RECURRENCE	"Recurrence"[Mesh] OR recurr*[tiab] OR relaps*[tiab]
Concept 4: INTRAPERITONEAL CHEMOTHERAPY	"Intraperitoneal"[TIAB] OR "intraperitoneal chemo"[TIAB] OR "intraperitoneal chemotherapy"[TIAB] OR "Hyperthermia, Induced"[Mesh] OR "Hyperthermia, Induced"[TIAB] OR "HIPEC"[TIAB] or "hyperthermic intraperitoneal chemotherapy"[TIAB] OR "neoadjuvant chemotherapy"[TIAB] OR "PIPAC"[TIAB] OR "Pressurized intraperitoneal aerosol chemotherapy"[TIAB]
Combination of concepts	(#1 AND #2 AND #3) OR (#1 AND #3 AND #4)
Results	2272 results

Concept	Search strategy (including index terms, free text words and probably a search filter; including Boolean, Proximity [when appropriate], Truncation operators [when appropriate] and field codes)
NAME OF DATABASE: Embase	
Concept 1: OVARIAN CANCER	'epithelial ovarian carcinoma':ab,ti OR 'epithelial ovary carcinoma':ab,ti OR 'ovary carcinoma'/exp OR ovary carcinoma:ab,ti OR ovary neoplas*:ab,ti OR 'ovary tumour':ab,ti OR tumour of the ovar*:ab,ti OR 'ovary tumor'/exp OR 'ovary tumor':ab,ti OR 'tumor of the ovary':ab,ti OR 'ovary cancer'/exp OR 'ovary cancer':ab,ti OR fallopian tube neoplas*:ab,ti OR 'uterine tube tumor'/exp OR 'uterine tube tumor':ab,ti OR 'uterine tube tumour':ab,ti OR 'tumor of the uterine tube':ab,ti OR 'tumour of the uterine tube':ab,ti OR 'tumor of the fallopian tube':ab,ti OR 'tumour of the fallopian tube':ab,ti OR 'cancer of the fallopian tube':ab,ti OR 'fallopian tube cancer':ab,ti OR 'cancer of the uterine tube':ab,ti OR 'uterine tube cancer':ab,ti OR 'fallopian tube carcinoma':ab,ti OR 'uterine tube carcinoma':ab,ti OR 'Primary peritoneal carcinoma'/exp OR 'primary peritoneal carcinoma':ab,ti OR primary peritoneal neoplas*:ab,ti OR 'primary peritoneal tumor':ab,ti OR 'primary peritoneal tumour':ab,ti OR 'primary peritoneal cancer'/exp OR 'primary peritoneal cancer':ab,ti OR 'carcinomatous peritonitis'/exp OR 'carcinomatous peritonitis':ab,ti OR 'primary peritoneal carcinoma':ab,ti
Concept 2: DEBULKING SURGERY	'Cytoreductive surgery'/exp OR 'cytoreductive surgery':ab,ti OR cytoreduction surgical procedure$:ab,ti OR cytoreductive surgical procedure$:ab,ti OR 'debulking procedure':ab,ti OR 'debulking surgery':ab,ti OR debulking surgical procedure$:ab,ti OR 'primary debulking':ab,ti OR 'primary cytoreductive surgery':ab,ti OR 'secondary debulking':ab,ti OR 'secondary cytoreductive surgery':ab,ti OR 'tertiary debulking':ab,ti OR 'tertiary cytoreductive surgery':ab,ti OR 'quaternary debulking':ab,ti OR 'quaternary cytoreductive surgery':ab,ti OR 'interval debulking':ab,ti OR 'interval cytoreductive surgery':ab,ti OR 'debulked':ab,ti
Concept 3: RECURRENCE	'recurrence risk'/exp OR 'recurrent disease'/exp OR recurr*:ab,ti OR relaps*:ab,ti
Concept 4: INTRAPERITONEAL CHEMOTHERAPY	'chemotherapy'/exp OR 'chemotherapy':ab,ti OR 'cancer chemotherapy'/exp OR 'cancer chemotherapy':ab,ti OR 'chemotherapeutics':ab,ti OR 'hyperthermic intraperitoneal chemotherapy'/exp OR 'hyperthermic intraperitoneal chemotherapy':ab,ti OR 'HIPEC':ab,ti OR 'Pressurized intraperitoneal aerosol chemotherapy':ab,ti OR 'PIPEC':ab,ti
Combination of concepts	(#1 AND #2 AND #3) OR (#1 AND #3 AND #4)
Articles	1046 results

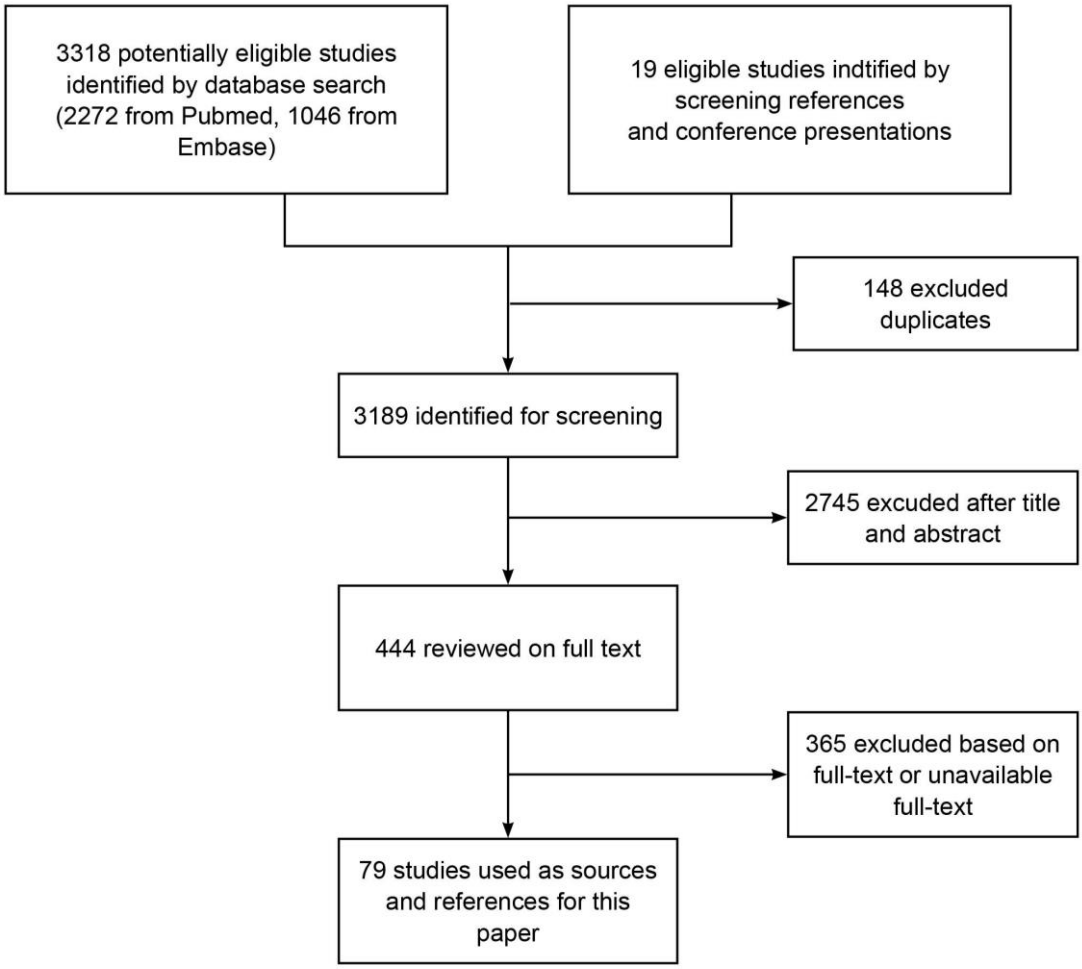


Figure 3 Selection of used papers

6. Results

6.1 The first data on secondary cytoreductive surgery

To date, no level of evidence I data on benefit in overall survival (OS) by secondary cytoreductive surgery have been published. In 1983, a report from Berek et al. first introduced the term secondary cytoreduction and reported the benefit of this surgery in a select group of patients. Median survival in patients in whom optimal debulking surgery was achieved (defined as largest residual disease less than 1.5 cm in diameter), was significantly higher than for patients receiving suboptimal debulking surgery (20 months versus 5 months, $p<0.01$) (67). This benefit was also reported by subsequent studies. Other reported prognostic factors regarding survival were treatment free interval, symptoms (back pain, bloating, frequently urinating, etc.), ascites, and initial tumour mass (67-76).

In a meta-analysis including 2019 patients from articles published between 1983 and 2007, Bristow et al. tried to determine the effect of several prognostic variables on survival after recurrence of disease, such as age, DFI, location of disease, tumour grade and histology, optimal cytoreduction, complete gross resection, etc. The definition of optimal cytoreductive surgery varied across the included studies: <2.5 cm (1 study), <2 cm (7 studies), <1.5 cm (1 study), ≤1 cm (17 studies), ≤0.5 cm (7 studies), ≤0.25 cm (1 study), and no gross residual disease (i.e. complete cytoreductive surgery) (6 studies). In short, the only clinical variable independently associated with longer overall survival was the achievement of complete cytoreductive surgery. Each 10% increase in the proportion of patients undergoing complete debulking surgery was associated with a 3.0 month increase in median overall survival (95%CI 0.50-5.53, $p=0.02$) (77).

However, whereas these studies showed a benefit from debulking, other studies did not come to this conclusion as no survival benefit was found for women who underwent secondary debulking surgery (78, 79).

6.2 The first randomised trials

The EORTC55963 trial, Late onset Recurrent Ovarian Cancer: Surgery or Not (LOROCSON) (2000), a multicentre controlled prospective randomized phase III trial, enrolled 38 patients with recurrent ovarian cancer, performance status 0-2 and PFI of at least six months. Patients with complete bowel obstruction; patients with metastasised carcinoma; and patients with leptomeningeal or brain metastases were excluded. Patients were randomised either to

chemotherapy without surgery, or secondary surgery followed by chemotherapy. The primary endpoint of this study was PFS, secondary endpoints were survival, toxicity, complications of surgery, and QOL (80).

The SOCceR Trial (2012), a Dutch multicentre randomised controlled phase III trial, enrolled 27 patients with recurrent ovarian cancer with performance status 0-1, a PFI of at least six months, ascites less than 500ml, and possible complete gross resection (estimated by gynaecological oncologist). Patients with nonepithelial tumours or borderline tumours; patients with platinum-refractory or resistant tumours; patients undergoing palliative surgery; patients that were inoperable; and patients with secondary, third and later recurrence were excluded. Patients were randomised either to chemotherapy without surgery, or secondary surgery followed by chemotherapy. The primary endpoint of this trial was PFS, secondary endpoints were overall survival, QOL, tumour response, and peri-operative morbidity and mortality (81).

Both studies were aborted prematurely, due to low recruitment (38/700 in the LOROCSON trial, 27/230 in the SOCceR trial). No conclusions could be drawn and the role of secondary cytoreductive surgery in treatment of women with relapsed ovarian cancer could not be established. Therefore they will not be discussed further in this thesis (80-82).

6.3 Prominent studies on secondary cytoreductive surgery

6.3.1 GOG213

The GOG213 (GOG: Gynaecologic Oncology Group) (2019), a phase III randomised, multicentre, international clinical trial included 674 patients from 67 dominantly academic centres from the USA (65/67), Japan (1/67), and South Korea (1/67). All patients had recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer; platinum-sensitive disease; and PFI≥6 months. First, all patients were screened to be a surgical candidate (485 patients) or not. If complete cytoreductive surgery was deemed to be possible, patients were randomised in a surgery- or no surgery-arm (see infra). All patients, both surgical candidates and non-surgical candidates were randomly assigned to a paclitaxel/carboplatin-arm (337 patients) or a paclitaxel/carboplatin plus bevacizumab-arm (337 patients). Two hypotheses were examined: whether or not (i) cytoreductive surgery, or (ii) bevacizumab would provide any overall survival benefit in women with recurrent ovarian cancer. The study design is shown in figure 4 (2, 53).

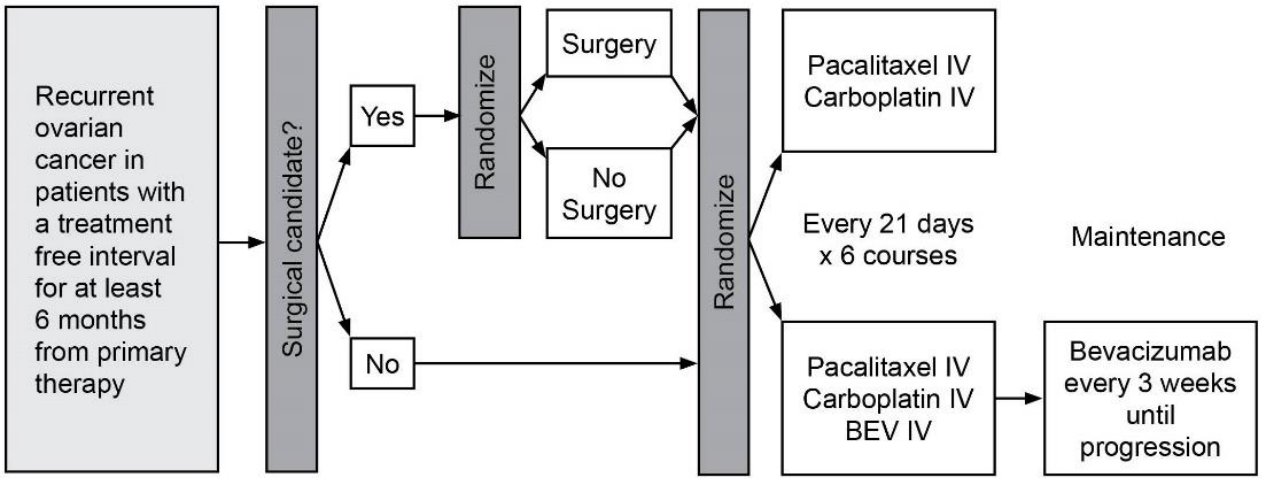


Figure 4 GOG213 trial design (2, 53)

485 patients with platinum-sensitive recurrent ovarian cancer and investigator-determined resectable disease were enrolled in the surgical study part (2). About half of these patients were from the USA (212 patients), the other half from South Korea (256 patients) and Japan (17 patients). Women who were inoperable (not fit for surgery), and women with diffuse carcinomatosis, ascites, or extra abdominal disease were excluded. Patients were randomly assigned to either a study arm receiving cytoreductive surgery plus chemotherapy (240 patients) or a study arm receiving chemotherapy alone (245 patients). Both arms were then randomised a second time, either assigning them to an arm receiving bevacizumab or an arm not receiving bevacizumab. The primary endpoint in this study was overall survival. Secondary endpoints were PFS (progression-free survival), safety analyses (30-day surgical morbidity and mortality, as well as treatment-related adverse events), and QOL (2, 53).

In 63% of the patients complete debulking was achieved. Compared to the incomplete resection group, complete resection was associated with longer overall survival (56.0 months versus 37.8 months, HR 0.61, 95%CI 0.40-0.93) and longer PFS (22.4 months versus 13.1 months, HR 0.51, 95%CI 0.36-0.71) (see figure 5) (2). When comparing the surgery-arm to the no surgery-arm, a non-significant difference in overall survival was seen of 50.6 months and 64.7 months respectively

(HR 1.29, 95%CI 0.97-1.72, p=0.08), and in progression-free survival of 18.9 months versus 16.2 months respectively (HR 0.82, 95%CI 0.66-1.01), this is shown is figure 6 (2, 53).

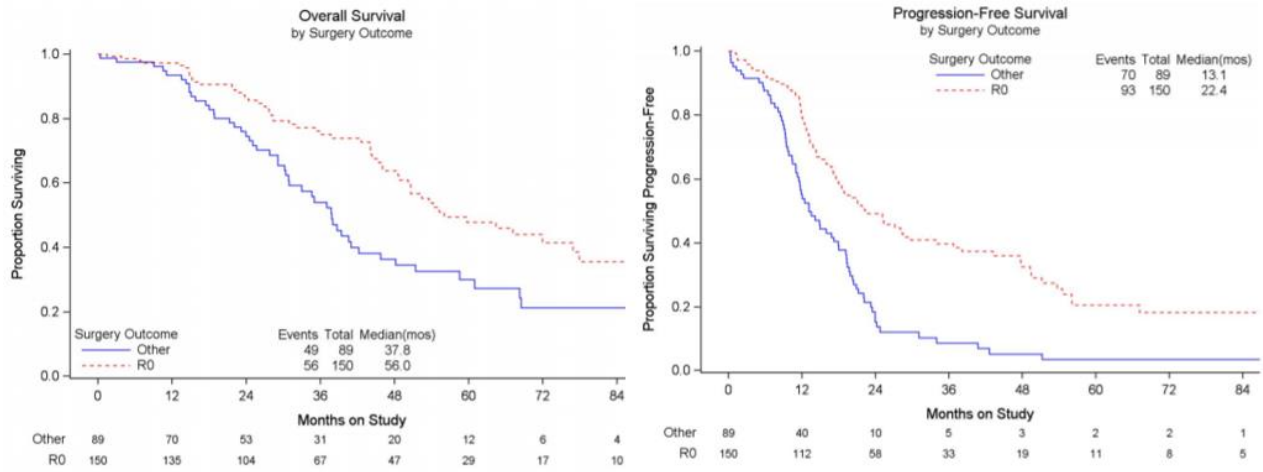


Figure 5 OS and PFS comparing R0 and other surgical result arms, GOG213 – Coleman RL et al. (2)

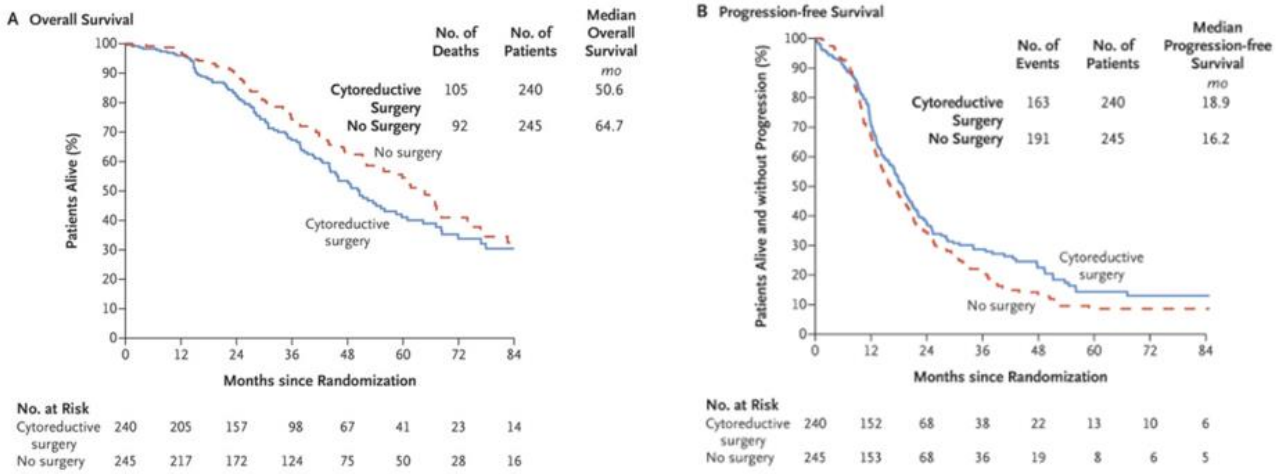


Figure 6 OS and PFS difference between surgery and no surgery, GOG213 - Coleman RL et al. (2)

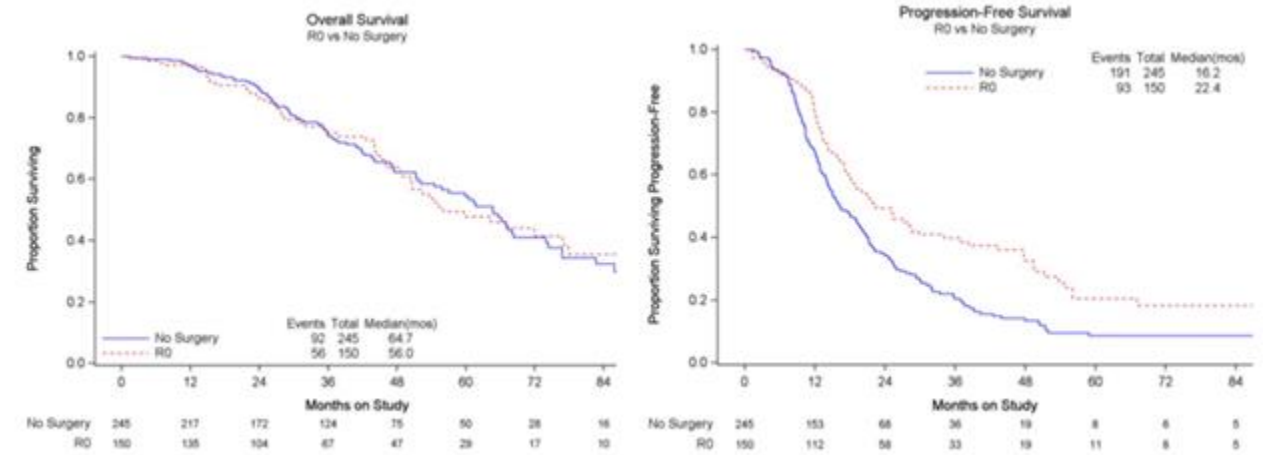


Figure 7 OS and PFS difference between R0 and no surgery, GOG213 - Coleman RL et al. OS (2)

Between the entire no-surgery group (245 patients), and the patients receiving complete gross resection (R0) (150 patients), no benefit in overall survival was seen for the R0-arm (56.0 months versus 64.7 months, HR 1.03, 95%CI 0.74-1.46), even though a PFS benefit was noted (22.4 months versus 16.2 months, HR 0.62, 95%CI 0.48-0.80) (figure 7) (2).

The study reported a diminished QOL in women who underwent cytoreductive surgery, a decrease in physical functioning, and an increase in surgery related discomforts and symptoms. After six weeks, the difference between the two groups levelled out and the QOL became even (2).

6.3.2 DESKTOP I

DESKTOP I (the Descriptive Evaluation of perioperative Selection KriTeria for OPerability in recurrent OVARian cancer), a retrospective study published in 2006, included 267 patients from twenty-five centres in Germany and Switzerland (both members of the AGO Ovarian Committee). All patients were diagnosed with recurrent epithelial ovarian cancer and received cytoreductive surgery between January 2000 and December 2003. Patients with nonepithelial ovarian cancer; patients with tumours of low malignant potential; and patients who underwent interval surgery, symptom-orientated surgery, or strictly palliative surgery were excluded. Patient characteristics are listed in table 4. The main objectives of this study were to define: (i) an appropriate surgical endpoint in relapsed ovarian cancer, and (ii) a predictive score for complete resection (55).

A significantly longer survival was seen in patients with complete resection compared to patients with any residual disease (median survival 45.2 months and 19.7 months respectively, HR 3.71, 95%CI 2.27-6.05, $p<0.0001$). The size of the residual tumour did not have any statistically significant impact on survival in patients where no complete resection could be achieved (median survival in patients with largest residual tumour 1-10 mm and >10 mm was respectively 19.6 months and 19.7 months, HR 0.84, 95%CI 0.51-1.40, $p=0.502$). Figure 8 shows the difference in OS between groups based on residual disease (RD; RD=0mm vs. RD 1-10 mm vs. RD>10mm) (55).
Three independent prognostic factors for postsurgical survival were identified: complete resection (residual tumour 0mm vs. >0mm), ascites (<500ml vs. ≥ 500ml), and postoperative chemotherapy (platinum-based vs not platinum-based). Factors significantly associated with complete resection were good performance status (Eastern Cooperative Oncology Group (ECOG) 0); no residual disease after primary surgery; early FIGO stage at initial diagnosis; ascites volume less than 500ml; cancer antigen (CA)-125 less than ten times the upper limit of normal (ULN); recurrent disease

limited to the pelvis only; and no radiological diagnosis of peritoneal carcinosis (55). The selected criteria were then combined into a predictive score of complete resection (positive predictive value [PPV] 0.79, negative predictive value [NPV] 0.58), which was deemed positive if a patient had (i) a good performance status (ECOG 0), (ii) no residual tumour after primary surgery or early FIGO stage at primary diagnosis (FIGO I/II), and (iii) a clinical diagnosis in preoperative imaging of ascites less than 500ml (54, 55).

Table 4 Patient characteristics. Adapted from DESKTOP I - P. Harter et al. (55)

		Median	Range
Age (years), median (range)		60	(24-84)
Treatment-free-interval (months)		n(%)	
	<6	36 (13.5)	
	6-12	63 (23.6)	
	>12	168 (62.9)	
Performance status: Eastern Cooperative Oncology Group (ECOG)		n(%)	
	0	118 (53.2)	
	1	86 (38.7)	
	2	16 (7.2)	
	3	2 (0.9)	
	Missing	45	
Ascites (ml)		n(%)	
	<500	231 (86.5)	
	≥500	36 (13.5)	
FIGO stage at initial diagnosis		n(%)	
	I	46 (18)	
	II	33 (12.9)	
	III	165 (64.7)	
	IV	11 (4.3)	
	Missing	12	
Residual disease after surgery for recurrence (mm)		n(%)	
	0	133 (49.8)	
	1-10	69 (25.8)	
	11-20	22 (8.2)	
	>20	43 (16.1)	

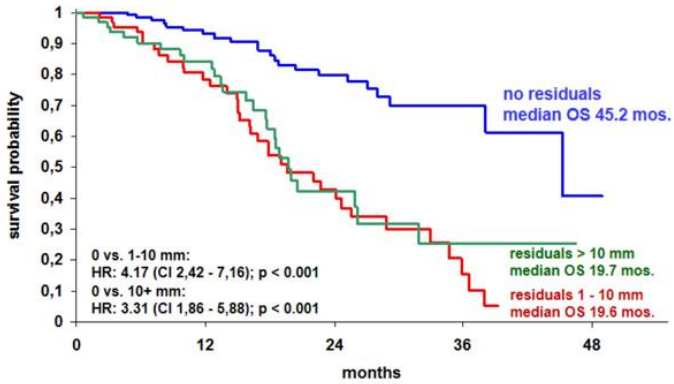


Figure 8 Survival of subgroups: R0 versus RD=0-10mm versus RD>10mm, after Surgery in recurrent ovarian cancer: the Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) DESKTOP OVAR trial – P. Harter et al. (55)

6.3.3 DESKTOP II

DESKTOP II, a prospective multicentre trial published in 2011, included 516 patients with recurrent epithelial ovarian cancer, who relapsed after a PFI of at least six months. Patients with nonepithelial or borderline tumours; patients who underwent interval surgery, second-look surgery, laparotomy or possibly interfering therapy; patients with third recurrence; and patients with platinum-refractory or platinum-resistant tumours (PFI<6 months) were excluded. 261 (51%) patients fitted all three AGO criteria (AGO score positive) and 255 of them were AGO score negative (of whom 171 fulfilled two criteria, and 78 fulfilled only one). 129 first relapse AGO-score positive patients (49% of all AGO- score positive patients) underwent cytoreductive surgery. Patient characteristics of this group are listed in table 5 (54).

The primary endpoint of this study was the positive prediction of complete resection in score-positive patients with first relapse. The secondary endpoint in this study was the assessment of a selection process for surgery in specialised centres, as well as the feasibility and complications of surgery in relapsing patients (54).

Complete resection rate in the AGO score positive group was 76% (95%CI: 69%-83%), thus meeting the predetermined requirement that the score should predict complete resection in at least 2 out of 3 patients in order to be clinically useful. In 24% of the first relapse and AGO score positive patients, no complete macroscopic debulking could be achieved. Unsuccessful surgery was mainly due to the location of the tumours which made them irresectable (19%). Other reasons were

patient-related factors (age or comorbidity) (2%), intraoperative morbidity (1%), and refusal of stoma placement by the patient (2%) (54).

Table 5 Patient characteristics of 129 first relapse, AGO-score positive patients included in DESKTOP II, adapted from DESKTOP II – P. Harter et al. (54)

		Median	Range
Age (years)		58.8	(22.1-82.9)
Interval since the end of first therapy (months)		25.3	(6.0-249.2)
CA-125 before surgery (U/mL)		76	(3-4218)
		n(%)	
CA-125 > 70 (mL)		61 (54)	
FIGO stage at first diagnosis		n(%)	
	I-II	34 (26)	
	III-IV	95 (74)	
Residual tumour after surgery for recurrence (mm)		n(%)	
	0	98 (76)	
	1-10	13 (10)	
	>10	18 (14)	

The positive predictive value of the AGO score at first relapse was 0.76 (AGO score positivity predicting a high possibility of complete resection), whereas the negative predictive value was only 0.38 with low specificity (0.53). As the trial was only powered to investigate the prediction of resectability, and not to perform any conclusion on score-negative patients, no statistical analysis could be performed to evaluate the score of irresectability. Out of the 255 AGO score negative patients (198 first relapse and 57 second relapse), 80 underwent surgery and complete resection was achieved in 63% in patients with first relapse (40 out of 64 patients) and in 69% of second relapse patients (11 out of 16 patients). In table 6, numbers and percentages in relation to the total study population are listed. Although not an endpoint in this trial, PFS and OS in patients with recurrent disease have been shown to be independently associated with complete cytoreductive surgery (54).

Table 6 Patient characteristics in numbers and percentages in relation to the total study population, after Prospective Validation Study of a Predictive Score – P. Harter et al. (54)

<table>
<tr><td colspan="8">All included patients in study
516 (100)</td></tr>
<tr><td colspan="3" rowspan="2">AGO score positive
261 (51)</td><td colspan="2">Two criteria fulfilled
171 (33)</td><td>One criterium fulfilled
78 (15)</td><td colspan="2">No criterium fulfilled
6 (1)</td></tr>
<tr><td colspan="5">AGO score negative
255 (49)</td></tr>
<tr><td colspan="2">Surgery
148 (29)</td><td>No surgery
133 (22)</td><td colspan="3">First relapse
198 (38)</td><td colspan="2">Second relapse
57 (11)</td></tr>
<tr><td colspan="2">First Relapse (= study cohort)
129 (25)</td><td>Second relapse
19 (4)</td><td colspan="2">Surgery
64 (12)</td><td>No surgery
134 (26)</td><td colspan="2">Surgery
16 (3)</td><td>No surgery
41 (8)</td></tr>
<tr><td>R0
98 (19)</td><td>No R0
31 (6)</td><td></td><td>R0
40 (8)</td><td>No R0
24 (4)</td><td></td><td>R0
11 (2)</td><td>No R0
5 (1)</td><td></td></tr>
</table>

6.3.4 DESKTOP III

DESKTOP III (2020) was a randomised, two-arm prospective international and multicentre trial. The study included a total of 407 AGO score-positive, platinum-sensitive patients at first relapse. Patients with nonepithelial or borderline tumours; undergoing second-look surgery, laparotomy, palliative surgery or interval debulking; platinum-refractory tumours; second, third or later relapse; and inoperable disease were excluded. Patients were deemed inoperable when using medication inducing surgical risk (e.g. anticoagulating agents); if they had non-accessible metastases for surgical removal; or a concomitant disease not allowing surgery and/or chemotherapy. Patient characteristics are listed in table 7. DESKTOP III randomised patients either to secondary cytoreductive surgery plus chemotherapy (n=206), or chemotherapy alone (n=201). The primary endpoint of this study was OS, secondary endpoints were PFS, resection rate and treatment burden, as well as QOL (3, 83).

Table 7 Patient characteristics, adapted from slides ASCO2020 Annual Meeting: DESKTOP III (3)

	No surgery	Surgery
Patients (n)	201	206
Age (years), median	62.2	60.8
PFI>12 months, n(%)	151 (75.1)	155 (75.2)
Median PFI (months)	18.7	21.1
Initial FIGO stage IIIB-IV, n(%)	147 (73.1)	155 (75.6)

206 patients underwent surgery, of whom a 74.2% macroscopic complete resection rate was achieved. A statistically significant difference of 7.7 months in median overall survival between the surgery- and no surgery-arm was noted in favour of the patients receiving cytoreductive surgery (53.7 months versus 46.0 months respectively, HR 0.75, 95%CI 0.58-0.96, p=0.02). PFS showed a statistically significant difference of 4.4 months between the surgery- and no surgery-arm (18.4 months versus 14.0 months respectively, HR 0.66, 95%CI 0.54-0.82, p<0.001) (figure 9). A difference in OS between patients with complete resection and patients with residual disease was found (61.9 months versus 28.8 months respectively, HR 0.4, 95%CI 0.28-0.59, p<0.001). Patients receiving complete resection had longer OS than patients in the no surgery-arm (61.9 months versus 46.0 months respectively, HR 0.57, 95%CI 0.43-0.76, p<0.001) (figure 10) (3).

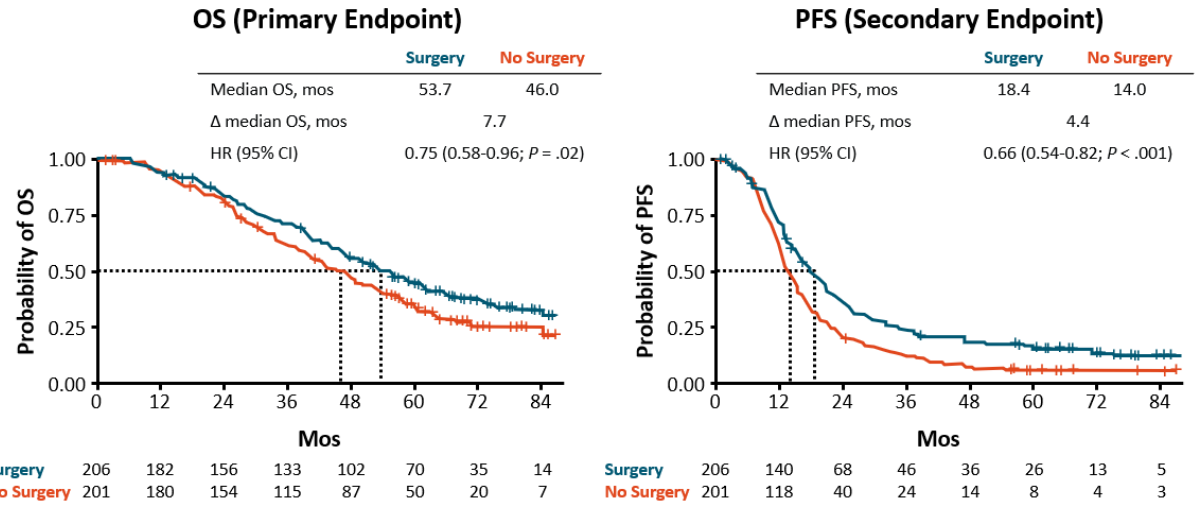


Figure 9 OS and PFS comparing the surgery- and no surgery-arm, figure credit: clinicaloptions.com (84)

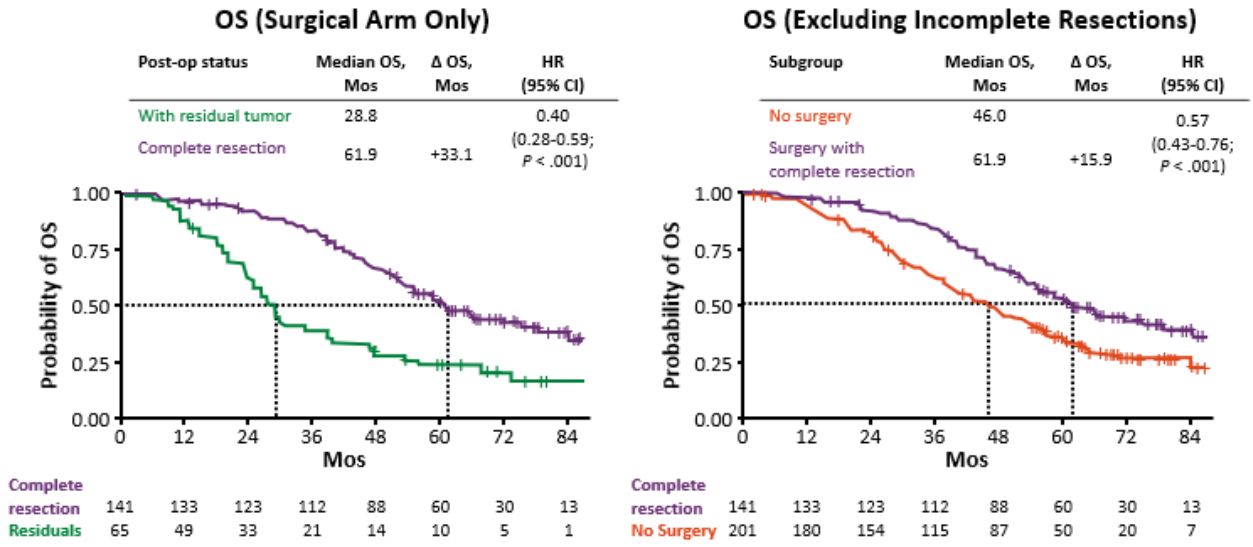


Figure 10 OS comparing complete resection-arm to OS in patients left with residual disease and compared to patients in the no surgery-arm, figure credit: clinicaloptions.com (84)

6.3.5 SOC1 Trial

The SOC1 (Surgery or Chemotherapy in Recurrent Ovarian Cancer) (still ongoing), a randomised phase III trial, by the Shanghai Gynecologic Oncologic Group, included 357 patients with recurrent ovarian cancer; who relapsed after a PFI of at least six months; had an iMODEL score≤4.7 (see infra); and were assessed by experienced surgeons who believed complete resection to be possible. Patients with nonepithelial or borderline tumours; patients undergoing second-look surgery, laparotomy, palliative surgery or interval debulking; patients with PFI less than six months; patients with second, third or later relapse; patients with no assessable resectability or inability to evaluate the score; and patients who were inoperable were excluded. Patient characteristics are listed in table 8. All included patients were randomly enrolled in the two arms of this study: surgery (182 patients) versus no surgery (175 patients). Primary endpoints were PFS and OS, secondary endpoints were treatment free survival (TFS), adjusted OS, safety, and QOL (4).

Table 8 Patients characteristics: no surgery- versus surgery-arm, after SOC1 - R. Zang et al. (4)

	No surgery	Surgery
Patients (n)	175	182
Age (years), median	53.1	55.2
Median PFI (months)	16.0	16.25
iModel score≤4.7 (%)	83.4	89.0
Initial FIGO stage III-IV (%)	83.4	81.3

182 patients underwent surgery, in whom a 76.7% macroscopic complete resection rate was achieved. At an interim analysis, a statistically significant difference in PFS of 5.5 months was found between the surgery- and the no surgery-arm (17.4 months versus 11.9 months, HR 0.58, 95%CI 0.45-0.74, p<0.001) (figure 11). In OS (data are still immature), a difference of 4.2 months between the two arms was found, showing a non-statistically significant benefit for the surgery-arm (58.1 months versus 53.9 months, HR 0.82, 95%CI 0.57-1.19) (figure 11). In patients receiving R0 surgery, a statistically significant longer PFS was seen compared to patients left with residual disease (19.2 months versus 12.6 months, HR 0.50, 95%CI 0.37-0.66). In patients receiving surgery but left with residual tumour post-OP, no statistically significant difference in PFS was seen with patients that were in the no surgery-arm (difference of 0.7 months, HR 1.10, 95%CI 0.74-1.63, p=0.650). OS data are still immature (4).

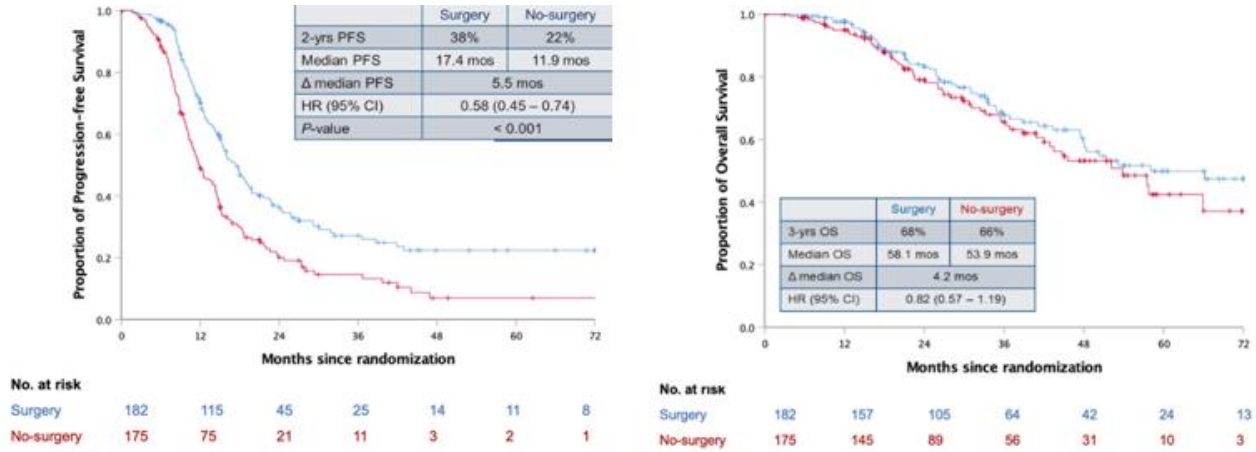


Figure 11 PFS and OS comparing surgery versus no surgery, after SOC1 - Zang et al. (4)

6.4 Other scoring systems

Several studies have been set up to determine which patients should be given the option of surgery. Most studies showed significance of either preoperative CA-125 levels (85-88), progression or disease free interval (DFI/PFI) length (89-93), ascites (86, 94), residual tumour (RT) at first surgery (86, 90), sensitivity to platinum (94), number of lesions and site of recurrence (90, 92-94), tumour histology (HGSC) (94), imaging (PET, laparoscopy, CT) (90, 95-97), or performance status (93). The cut-off values of the above-mentioned variables differ throughout all different studies.

6.4.1 Memorial Sloan-Kettering Cancer Centre (MSKCC) selection criteria

Dennis S. Chi et al. (2006), reviewed 153 patients with recurrent epithelial ovarian cancer; who underwent primary cytoreductive surgery followed by platinum-based chemotherapy; who had a PFI of at least six months; and who underwent secondary cytoreductive surgery in the period from January 1987 to December 2001. Patients with cancer of low-malignant potential, patients undergoing second-look surgery, or surgery for malignant bowel obstruction were excluded. The objectives of this study were to identify prognostic factors for longer overall survival and to provide selection criteria for secondary cytoreductive surgery (98, 99).

On multivariate analysis, a survival benefit was seen in women left with disease that measured from no macroscopic disease to 0.5 cm compared to women who had larger disease left (median survival 56.2 months [95%CI 48.2-66.6] versus median survival 26.7 months [95%CI 21.9-31.0] respectively, $p<0.001$). Therefore optimal cytoreductive surgery was defined as residual disease less than 0.5 cm. The prognostic factors that were related to statistically significant longer survival, were (i) longer disease-free interval ($p=0.004$), (ii) a lower number of sites of recurrence ($p=0.01$), and (iii) residual disease ≤0.5cm after secondary surgery ($p<0.001$). These prognostic factors were combined into selection criteria, shown in figure 12 (98).

DFI (months)	One site	Multiple sites, no carcinomatosis	Carcinomatosis
6-12	Offer SC	Consider SC	No SC
13-30	Offer SC	Offer SC	Consider SC
>30	Offer SC	Offer SC	Offer SC

Figure 12 MSKCC criteria, after Guidelines and selection criteria for secondary cytoreductive surgery (SC) in patients with recurrent, platinum-sensitive epithelial ovarian carcinoma - Dennis S. Chi et al. (98)

6.4.2 iMODEL/Tian selection criteria

Tian et al. (2011), conducted an international retrospective review of 1075 patients with platinum-sensitive recurrent ovarian cancer undergoing secondary surgery from 1982 to 2006. Additional data of 117 patients who underwent cytoreductive surgery was reviewed and used as an external validation of this model. Patients with tumours of malignant mixed mullerian type; a PFI<6 months; or unavailable survival data were excluded. The aim of this study was to develop a risk model for predicting complete macroscopic debulking in patients with recurrent ovarian cancer (99).

It was demonstrated that FIGO stage (p<0.001), residual disease after primary cytoreduction (<0.001), PFI (p<0.001), ECOG performance status (p<0.001), CA-125 (p<0.001), ascites at recurrence (p<0.001), and FIGO stage III/IV (p=0.036) were statistically significant associated with R0 after secondary cytoreduction. Every predictor was assigned to a risk score as shown in figure 13. The risk model showed a sensitivity of 80.4% and specificity of 52.6%, the PPV and NPV were 0.804 and 0.474, respectively in an intern validation. Complete resection was achieved in 53.4% of the women at low risk and in 20.1% of the women at high risk. In the external validation, a sensitivity of 83% and a specificity of 58% was found. Complete resection was achieved in 83.3% of women at low risk and 42.4% in women at high risk (99).

Prognostic factors	**Scoring**					
	0	0.8	1.5	1.8	2.4	3.0
FIGO STAGE	I/II	III/IV				
Residual disease after primary debulking surgery	0		>0			
PFI (months)	≥16				<16	
ECOG performance status	0-1				2-3	
CA-125 at recurrence (U/ml)	≤105			>105		
Ascites	Absent					Present

Figure 13 iModel or Tian risk model for secondary cytoreductive surgery in recurrent ovarian cancer: Low risk ≤ 4.7, High risk: >4.7 (cumulative score of prognostic factors), adapted from A Risk Model for Secondary Cytoreductive Surgery in Recurrent Ovarian Cancer: An Evidence-Based Proposal for Patient Selection - Wen-Juan Tian (99)

6.4.3 External validation of selection criteria

As noted, the AGO score was further explored and validated in the prospective DESKTOP II study and later in the randomised trial, DESKTOP III (see supra). Van de Laar et al (2015), retrospectively validated the AGO and iMODEL score, by reviewing data of 408 patients who underwent surgery between 2000 and 2013 in 38 Dutch hospitals. Hospitals were either a regional tertiary referral hospital (12/38) or a large semi-specialized hospital (26/38), performing at least 20 debulking surgeries annually. Patients undergoing palliative surgery or symptom-oriented surgery; as well as patients undergoing interval surgery were excluded. None of the patients was part of the studies developing the prediction models, and as such they formed a valid external validation cohort. The positive predictive values reported were 82% and 80.3% for AGO and iMODEL score respectively, the negative predictive values were 68.5% and 55.6% respectively (100).

Cowan et al. (2017) retrospectively validated the Memorial Sloan Kettering Cancer Centre (MSKCC), iMODEL, and AGO score models in patients who underwent cytoreductive surgery between May 2001 and June 2014. Patients who received chemotherapy prior to debulking surgery, were excluded. The article reported high positive predictive values (PPV 87-88%) for all three models. The accuracy of the AGO Score, MSKCC and iMODEL prediction models were 49%, 86%, and 88% respectively. Using the AGO score, 51% of the women would have been excluded from surgery, however in 86% of these AGO-score negative patients, complete macroscopic debulking was achieved. Out of the 4% iMODEL ‘high risk’-labelled women, in 33% full macroscopic debulking was achieved. The MSKCC model has a good agreement with the iMODEL (101).

6.5 HIPEC in recurrent ovarian cancer

The first randomised phase III study by Spiliotis et al. in 2015, included 120 women with recurrent ovarian cancer; age between 18 and 70 years; performance status 1 or 2; and no disease beyond the abdomen. Women had stage IIIC and IV epithelial ovarian cancer and underwent primary debulking surgery, followed by chemotherapy as initial therapy. Women with performance status 3 or 4; pleural disease and/or lung metastasis; malignant bowel obstruction (MBO); or women with retroperitoneal disease were excluded. Patients were randomised into either a group undergoing cytoreductive surgery followed by HIPEC, or a group receiving cytoreductive surgery and systemic chemotherapy. Study outcomes were overall survival, platinum responsiveness, residual disease, peritoneal cancer index, and treatment with HIPEC (42).

60 patients received HIPEC after surgery for recurrence, and 60 patients received systemic chemotherapy, and a difference in overall survival of 13.3 months was seen (26.7 months versus 13.4 months respectively, p<0.006). In the HIPEC-arm, the three-year survival was 75%, in the non-HIPEC-group 18% (p<0.01). No statistically significant difference in overall survival was seen in the HIPEC-group between patients with platinum-resistant and platinum-sensitive disease (26.6 months versus 26.8 months respectively, p=0.287), whereas this was seen in the non-HIPEC-group (10.2 months versus 15.2 months respectively, p=0.002) (42).

In platinum-sensitive disease, an overall survival benefit was seen for women receiving HIPEC compared to the no-HIPEC group (26.8 versus 15.2 months respectively, p=0.035). In platinum-resistant disease, no statically significant difference in overall survival was seen between both groups (26.6 months in the HIPEC group versus 10.2 months in the non-HIPEC group) (see figure 14) (42).

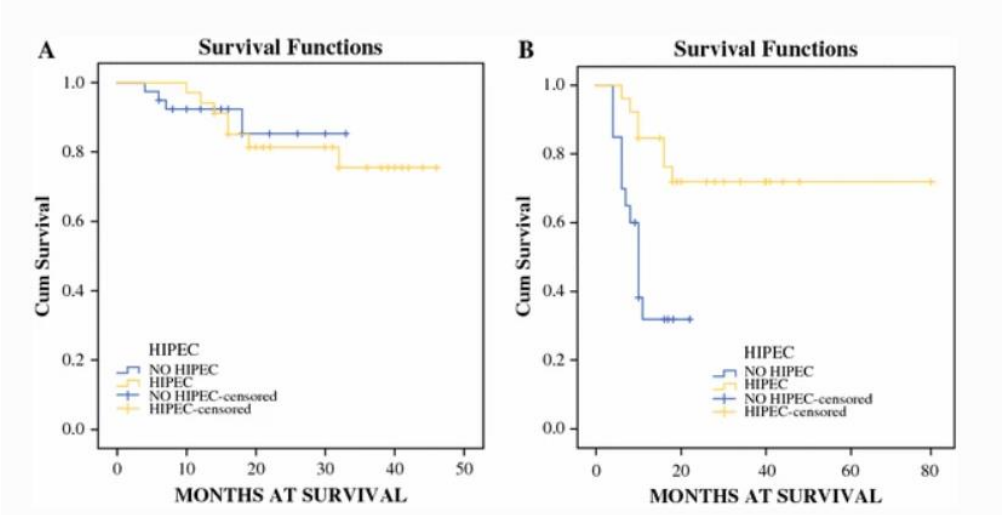


Figure 14 a Survival in platinum-sensitive disease, HIPEC versus no HIPEC. b Survival in platinum-resistant disease, HIPEC versus no HIPEC. From: Cytoreductive Surgery and HIPEC in Recurrent Epithelial Ovarian Cancer: A Prospective Randomized Phase III Study – Spiliotis et al. (42)

Achievement of complete cytoreductive surgery, showed a statistically significant higher survival in the HIPEC-group than in the non-HIPEC-group (30.9 months versus 16.9 months respectively, p=0.038). In the non-HIPEC-group, an overall survival benefit was seen in patients in who no residual disease was left (16.1 months in CC-0 versus 6.7 months in CC-2, p=0.002) (42). The peritoneal cancer index (PCI) showed a statistically significant longer survival in the HIPEC-group versus the non-HIPEC-group, both in patients with PCI≤15 (p=0.031) and PCI>15 (p=0.049) (42).

More randomised studies have been set up, but are not published yet: HORSE, IPHC, CHIPOR, and a study by the Memorial Sloan Kettering Cancer Centre (MSKCC) (50).

7. Discussion

The role of surgery in relapsed ovarian cancer has not been clearly defined. Whether or not patients receive debulking surgery depends on their clinician, surgeon, and health institution. Up until the publication of GOG213 in 2019, there was no level of evidence I data available on survival benefit (both OS and PFS) after secondary cytoreductive surgery. GOG213 showed no benefit for secondary debulking surgery compared to no surgery in OS, nor in PFS (2). In 2020, a second randomised trial was presented, DESKTOP III, showing a statistically significant survival benefit in women undergoing secondary cytoreductive surgery compared to women who did not get debulking surgery, both in OS, as well as in PFS (3, 84). A third major randomised trial on secondary cytoreductive surgery, SOC1, is still ongoing. An interim analysis showed a statistically significant difference in PFS in favour of the surgery-arm, compared to the no surgery-arm. SOC1-data on OS are still immature (4).

Subgroup analysis comparing women with no residual disease after surgery and women with any residual disease, showed a statistically significant survival benefit (PFS and OS), both in GOG213 and DESKTOP III (2, 3). When comparing women receiving complete macroscopic debulking and women receiving no surgery, in GOG213 no statistically significant difference was seen in OS, although there was a statistically significant difference in PFS (2). DESKTOP III showed an OS and PFS difference between patients receiving complete resection and patients in the no surgery-arm, in favour of women in whom complete macroscopic debulking was achieved (3, 55). The third large randomised trial, SOC1, is still ongoing, and OS data are immature. When comparing the R0 group and the group left with residual disease, a statistically significant PFS benefit was seen in the R0 group. No PFS difference was established between patients in whom no complete macroscopic debulking was achieved, compared to patients receiving no surgery (4). The survival benefit for women in whom no macroscopic disease was left compared to women left with residual disease, is therefore clear. The benefit for women in whom R0 was achieved, compared to women who did not undergo surgery, is less clear, as this OS benefit was not seen in GOG213. We may conclude that if the option of secondary cytoreduction surgery is chosen by clinician and patient, R0 disease after surgery should be the goal of surgery (2-4, 55).

GOG213 shows no survival benefit for women undergoing surgery (OS and PFS), whereas DESKTOP III concluded in a survival benefit (OS and PFS) for the surgery-arm compared to the no surgery-arm (2, 3). There are however some major differences between the two studies which

might provide an explanation for the contradictory results. Firstly, 49.5% of the enrolled patients in GOG213 were Asian, whereas Asian patients accounted for only 2% in DESKTOP III (102). Asian patients show longer survival in general, present at a younger age, undergo primary cytoreductive surgery (R0 is achieved more often), more often have low-grade serous ovarian cancer, and have an earlier stage of disease at first diagnosis. In short, they have an overall better prognosis than white women (103). Secondly, the use of bevacizumab differed in both studies, since 80.4% of women enrolled in GOG213 received second line treatment with bevacizumab versus 20% of women enrolled in DESKTOP III (102). The use of bevacizumab has been shown to prolong survival and might have given the women in the control-arm (no surgery) of GOG213 a survival benefit (61, 62). Another difference between GOG213 and DESKTOP III was the selection of patients before randomisation into a surgery- and no surgery-arm. Surgical decision-making in GOG213 was based on the insight and estimations of surgeons and investigators, whereas DESKTOP III used the validated AGO score to decide whether women should undergo surgery or not (2, 3, 53, 102). Resection rates were respectively 63% and 74.2% in GOG213 and DESKTOP III. Although the use of selection criteria might be one explanation for the higher resection rate in DESKTOP III, another important factor herein is a well-trained and experienced surgeon. In order to be deemed eligible for DESKTOP III, surgeons (and centres) were selected according to their prior performance and participation in other (surgical) trials, whereas no formal selection criteria were applied in order to participate in the GOG213 (2, 3, 53, 102).

The score system used in DESKTOP III is the AGO score, which is deemed positive if patients have (i) a good performance status (ECOG 0), (ii) no residual tumour after primary surgery or early FIGO stage at primary diagnosis (FIGO I/II), and (iii) a clinical diagnosis in preoperative imaging of ascites less than 500ml (55). Before it was used for patient selection in DESKTOP III, the AGO score was established in DESKTOP I, a retrospective study, and thereafter prospectively validated in DESKTOP II. In DESKTOP II, complete resection was achieved in 76% of AGO score positive patients, a PPV of 0.76 and an NPV of 0.38 were found (54). Other score systems used in clinical practice, are the iMODEL and the MSKCC criteria. Internal validation of the iMODEL showed a sensitivity of 0.804 and specificity of 0.526, a PPV of 0.804, and an NPV of 0.474. Complete resection rate was 53.4% for the women at low risk and in 20.1% for the women at high risk. In an external validation, a sensitivity of 0.83 and a specificity of 0.58 were found. Complete resection was achieved in 83.3% of the women at low risk and in 42.4% of the women at high risk (99). The iMODEL was used in SOC1 for patient selection, where a 76.7% resection rate was achieved (4). An external validation by van de Laar et al. (2015), concluded that both AGO and iMODEL score

models show a high positive predictive value (0.82 and 0.803 respectively), but also a rather low negative predictive value (0.685 and 0.556 respectively) for complete cytoreductive surgery. This was coherent with the findings in other studies aiming to validate the AGO criteria (54, 55, 100, 101, 104, 105). Cowan et al. (2017), externally validated and compared AGO, MSKCC, and iMODEL, reporting high positive predictive values (PPV 0.87-0.88) for all three models (101). In conclusion, the above-mentioned selection and predictive models (MSKCC, iMODEL, and AGO), show a high positive predictive value (varying from 0.76 to 0.88), but a low negative predictive value (varying from 0.38 to 0.68). In patients with a positive score, resection rates varied throughout all three models from 53.4% to 83.3% (3, 54, 55, 100, 101, 105, 106). Scoring systems for patient selection are therefore not yet on point, and we might find benefit in combining them. However, the main concern should be to identify patients with false negative scores, seeing as complete macroscopic debulking can sometimes be achieved even in score negative patients. Data from above mentioned studies for example, show resection rates of 20.1%-42.4% in women with an iMODEL high risk score; 86% in women with a negative AGO score; and 33% in women with MSKCC high risk score (100, 101).

Besides the cytoreductive surgery itself, the way chemotherapy is administered, is also a subject of debate. By administering hyperthermic chemotherapy into the abdomen after cytoreductive surgery (HIPEC: hyperthermic intraperitoneal chemotherapy), an extensive locoregional approach might improve the overall survival of women with recurrent disease. Apart from one small study by Spiliotis et al., there is no level of evidence I data on survival benefits by administration of HIPEC (42, 107-112). This first randomised trial, published by Spiliotis et al in 2015, found 13-month improvement in survival with the addition of HIPEC to secondary cytoreductive surgery, a benefit found in both platinum-sensitive and platinum-resistant cohorts (42). However, there are many points of criticism that can be addressed in this study. Firstly, the trial was not registered in any database, as it should have been. Furthermore, there was no description of statistical analysis included, and the study endpoints were not clearly defined. Nor was it specified how the sample size was calculated (120 patients were included). It is impossible to ascertain if this study was powered to provide any conclusions on the study-endpoints (overall survival, platinum responsiveness, residual disease, peritoneal cancer index, and treatment with HIPEC). PFI, morbidity, mortality, adverse effects, QOL, etc. are not mentioned. Based on this criticism, no conclusions can be drawn from this trial (57, 113). Results from trials like HORSE, IPHC, CHIPOR, and a study by the MSKCC are not yet published. Until further results are published, there is not enough evidence to draw conclusions on longer overall survival or on the nature of any side effects

by the use of HIPEC. Therefore, it is not recommended to offer HIPEC to women with relapsed ovarian cancer as standard of care (50).

Although this thesis investigates the role of surgery in recurrent ovarian cancer, other paths in the treatment of these women should be explored as well. We will not discuss them in detail as this would lead us too far. Parallel investigations have explored therapeutic options besides cytoreductive surgery, mainly focussing on specific driver molecular pathways of ovarian cancer. For instance, bevacizumab, a monoclonal antibody targeting vascular endothelial growth factor (VEGF), which decreases the VEGF expression, leads to reduced tumour vascularization and less angiogenesis. Bevacizumab is given both in combination with chemotherapy, as well as maintenance therapy in women with recurrent ovarian cancer (15, 41, 53, 59-62). The randomised controlled phase III trials OCEANS and AURELIA both showed prolonged survival in patients with recurrent ovarian cancer receiving treatment with bevacizumab (61, 62). Another molecularly targeted therapy getting attention in ovarian cancer is the use of PARP inhibitors. Currently there are three approved PARP inhibitors (PARPi) used in the treatment of platinum-sensitive ovarian cancer: olaparib, niraparib, and rucaparib. PARPi can be given both in combination therapy or in monotherapy as maintenance (in Europe, only rucaparib is licensed by the EMA as monotherapy). Their use has been investigated in multiple studies, such as study 19 (olaparib), SOLO2 (olaparib), NOVA (niraparib), ARIEL3 (rucaparib), SOLO3 (olaparib), etc. Overall, an improvement in PFS was established, which was most clear in *BRCA* mutated patients, yet not limited to them, as it could not be excluded that patients without a *BRCA* mutation did not experience PFS advantage (50, 114-118). The downside to all of this is the toxicity that comes with PARPi, such as increased risk of infection, feeling sick, fatigue, diarrhoea, headaches, as well as liver and kidney malfunctions. However, by adapting the dose of those medicines, most of the aforementioned problems are manageable (115-117, 119, 120). With the development of new drugs, we need to ask ourselves if surgery still has a role in the treatment of women with recurrent ovarian cancer, and, if so, which kind of role. GOG213, and DESKTOP III, were conducted right before the start of this new era of molecular therapy and as these new therapies have found their way into clinical practice, we need to take them into account and consider different treatment options or combinations. As seen in GOG213, the use of bevacizumab might have been one of the reasons no statistically significant difference was found in OS between the surgery- and no surgery-arm (53). If new emerging therapies can provide equivalent or better survival and/or quality of life in these patients, then a surgical approach of this disease might even be outdated.

In the GOG213, patient-reported quality of life was an important secondary endpoint. Immediately after surgery, a decrease in QOL was reported by patients receiving cytoreductive surgery. However, after six weeks, this difference was levelled out and every subsequent quality of life follow-up was seen to be equal in both groups. Despite the decrease in QOL after surgery, mainly by lessened physical functioning and the increase in surgery related symptoms, overall, women undergoing surgery have no significantly lower long-term QOL (2). An important secondary endpoint in the AURELIA trial was patient reported outcome, which showed that the use of bevacizumab resulted in an improvement of gastrointestinal symptoms, and a better QOL (62, 121). The management of women with relapsed ovarian cancer should focus on survival on one hand, but on the other hand, also on palliation and quality of life. Even in this setting, surgery plays a role. As malignant bowel obstruction (MBO) is common in relapsed ovarian cancer, palliative surgery is often needed. This surgery should be performed within a multidisciplinary setting, with possibilities of an adequate infrastructure to support the patient (e.g. home care support) as this might lead to short bowel syndrome (SBS), making the patient depending on parenteral nutrition for the rest of her life. Given the difficulties these women experience post-operatively, patients should be carefully selected and counselled. This way, one can determine which women should and which should not undergo this surgery, rather than operating all of them, resulting in a general low quality of life and poor survival outcomes. Therefore, MBO should be handled on an individual basis, considering patient satisfaction, as well as future quality of life, pain control, and surgical complications (122-124).

It is known that once women with ovarian cancer relapse, they will undergo an alternation of progression-free and symptomatic/treatment periods. One should therefore also evaluate the above elements – as discussed in relation to secondary relapse – with respect to women with tertiary relapse, quaternary relapse, etc. There is no level of evidence I data on these settings, however some studies have shown that surgery in these cases is still possible and might benefit those women in whom complete macroscopic debulking was achieved, on condition of a strict patient selection. Even in these cases, postoperative residual disease remains the number one predictor of survival (125-131).

8. Concluding remarks and outstanding questions

In conclusion, there is still no straightforward and generally applicable answer to the question whether – and if so, which – patients with recurrent ovarian cancer should be offered cytoreductive surgery as standard of care. A holistic approach of the individual patient is key and should be the norm. This approach should be based on performance status; age; comorbidity and willingness to be operated; as well as disease (ascites, metastasis locations, resectable tumour or not, use of scoring system, etc.); clinic (presence of intensive care, interprofessional management, qualitative resources, sufficient pain management, etc.); and choice of a surgeon with know-how and skills, well-trained in the matter and with the right amount of expertise.

Besides cytoreductive surgery, other treatment options are on their way. By targeting molecular pathways, investigators hope to accomplish an efficient and harmless treatment method. Examples of these medicines are bevacizumab and PARPi, both of which are being investigated and used in recurrent ovarian cancer. Future investigations might lead to ground-breaking conclusions on molecular pathways or tumour genetics, and drugs might be developed to interfere with tumour-sustaining mechanisms. As molecular therapies found their way into the treatment of ovarian cancer, we cannot be sure if the results from surgical studies can be extrapolated to the current treatment setting and we need to keep multiple treatment options for patients in mind.

Recurrent ovarian cancer as we know it, has become a chronic disease. Women experiencing recurrent disease are likely to relapse multiple times. More trials and investigations in these subgroups are needed to provide answers on treatment in this setting. Given the incurability of relapsed ovarian cancer, the priority should be to manage disease related symptoms. It is essential to manage this disease with attention for prolonging overall survival; controlling and delaying the disease progression; minimizing side effects of treatment; and maintaining or improving the general quality of life.

9. References

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10. Appendix

10.1 Overview of randomised trials in recurrent ovarian cancer

Table 9 Overview of primary endpoints, sizes, study arms, resection rates, and survival data (PFS and OS) of randomised trials investigating cytoreductive surgery in recurrent ovarian cancer (2-4, 53, 80-82)

Study	EORTC-55963 (LOROCSON)	SOCcer	GOG213	DESKTOP III	SOC1
Year	2000	2012	2019	2020	Ongoing
Primary endpoint	Progression-free survival	Progression-free survival	Overall survival (surgery and bevacizumab)	Overall survival	Overall survival
Number of Patients	700	230	485	408	357
Study arms	1. Surgery + Chemo	1. Surgery + Chemo	1. Surgery + Chemo +/- bevacizumab	1. Surgery + Chemo	1. Surgery + Chemo
	2. Chemo alone	2. Chemo alone	2. Chemo alone +/- bevacizumab	2. Chemo alone	2. Chemo alone
Optimal resection rate, (%)	Study aborted prematurely	Study aborted prematurely	Arm 1: 63	Arm 1: 74.2	Arm 1: 76.7
			Arm 2: /	Arm 2: /	Arm 2: /
Medi-an PFS (months)			Arm 1: 18.9	Arm 1: 18.4	Arm 1: 17.4
			Arm 2: 16.2	Arm 2: 14.0	Arm 2: 11.9
Median OS (months)			Arm 1: 50.6	Arm 1: 53.7	Pending
			Arm 2: 64.7	Arm 2: 46.0	

10.2 GOG213, results on OS and PFS by the use of bevacizumab.

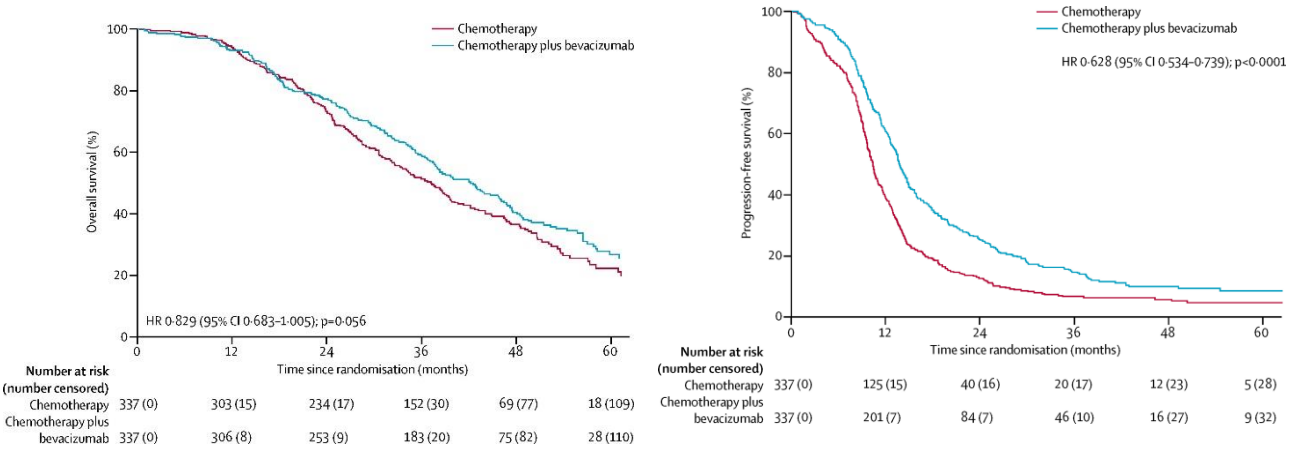

Figure 15 A. Overall survival difference between chemotherapy and chemotherapy plus bevacizumab, B. Progression-free survival difference between chemotherapy and chemotherapy plus bevacizumab - GOG213 - Coleman RL et al. (53)

Between the bevacizumab- and no bevacizumab-arms, an improvement in overall survival of 4.9 months (42.2 months versus 37.3 months, HR 0.823, 95%CI 0.680-0.996, p=0.0447) (figure 15) and in PFS of 3.4 months was seen in the chemotherapy plus bevacizumab group (10.4 months versus 13.8 months, HR 0.628, 95%CI 0.534-0.739, p<0.001) was seen (figure 16) (53).