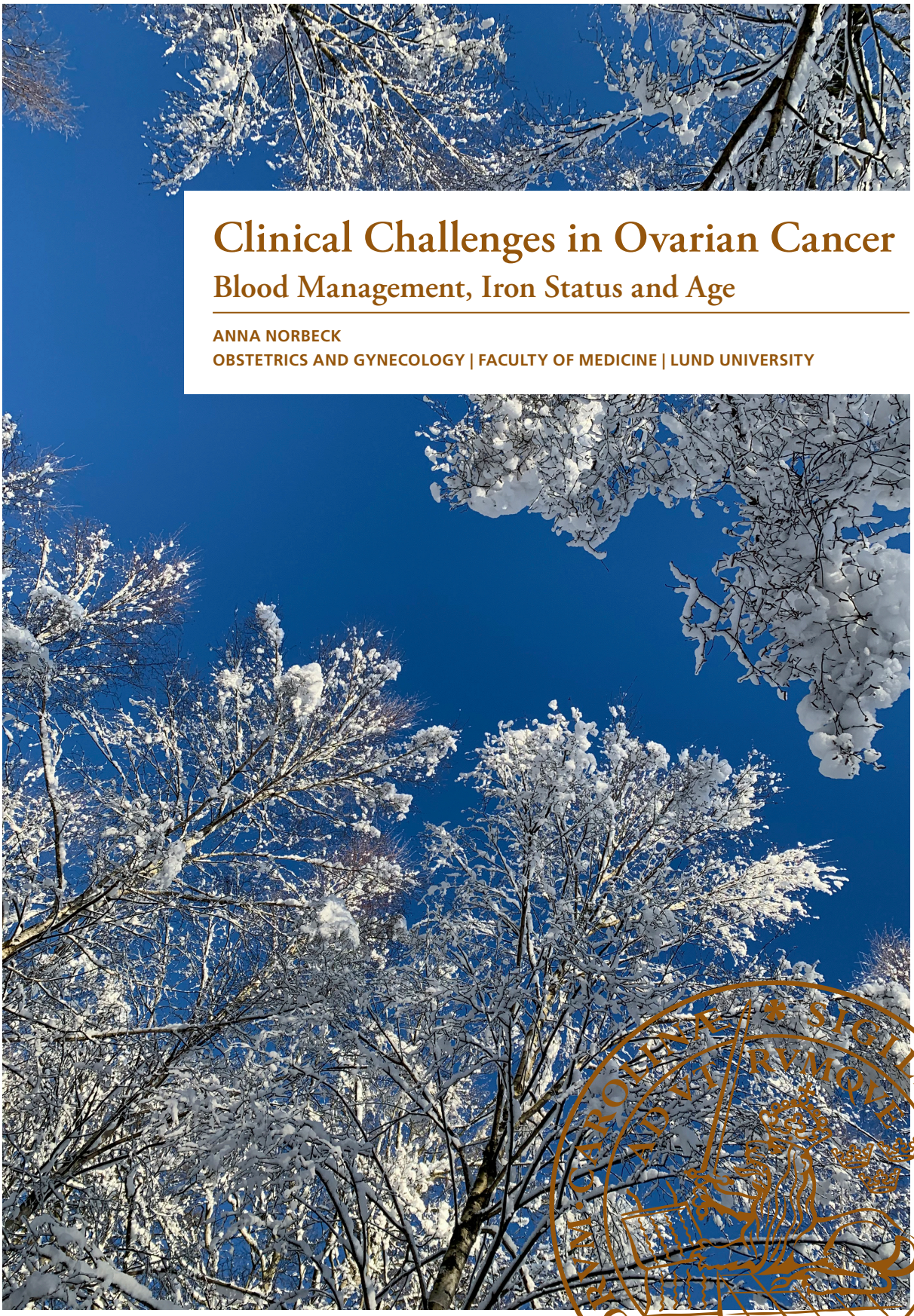
Clinical Challenges in Ovarian Cancer - Blood Management, Iron Status and Age

Norbeck, Anna

2026

Document Version:
Publisher's PDF, also known as Version of record



Clinical Challenges in Ovarian Cancer

Blood Management, Iron Status and Age

ANNA NORBECK
OBSTETRICS AND GYNECOLOGY | FACULTY OF MEDICINE | LUND UNIVERSITY

Printed by Media-Tryck, Lund 2026 NORDIC SWAN ECOLABEL 3041 0903

LUND UNIVERSITY

FACULTY OF MEDICINE

Department of Obstetrics and Gynecology

Lund University, Faculty of Medicine
Doctoral Dissertation Series 2026:9
ISBN 978-91-8021-807-8
ISSN 1652-8220

Clinical Challenges in Ovarian Cancer

Blood Management, Iron Status and Age

Anna Norbeck

LUND
UNIVERSITY

DOCTORAL DISSERTATION

Doctoral dissertation for the degree of Doctor of Philosophy (PhD) at the Faculty of Medicine at Lund University to be publicly defended on January 23rd, 2026, at 09.00 at the Department of Obstetrics and Gynecology, Klinikgatan 12, Lund

Faculty opponent
Docent Ulrika Ottander, Umeå University

Organization: LUND UNIVERSITY

Document name: Doctoral dissertation **Date of issue** January 23rd 2026

Author(s): Anna Norbeck **Sponsoring organization:**

Title and subtitle: Clinical Challenges in Ovarian Cancer – Blood Management, Iron Status and Age

Abstract: Ovarian cancer often presents with vague and non-specific symptoms, leading to the diagnosis of the majority of patients at an advanced stage, which carries poor prognosis. The standard treatment is primary debulking surgery followed by chemotherapy. The overall aim of this thesis was to evaluate factors that delay the time to diagnosis, assess how patient blood management (PBM), preoperative anemia, and iron deficiency affect postoperative recovery and determine how older patients tolerate debulking surgery.

Study I: This retrospective cohort study included 249 patients with advanced ovarian cancer (AOC). The primary outcome was the time period from first consultation with predefined symptoms to a reasonable suspicion of ovarian cancer. The median time was 24 days. Older age delayed access to the diagnosis (55%). Consultation in specialized care decreased the delay by 70% compared to primary care.

Study II: This retrospective cohort study analyzed 354 women who underwent surgery for AOC before and after the implementation of patient blood management routines. Blood transfusions declined from 83% to 52%, (p <0.001) during the study. No difference in severe complications was recorded, (adjusted odds ratio 0.55 (95% CI 0.26-1.17)). The mean difference in hemoglobin (Hb) levels before start of chemotherapy was -1.32 g/L (95% CI -3.93 to -0.22).

Study III: This retrospective cohort study, including 262 patients with AOC undergoing surgery, evaluated the impact of preoperative anemia and iron deficiency. Suboptimal surgery (with ≥ 1 cm of residual disease) was performed in 24% of patients with iron deficiency anemia, compared to 6% and 8% in patients with no anemia or no iron deficiency (p 0.005). Iron deficiency was associated with a higher rate of severe complications compared to patients without iron deficiency (adjusted odds ratio 2.47 (95% CI 1.11-5.50)).

Study IV: This retrospective cohort study of 486 patients assessed treatment in older patients, postoperative outcomes and overall survival. Radical surgery was achieved in 61.4% of those aged 70-79 years and in 43.5% of patients aged ≥ 80 years. No difference in severe complications was found. Restricted mean survival time at 36 months decreased with higher age.

Conclusions: Higher age and primary consultation at general practitice delayed the time to diagnosis. Preoperative anemia, iron deficiency and higher age (≥ 80 years) appeard to impact postoperative recovery. Patients presenting with iron deficiency seemed to have more advanced disease.

Key words: Advanced ovarian cancer, time to diagnosis, patient blood management, anemia, iron deficieny, debulking surgery, older patients

Classification system and/or index terms (if any) Supplementary bibliographical information

Language English **Number of pages**: 66

ISSN 1652-8220 **ISBN:** 978-91-8021-807-8

Recipient's notes Price Security classification

Clinical Challenges in Ovarian Cancer

Blood Management, Iron Status and Age

Anna Norbeck

LUND
UNIVERSITY

Cover image by Anna Norbeck

Faculty of Medicine

Department of Obstetrics and Gynecology

ISBN 978-91-8021-807-8

ISSN 1652-8220

Printed in Sweden by Media-Tryck, Lund University,
Lund 2025

Media-Tryck is a Nordic Swan Ecolabel
certified provider of printed material.
Read more about our environmental
work at www.mediatryck.lu.se

MADE IN SWEDEN

To my Grandmother

Table of Contents

Thesis at a glance

Study	Aim	Results	Conclusion
Study I: Age and Referral Route Impact the Access to Diagnosis for Women with Advanced Ovarian Cancer	To evaluate the timeline from the first consultation with symptoms to reasonable suspicion of cancer.	The median time was 24 days. Specialized care had a 70% decrease in delay compared to primary care. Older age had a 55% increase in delay.	First consultation in primary care, a planned visit, or older age were associated with delay to diagnosis.
Study II: Safe to save blood in ovarian cancer surgery - time to change transfusion habits	To assess patient recovery after the implementation of patient blood management.	The number of patients transfused was reduced from 83% to 52% without increasing severe complications.	Patient recovery was not negatively impacted by the reduction of red blood cell transfusions and the introduction of patient blood management.
Study III: Iron deficiency restrains the short-term recovery in patients undergoing surgery for advanced ovarian cancer	To evaluate the effects of preoperative anemia and iron deficiency on short-term recovery and surgical outcome.	Patients with iron deficiency had a higher risk of severe complications (odds ratio 2.47). Suboptimal surgery increased in patients with iron deficiency.	Iron deficiency might serve as a possible marker of higher tumor burden and may predict an elevated risk of severe postoperative complications.
Study IV: Treatment Patterns and Outcomes in Older Patients with Ovarian Cancer: A Real-World Data Analysis	To assess surgical tolerance, postoperative outcomes and overall survival in patients aged $\geq$ 70 years.	Radical surgery was achieved in 61% of patients aged 70-79 years, and in 44% of patients aged $\geq$ 80 years. Increasing age was associated with a shorter restricted mean survival time at 36 months.	With increasing age, the patient was less likely to undergo radical surgery. There was no difference in severe complications, but survival after surgery decreased with higher age.

Original papers

This thesis is based on the following papers, referred to in the text by their Roman numerals.

I. **Norbeck A,** Asp M, Carlsson T, Kannisto, P, Malander S. Age and Referral Route Impact the Access to Diagnosis for Women with Advanced Ovarian Cancer. *Journal of Multidisciplinary Healthcare.* 2023 May 3, 16:1239-1248

II. **Norbeck A,** Bengtsson J, Malander S, Asp M. Kannisto P. Safe to save blood in ovarian cancer surgery - time to change transfusion habits. *Acta Oncologica*. 2024 Sep. 25, 63:728-735

III. **Norbeck A,** Asp M, Malander S, Kannisto P. Iron deficiency restrains the short-term recovery in patients undergoing surgery for advanced ovarian cancer. Manuscript submitted.

IV. **Norbeck A,** Alson S, Asp M. Treatment Patterns and Outcomes in Older Patients with Ovarian Cancer: A Real-World Data Analysis. Manuscript unpublished.

Populärvetenskaplig sammanfattning

Äggstockscancer är den åttonde vanligaste cancerformen bland kvinnor globalt och har den högsta dödligheten av alla gynekologiska maligniteter. I Sverige insjuknar cirka 700 kvinnor årligen. De flesta patienter upplever symptom före diagnos, men eftersom symptomen ofta är ospecifika och vaga, diagnosticeras ungefär 80% av patienterna i ett avancerat stadium när sjukdomen redan har spridit sig. Femårsöverlevnaden för äggstockscancer i Sverige ligger runt 50%.

Den rekommenderade primära behandlingen för avancerad äggstockscancer är kirurgi följt av cellgiftsbehandling. Kirurgin är omfattande och innebär att äggstockar, äggledare, livmoder, tarmkäx samt så mycket som möjligt av den spridda tumören avlägsnas.

Om primär kirurgi inte är möjligt - till exempel på grund av nedsatt allmäntillstånd eller utbredd tumörspridning - behandlas patienten först med cellgifter för att krympa tumören. Därefter genomgår patienten kirurgi följt av ytterligare cellgiftsbehandling. Många patienter som diagnostiseras i ett avancerat stadium är påverkade av sin sjukdom, vilket ofta yttrar sig som lågt blodvärde och järnbrist. Inför en stor operation är det avgörande att optimera patientens allmäntillstånd för att förbättra förutsättningarna för en god återhämtning. Med stigande ålder ökar även risken för andra kroniska sjukdomar, vilket kan påverka patientens hälsa och operationsförmåga.

I de fall där patienten bedöms vara oförmögen att klara av någon form av kirurgi ges enbart cellgiftsbehandling för att krympa tumören så mycket som möjligt. Om patienten inte heller bedöms klara av cellgiftsbehandling ges endast stödjande behandling.

Syfte och Studier

Syftet med denna avhandling är att utvärdera vilka faktorer som påverkar ledtiden till diagnosen äggstockscancer. Vidare undersöks hur faktorer som lågt blodvärde, järnbrist, blodtransfusioner och ålder påverkar äggstockscancerpatienternas återhämtning efter kirurgin.

Studie I undersökte tidsintervallet från det att patienten sökte vård med symptom till dess att en mycket stark misstanke om äggstockscancer förelåg. Resultaten visade att äldre patienter ofta hade ett längre tidsintervall jämfört med yngre patienter. Tidsintervallet var längre om patienten sökte på vårdcentral jämfört med om det första besöket skedde inom specialiserad vård, som på ett sjukhus eller hos en privat gynekolog. Akuta mottagningsbesök hade ett kortare tidsintervall jämfört med planerade mottagningsbesök. Nästan hälften av patienterna sökte initialt för buksmärtor.

Studie II utvärderade patienternas återhämtning efter kirurgi efter att riktlinjer för Patient Blood Management (PBM) hade införts. PBM syftar till att optimera användningen av transfunderat blod i vården. Detta uppnås genom medicinering som minskar blodförlusten under operation, restriktivare blodtransfusioner samt behandling av järnbristanemi med järninfusioner före eller efter operation. Studien visade att antalet patienter som behövde blodtransfusioner minskade avsevärt efter införandet av PBM. Blodvärdet inför start av cellgiftsbehandling (cirka tre veckor efter operationen) sjönk något efter införandet av riktlinjerna. Antalet komplikationer ökade dock inte, och vårdtiden förkortades med ett dygn.

Studie III undersökte hur lågt blodvärde och järnbrist före operationen påverkade återhämtningen efter kirurgi. Studien visade att när järnbristen ökade hos patienterna, ökade risken för att de inte skulle kunna genomgå radikal kirurgi. Järnbrist före kirurgi kan därför markera en mer spridd sjukdom. Järnbrist, med eller utan anemi, var associerat med en större risk för svåra komplikationer efter kirurgin. Järninfusioner givna kort före eller efter kirurgin tenderade att upprätthålla blodvärdet inför den efterföljande kemoterapin.

Studie IV analyserade hur väl patienter 70 år och äldre tolererar kirurgi jämfört med yngre patienter. Resultaten visade att med stigande ålder ökar risken för att all tumör inte kan opereras bort, och att patienterna inte kan ges all planerad kemoterapi. Patienter som var ≥ 80 år hade kortare operationstid. Det fanns ingen skillnad i antalet svåra komplikationer mellan de olika åldersgrupperna som definierades i studien, (under 70 år, 70–79 år samt ≥ 80 år). Överlevnaden efter start av behandling med kirurgi och kemoterapi minskade med stigande ålder.

Slutsatser

Äldre patienter och de som först sökte vård i primärvården fick ofta vänta längre tid innan de fick sin diagnos. När patienterna genomgick operation visade det sig att de nya rutinerna för PBM som minskade behovet av blodtransfusioner tolererades väl. Järnbrist före operationen kan vara ett tecken på att tumörbördan är större och att risken för komplikationer efter operationen därmed ökar. Slutligen, med stigande ålder blev det svårare att genomföra radikal kirurgi, det vill säga att få bort all tumör, och överlevnaden 36 månader efter operationen minskade med åldern.

Abstract

Background

Epithelial ovarian cancer (EOC) is the eighth most common cancer among women globally and represents the most lethal gynecological malignancy. In Sweden, approximately 700 women are diagnosed with ovarian cancer annually. Most patients receive a diagnosis at an advanced stage, which is associated with a poor prognosis; the five-year survival rate in Sweden is around 50%. Symptoms are often vague and non-specific, contributing to delays in diagnosis. Anemia and iron deficiency are frequently observed before surgery. Complete cytoreduction is recognized as one of the most critical prognostic factors for survival. However, the surgery is often extensive, leading to an increased risk of perioperative blood loss and postoperative complications.

Aims of the studies

Study I: To identify factors affecting the diagnostic timeline from the first physician consultation for predefined symptoms to reasonable suspicion of ovarian cancer.

Study II: To evaluate how the gradual implementation of Patient Blood Management (PBM) clinical routines affects patients' recovery.

Study III: To assess if preoperative anemia and iron deficiency impact short-term recovery after debulking surgery and the surgical outcome.

Study IV: To evaluate surgical tolerance, postoperative outcomes, and overall survival in patients aged ≥ 70 years compared to younger patients.

Materials and methods

All studies were retrospective cohort studies conducted on patients with Advanced Ovarian Cancer (AOC) who were referred to or underwent surgery at Skåne University Hospital in Lund.

Study I: Included 249 patients diagnosed with AOC between January 2017 and December 2019. The study specifically examined the time interval between the first consultation for symptoms and the reasonable suspicion of cancer.

Study II: Included 354 patients with AOC who underwent surgery between January 2016 and December 2021. The gradual implementation of PBM clinical routines was assessed by dividing the cohort into three consecutive periods.

Study III: Included all patients (n=262) who underwent surgery for AOC between January 2020 and December 2023. The cohort was stratified into four groups based on preoperative anemia and iron deficiency.

Study IV: Included 486 patients with AOC referred between January 2018 and December 2023. Patients were stratified into three age groups, <70 years, 70-79

years and ≥80 years. Restricted Mean Survival Time (RMST) was calculated for 12, 24, and 36 months.

Results

Study I: The median time from first consultation to reasonable suspicion of cancer was 24 days. Older age was associated with an increase in delay of the geometric mean by 54.7%. Consultation in specialized care resulted in a 70% decrease in time delay compared to primary care. Emergency consultations had a 52.2% decreased delay when compared to planned consultations.

Study II: Among the 354 patients, the proportion of patients receiving one or more units of red blood cell (RBC) transfusion decreased from 83% to 52% during the study period (p <0.001). The mean difference in hemoglobin before the start of chemotherapy was -1.32 g/L (95% CI -3.93 to -0.22) between the first and last group. The median time of length of hospital stay decreased from 8.5 days to 7.5 days (p 0.002). There was no difference in severe complications across the three groups (adjusted odds ratio 0.55 (95% CI 0.26-1.17)).

Study III: Among patients with preoperative iron deficiency anemia, 24% underwent suboptimal surgery (with ≥ 1 cm of residual disease), compared to 6% of patient with no iron deficiency and 8% of patients with no anemia, (p 0.005). Iron deficiency, with or without anemia, was associated with a higher rate of severe complications, compared to patients without iron deficiency (adjusted odds ratio 2.47 (95% CI 1.11-5.50)).

Study IV: Of the 486 patients, 38.4 % were aged 70-79 years and 13.4% were aged ≥ 80 years. The rate of achieving complete cytoreductive surgery decreased with age (72.6% in patients <70 years, 61.4% in patients who were 70-79 years, and in 43.5% of patients aged ≥ 80 years). There was no difference in severe complications across the age groups. RMST at 36 months decreased with age.

Conclusions

Patients who were older patients and those who initially presented with symptoms in primary care had more often experienced a longer time interval to diagnosis. For patients undergoing surgery, PBM clinical routines and the reduction of RBC transfusions were well tolerated. Preoperative iron deficiency might indicate a higher tumor burden and an increased risk for postoperative complications. Furthermore, the likelihood of radical surgery decreased with increasing age, and the survival rate at 36-months after surgery also decreased with age, but selected older patients may still benefit from surgery.

Abbreviations

AOC	Advanced ovarian cancer
BSC	Best supportive care
CD	Clavien Dindo
CI	Confidence interval
CPP	Cancer patient pathway
CT	Computed tomography
ECOG	Easter Cooperative Oncology Group
EOC	Epithelial ovarian cancer
ERAS	Enhanced Recovery After Surgery
FIGO	International Federation of Gynecology and Obstetrics
Hb	Hemoglobin
HRD	Homologous recombination deficiency
IDS	Interval debulking surgery
IQR	Interquartile range
MDT	Multidisciplinary team
NACT	Neoadjuvant chemotherapy
OS	Overall survival
OR	Odds ratio
PARP	Poly (ADP) ribose polymerase
PC	Palliative chemotherapy
PDS	Primary debulking surgery
PBM	Patient blood management
PFS	Progression free survival
RBC	Red blood cell
RMST	Restricted Mean Survival Time
STIC	Serous tubal intraepithelial carcinoma
TSAT	Transferrin saturation
TXA	Tranexamic acid

Introduction

Advanced Ovarian Cancer

Epidemiology

Ovarian cancer is the eighth most common cancer in women worldwide and is the most lethal gynecological malignancy. Globally, more than 324 000 new cases were diagnosed, and over 206 000 deaths occurred in 2022 (1). The age-standardized incidence rates show geographical variation, with the highest rates found in Eastern Europe and Northern Europe and lowest incidence is in Africa (2). While the incidence is declining in Northern Europe and North America, it is increasing in parts of Eastern Europe and Asia (3). By 2050, the global incidence is predicted to increase by 55%, with the largest growth expected in low- and middle-income countries (4). In Sweden, approximately 700 new cases of ovarian cancer are diagnosed annually (5). Ovarian cancer can affect women of all ages, yet it is most common in postmenopausal women, with a median age of 65 years at diagnosis (6).

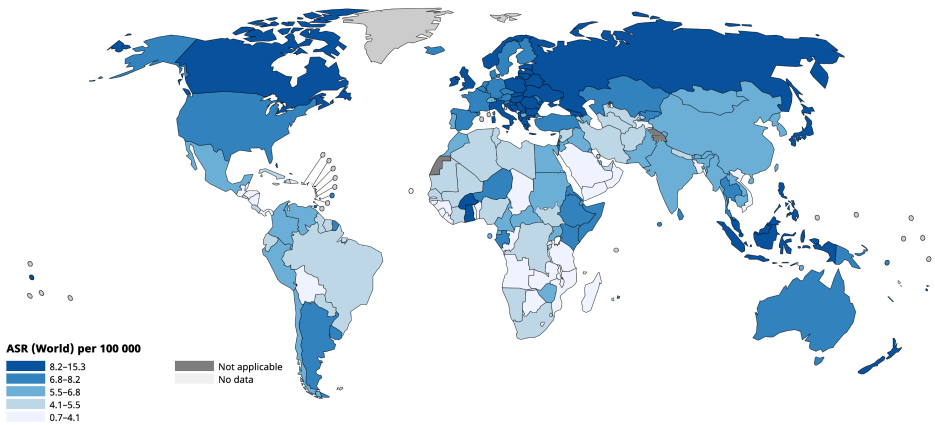


Figure 1. Worldwiede estimated age-standarized incidens rates for ovarian cancer of all ages in 2022. Source GLOBOCAN 2022. Graph production: IARC (https://gco.iarc.who.int/today) World Health Organization.

Prognosis of Ovarian Cancer

For accurate prognostication, it is essential to divide the tumor into early and late stages using the FIGO (International Federation of Gynecology and Obstetrics). Stage I describes the tumor confined to the adnexa, and Stage II involves disease present within the pelvis (7). These two early stages are associated with a five-year overall survival (OS) of 70-90%. Unfortunately, most patients (80%) are diagnosed at an advanced stage (FIGO stage III and IV), where the tumor has spread to lymph nodes and the abdominal cavity (stage III) or when distant metastases are present (stage IV). In these late stages, the five-year OS drops significantly to 20-40% (7-9).

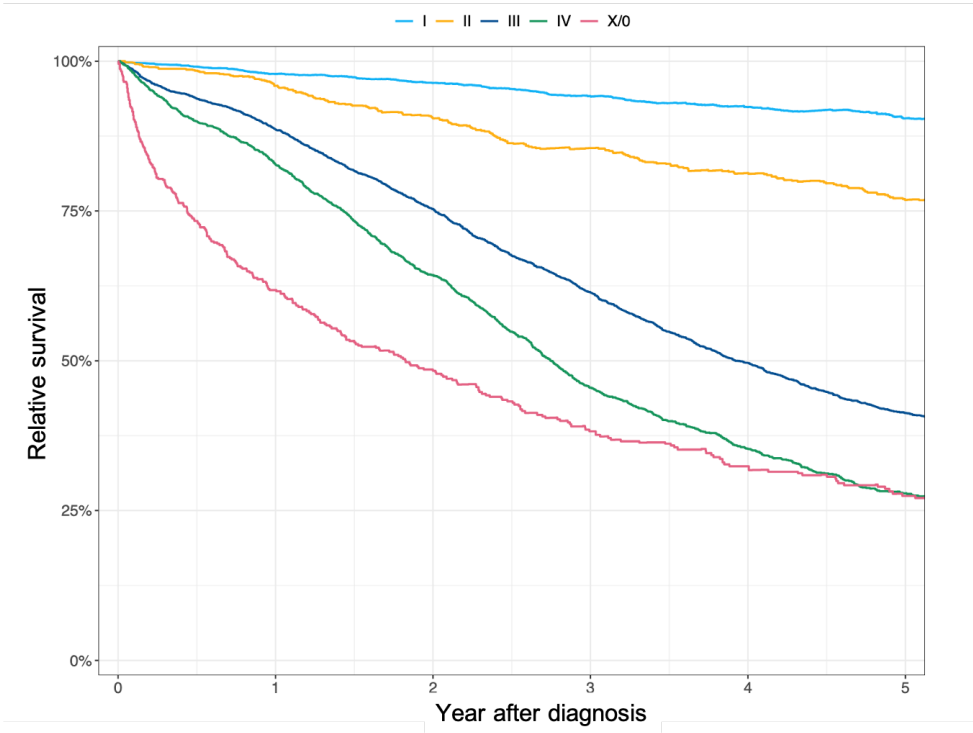


Figure 2. Relative survival rates in ovarian, fallopian tube and primary peritoneal cancer by FIGO stage, based on diagnoses 2012-2024. Source: Swedish Quality Registry of Gynecological Cancer (RCC). Blue: Stage I, yellow: Stage II, dark blue: Stage III, green: Stage IV, red: Stage X/0.

Risk Factors and Protective Factors

Hereditary factors account for roughly 22-25% of epithelial ovarian cancer (EOC) cases (10). The most common genetic risk factor is a germline mutation in the *BRCA1* and *BRCA2* tumor suppressor genes, associated with hereditary breast and ovarian cancer syndrome, which accounts for around 10-15% of EOC (11,12). Carriers of *BRCA1* face a 30-60% increased lifetime risk of EOC, while the risk for *BRCA2* carriers is 10-25% (13). Consequently, prophylactic salpingo-oophorectomy is recommended for risk reduction in women with *BRCA1/2* mutations (14). Other genetic factors linked to hereditary ovarian cancer include Lynch syndrome (mismatch repair genes), Li-Fraumeni syndrome (*TP53*) and Peutz-Jeghers syndrome (*STK11*) (12).

Specific conditions also pose a risk. Endometriosis is associated with an increased risk of clear cell and endometrioid ovarian cancer (15). Menopausal hormone therapy (MHT) in postmenopausal women has been described as a risk factor, as oestrogen has a carcinogenetic effect on the ovary, though progestogen may offer some mitigating effect (16,17). Factors that increase the lifetime number of menstrual cycles, and ovulations, such as early menarche, late natural menopause, and infertility, are associated with an increased risk of ovarian cancer (3). A history of pelvic inflammatory disease has also been associated with increased risk (18). Furthermore, lifestyle factors such as obesity and smoking have been shown to increase the risk of some histological types of ovarian cancer (3). Conversely, factors that reduce ovulation, such as oral contraceptives, pregnancy, and breastfeeding, have been shown to reduce the risk of ovarian cancer (10).

Tumor Histopathology

Ovarian cancer, encompassing fallopian tube and primary peritoneal cancer, is a heterogeneous disease with varied tumor characteristics. EOC constitutes 90% of all ovarian cancer, while non-epithelial ovarian cancer - consisting of germ cell and sex cord stromal tumors - represents around 10% (7). As the main focus of this thesis, EOC is divided into five main histological subtypes; high grade serous carcinoma, endometrioid carcinoma, clear cell carcinoma, mucinous carcinoma and low-grade serous carcinoma (19).

A dualistic model has been proposed classifying EOC into two groups, Type I and Type II tumors, which progress along two disticnt tumorigenic pathways (20-22).

Type I tumors include low-grade serous carcinoma, endometrioid carcinoma, clear cell carcinoma, mucinous carcinoma and Brenner tumors. These carcinomas develop stepwise from benign precursor lesions, such as endometriosis and cystadenomas, to borderline tumors and subsequently to invasive carcinomas. Endometrioid carcinomas and clear cell carcinomas can be developed from endometriosis. Type I tumors are genetically stable and grow slowly. Mutations can

be seen in, *BRAF, KRAS, PTEN, ERBB2, PIK3CA, CTNNB1, ARID1A* and in the DNA mismatch repair (MMR) genes. These carcinomas are often diagnosed at an early stage and carry a good prognosis. However, when diagnosed at an advanced stage, the prognosis is poor (22).

Type II tumors include high-grade serous carcinoma, carcinosarcoma and undifferentiated carcinoma. Most Type II tumors develop from precursor lesions in the fallopian tubes, specifically serous tubal intraepithelial carcinoma (STIC), and then disseminate to the ovaries and peritoneum. These tumors are highly aggressive, spread rapidly, and are typically diagnosed at and advanced stage. They have a poor prognosis and account for 90% of deaths from ovarian cancer. Type II tumors are characterized by high chromosomal instability with *TP53* mutations. Homologous recombination deficiency (HRD), including *BRCA* mutations, is common in these tumors (20, 22). *TP53* mutations can be found in fallopian tube epithelial cells, referred to as the p53 signature, and are considered to precede STIC. It is important to note that *TP53* mutations alone are insufficient to cause cancer and can also be found in benign fallopian tubes (23).

Table 1. Feautures of the five major subtypes of epithelial ovarian carcinoma (Kurman et al 2016, Kossa et al 2018).

	High-grade serous carcinoma	**Low-grade serous carcinoma**	**Endometrioid carcinoma**	**Clear-cell carcinoma**	**Mucinous carcinoma**
Frequency	70%	<5%	10%	5-10%	2-3%
Immunophenotype	CK7+, CK20, PAX8+, WT1+	CK7+, WT1+, ER+	CK7+, PAX8+, CK20-, WT1-	Napsin A+, WT1-, p53-, ER-	CK7+, CK20-, ER-, PR-, WT1-
Precursor lesion	STIC	Low-grade malignant potential lesions	Endometriosis	Endometriosis	Borderline mucinous lesions
Molecular abnormalities	*TP53, BRCA1/2*	*BRAF, KRAS*	*PTEN, ARID1A*	*ARID1A, PIK3CA*	*KRAS, HER2*
Prognosis	Poor	Intermediate	Favourable	Intermediate	Good

Ovarian Cancer Staging

In the majority of cases ovarian cancer is diagnosed at an advanced stage after spreading to the pelvis or abdomen. Ovarian, fallopian tube and primary peritoneal cancer are surgically and pathologically staged according to the FIGO classification system (7).

Table 2. FIGO staging classicifation system of the ovary, fallopian tube and peritoneum (Prat et al 2014).

Stage I: Tumor confined to ovaries or fallopian tube(s)
IA: Tumor limited to one ovary (capsule intact) or fallopian tube; no tumor on ovarian or fallopian tube surface; no malignant cells in the ascites or peritoneal washings
IB: Tumor limited to both ovaries (capsule intact) or fallopian tubes; no tumor on ovarian or fallopian tube surface; no malignant cells in the ascites or peritoneal washings
IC: Tumor limited to one or both ovaries or fallopian tubes, with any of the following: IC1: Surgical spill IC2: Capsule ruptured before surgery or tumor on ovarian or fallopian tube surface IC3: Malignant cells in the ascites or peritoneal washings
Stage II: Tumor involves one or both ovaries or fallopian tubes with pelvic extension (below pelvic brim) or peritoneal cancer
IIA: Extension and/or implants on uterus and/or fallopian tubes and/or ovaries
IIB: Extension to other pelvic intraperitoneal tissues
Stage III: Tumor involves one or both ovaries or fallopian tubes, or peritoneal cancer, with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastases to the retroperitoneal lymph nodes
IIIA1: Positive retroperitoneal lymph nodes only (cytologically or histologically proven) IIIA1(i) Metastasis up to 10 mm in greatest dimension IIIA1(ii) Metastasis more than 10 mm in greatest dimension
IIIA2: Microscopic extrapelvic (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
IIIC: Macroscopic peritoneal metastasis beyond the pelvis more than 2 cm in greatest dimension, with or without metastases to the retroperitoneal lymph nodes (includes extension of tumor to capsule of liver and spleen without parenchymal involvement of either organ)
Stage IV: Distant metastasis excluding peritoneal metastases
Stage IVA: Pleural effusion with positive cytology
Stage IVB: Parenchymal metastases and metastases to extra abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)

Symptoms and Diagnosis

Symptoms

Given that the majority of patients with EOC are diagnosed at an advanced stage (FIGO stage III and IV), their prognosis is poor (9). More than 90% of patients experience symptoms prior to the ovarian cancer diagnosis, sometimes several months before it is confirmed (24, 25). Symptoms are frequently diffuse and non-specific; the most common include abdominal or pelvic pain, bloating, increased abdominal size, urinary tract symptoms, loss of appetite, and fatigue. Due to their diffuse nature, these symptoms are often wrongly attributed to other causes or simply the normal ageing process. Symptoms that are of recent onset, more frequent, or more severe are, however, more likely to be caused by ovarian cancer (24). A study by Chan et al. demonstrated that more than 70% of patients with early-stage EOC presented with one or more symptom. The most common symptom observed is abdominal or pelvic pain (26).

The time to diagnosis is significantly affected by how the physician interprets these symptoms - whether as alarming or vague. Among women with gynecological cancer, diagnostic delays can occur because cancer is not suspected or a benign disease is suspected instead (27). A study by Baun et al. showed that only one third of ovarian cancer patients presenting with symptoms to a general practitioner were urgently referred to cancer patient pathway (CPP). Patients with comorbidities or those presenting with non-specific vague symptoms face a longer time interval to diagnosis (28).

The FIGO stage at diagnosis remains one of the most important prognostic factors for the patient (9). Efforts to detect ovarian cancer at earlier stages have included screening programs using vaginal ultrasonography combined with biomarkers such as CA125 in asymptomatic patients. However, these efforts have not impacted survival. Two large randomized trials, the Prostate Lung Colorectal Ovarian (PLCO) and the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS), which screened asymptomatic postmenopausal women with vaginal ultrasound and CA125, showed no reduction in mortality rate (29, 30). Therefore, screening for ovarian cancer in the general population is not recommended using current screening modalities (30-32).

Cancer Patient Pathway

In 2015, the first official CPPs were introduced into Swedish cancer care. The CPP for ovarian cancer was implemented in Sweden in 2016, covering patients with primary ovarian cancer, fallopian tube and primary peritoneal cancer. The system mandates that referral and further investigation should be well organized and

conducted without unnecessary waiting time. When a patient presents with predefined alarm symptoms and the physician suspects ovarian cancer, the patient is referred to a gynecologist for a filter function within 10 days. Both general practitioners and other specialists can refer patients to this filter function.

The predefined alarm symptoms include increased abdominal size, abdominal or pelvic pain, frequent need to urinate, venous thromboembolism, loss of appetite, change in bowel habits, and newly diagnosed irritable bowel syndrome in women aged > 50 years. The filter function involves a gynecological examination, CA125 measurement, vaginal ultrasonography, and calculation of the Risk of Malignancy Index (RMI) (33, 34). If a reasonable suspicion of ovarian cancer is confirmed, the patient undergoes further investigation with computed tomography (CT) of the thorax, abdomen and pelvis, and sometimes a guided tumor biopsy. Subsequently, the patient is referred to a tertiary cancer center for a multidisciplinary team (MDT) meeting. The mandated lead time from well-founded suspicion of ovarian cancer to the start of treatment is 24 days for Primary Debulking Surgery (PDS) and 22 days for chemotherapy (34).

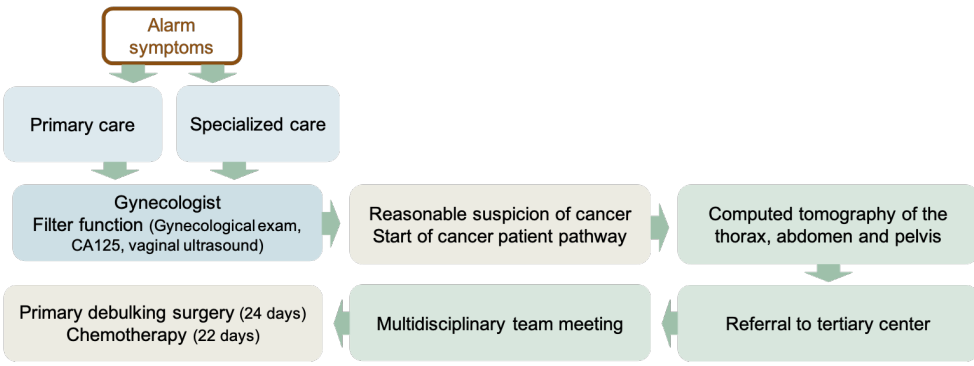


Figure 3. Overview of the cancer patient pathway for ovarian cancer. Adapted from Regionala cancercentrum.

Imaging Modalities

Ultrasound

Transvaginal ultrasound examination is the imaging method of choice for investigating patients with adnexal tumors and those with symptoms suggestive of an adnexal mass (35). To increase diagnostic accuracy, the International Ovarian Tumor Analysis (IOTA) group, has recommended using standard terminology and definitions to describe adnexal tumors (36). Ultrasound may also be used for pre-operative assessment of tumor extent and resectability in the abdomen (37).

Computed tomography and magnetic resonance imaging

CT is the most frequently used imaging modality for pre-operative assessment of the disease extent, including predicting tumor load, tumor localization, and the likelihood of complete resection (38, 39). Although highly available, CT has disadvantages, such as limitations in detecting small-volume carcinomatosis and in characterizing primary tumors (38). Magnetic resonance imaging (MRI), however, can be useful for differentiating between benign, malignant, and borderline tumors, and for detecting small peritoneal metastases (40).

Histopathological Diagnosis

Tru-cut biopsy

Tru-cut biopsy can be used to obtain a tissue sample to determine the histopathological type of the tumor. This is necessary for patients where primary surgery is not possible or when the tumor histology is unclear. Ultrasound-guided tru-cut biopsy is recommended due to its sensitivity and low risk of complications. It can be performed using different approaches: transvaginal, percutaneous, transrectal, and transcervical. CT or MR guidance can be used if it provides easier access to the tumor (41).

Frozen section

A frozen section is performed when an intraoperative histopathological diagnosis is required to determine the extent of the surgery (42). This technique is particularly useful in early-stage ovarian cancer without a definitive preoperative diagnosis, as tru-cut biopsy is not recommended in these cases due to the risk of dissemination (41, 43). While frozen section has a high accuracy, it can sometimes underestimate malignancy (44).

Multidisciplinary Team (MDT) Meeting

The Swedish national guidelines recommend that all patients with advanced ovarian cancer (AOC) to be referred to an MDT meeting to determine the preferred treatment strategy (45). The MDT meeting is held weekly and involves a collaboration of different specialties, including gynecological oncology surgeons, gynecological oncologists, radiologists, and pathologists with special expertise in gynecological oncology, along with nurses and coordinators.

Prehabilitation

Prehabilitation is defined as the process, starting from diagnosis up to surgery, that aims to improve patients' physiological reserve and functional capacity. This is achieved through nutritional optimization, physical exercise, and psychological support to help patients withstand surgical stress, improve post-operative outcome, and facilitate recovery (46). Because the time between diagnosis and surgery is relatively short, a multimodal approach is often employed (47). This approach typically includes assessment of nutritional status (using albumin level), psychological and physiological status, screening and correction of preoperative anemia, and smoking cessation (47, 48). The process may involve contact with a dietitian, physiotherapist and contact nurse. In several surgical fields, prehabilitation has been shown to decrease the rate of postoperative complications (49-51). Patients with AOC are often malnourished due to the high tumor burden (52).

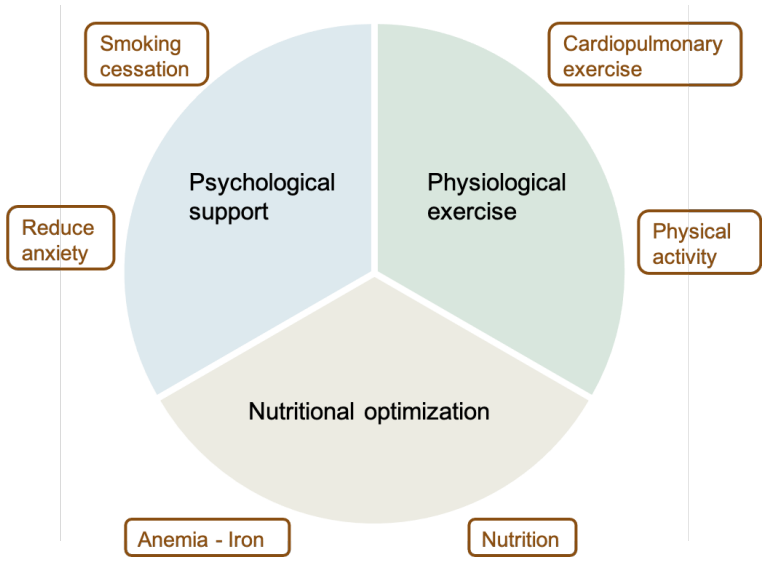


Figure 4. Multimodal prehabilitation before surgery.

Despite the potential benefits, there are few studies on prehabilitation before ovarian cancer surgery, and those that exist have relatively small sample sizes. Multimodal prehabilitation has been shown to increase patients' physical function and decrease emotional stress before ovarian cancer surgery (53). Moreover, prehabilitation is associated with fewer Red Blood Cell (RBC) transfusions during surgery, a shorter hospital stay, shorter time to the start of adjuvant chemotherapy, and better tolerance for adjuvant chemotherapy (54-56). This thesis primarily focuses on preoperative anemia and iron deficiency.

The Enhanced Recovery After Surgery (ERAS) programs comprise preoperative, perioperative, and postoperative strategies designed to improve postoperative recovery (57, 58). In the context of AOC, the implementation of ERAS guidelines has been associated with a decreased length of hospital stay and fewer readmissions (59).

Patient Blood Management (PBM)

PBM is a person-centred approach introduced in many clinical settings that aims to improve patient outcomes by managing and preserving patients' own blood. PBM strategies include the detection and treatment of preoperative anemia, minimizing blood loss, and optimizing the patient's physiological reserve. Furthermore, PBM advocates for a more restrictive policy regarding RBC transfusions (60). PBM has been demonstrated to be associated with improved clinical outcome, including a reduced rate of complications and RBC transfusions (61).

Anemia

According to the World Health Organization, anemia is defined as a hemoglobin (Hb) level <120 g/L for non-pregnant women and Hb<130 g/L for men (62). Iron deficiency anemia is the most common type of preoperative anemia observed in patients undergoing gynecological surgery (63).

Anemia is common in patients with AOC, with preoperative anemia reported in 30-40% of patients (64, 65). Patients receiving Neoadjuvant Chemotherapy (NACT) have an elevated risk of preoperative anemia and a corresponding increased risk of perioperative RBC transfusions (66). Preoperative anemia is linked to an increased risk of RBC transfusions, postoperative complications, and poor recovery (65, 67). Similarly, patients who develop postoperative anemia have been shown to have a higher risk of postoperative morbidity and mortality (68). Anemia in cancer patients is multifactorial, potentially caused by nutritional deficiencies, chronic inflammation, and chemotherapy-induced myelosuppression (69).

Iron Deficiency

Iron is essential for Hb synthesis and myoglobin synthesis in muscle tissue. Total body iron is around 4 g; half of this binds to ferritin in the spleen, liver, and bone marrow, while the other half is utilized by red blood cells and muscle tissues. Iron circulates bound to transferrin in the plasma and is stored in cells as hemosiderin or ferritin (70).

Hepcidin, primarily produced in the liver, regulates iron homeostasis. Hepcidin expression decreases iron levels by reducing dietary absorption and inhibiting iron

release from macrophages. As an acute-phase reactant, hepcidin is upregulated by infection and inflammation (71).

Transferrin saturation (TSAT) measures the amount of iron bound to transferrin in the blood (71). Total iron-binding capacity (TIBC) measures the capacity at which transferrin binds with iron in the blood. TSAT is calculated using the formula: TSAT (%)=(Serum iron level x100)/TIBC (70). Iron deficiency can be defined as TSAT < 0.20 or serum ferritin < 30 μg/L. Ferritin, being an acute phase reactant, can be elevated in cancer patients due to inflammation (71, 72).

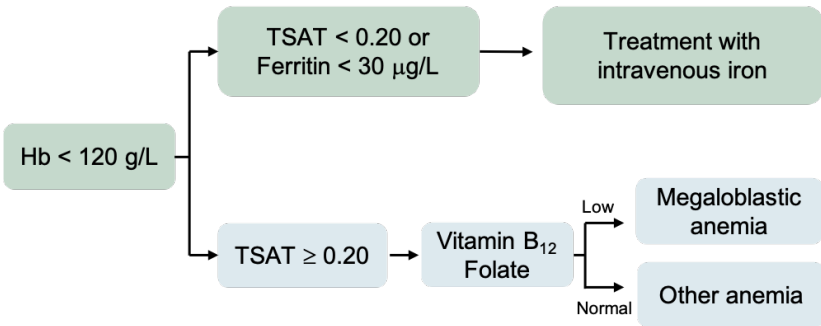


Figure 5. Algorithm for anemia and iron deficiency.

Absolute iron deficiency is characterized by depleted iron stores insufficient to maintain erythropoiesis, defined as TSAT < 0.20 or ferritin < 30 μg/L, Hb > 130 g/L and low hepcidin. Iron sequestration involves normal iron but inadequate mobilization of iron due to increased demands, defined as ferritin > 100 μg/L and TSAT < 0.20, CRP may be increased. Inflammation and iron deficiency is caused by reduced availability or supply of iron for erythropoiesis, defined as ferritin 30-100 μg/L, TSAT < 0.20, CRP > 5mg/L, and increased hepcidin (71).

Table 3. Characteristics of different types of iron deficiency. Adapted from Shah et al 2023.

Iron status	Definition	Laboratory findings
Absolute iron deficiency	Depleted iron stores	Hb >130 g/L, ferritin < 30 μg/L or TSAT < 0.20
Iron deficiency anemia	Insufficient iron availability	Hb <130g/L, ferritin < 30 μg/L or TSAT < 0.20
Iron sequestration (Functional iron deficiency)	Insufficient mobilisation of iron stores, increased demand. Normal iron stores.	Ferritin >100 μg/L and TSAT < 0.20
Iron deficiency and inflammation	Reduced supply or availability of iron	Ferritin 30-100 μg/L, TSAT < 0.20

Treatment of Anemia

Screening

Screening for anemia and its underlying cause, such as iron deficiency, is recommended for all patients undergoing elective major surgery (73). According to a consensus statement by Munoz et al., treating anemia before surgery is recommended if Hb<130 g/L and the expected blood loss exceeds 500 ml (74).

Tranexamic Acid

Administration of tranexamic acid (TXA) reduces perioperative blood loss and RBC transfusions during major elective abdominal and pelvic cancer surgery (75). In cytoreductive surgery for AOC, TXA has demonstrated the same effect, resulting in reduced perioperative blood loss and transfusion rates (76). The European Society of Gynecological Oncology recommends perioperative TXA use to reduce blood loss (77). No adverse effects have been reported following a preoperative single dose of TXA (76).

Red Blood Cell Transfusion

Blood transfusions can exert an immunosuppressive effect, and perioperative RBC transfusions are associated with an increased risk of morbidity and mortality (78, 79). However, one study by Hunsicker et al. did not show an increased risk of cancer recurrence among AOC patients receiving perioperative RBC transfusions (80). Conversely, a recent study demonstrated that RBC transfusions are associated with decreased OS survival in patients with ovarian cancer (81).

Intravenous Iron

Preoperative administration of intravenous iron to correct iron deficiency anemia has been shown to reduce the rate of RBC transfusions and enhance iron stores in patients undergoing major abdominal surgery (82). For optimal efficacy, intravenous iron administration is recommended four weeks before surgery, although it can still be given in close proximity to the surgical date (73). Specifically, administration 10 days before surgery has also been shown to positively affect the Hb level (83). ERAS guidelines recommend intravenous iron for correcting preoperative anemia (57). This is also recommended by The European Society of Gynecological Oncology (77). Intravenous iron treatment can also be considered postoperatively to correct iron deficiency anemia (84). Generally, intravenous iron is well tolerated with a low rate of adverse effects (85).

Epithelial Ovarian Cancer Treatment

Surgical Treatment

The preferred treatment for EOC is PDS followed by six cycles of chemotherapy. If PDS is not feasable, the recommendation shifts to Neoadjuvant Chemotherapy (NACT) for three cycles, followed by Interval Debulking Surgery (IDS), and then a further three cycles of chemotherapy, potentially including additional angiogenesis inhibitors. Complete resection of the tumor, leaving no macroscopically visible residual disease is the single most important prognostic factor (86, 87). Higher residual disease burden is associated with decreased Progression-Free Survival (PFS) and OS compared with less residual disease (88). Despite treatment, around 70% of patients with AOC relapse within three years (31).

Surgical Treatment in Early-Stage Ovarian Cancer

In early-stage ovarian cancer, the diagnosis and histological subtype are often unknown preoperatively. For young patients, fertility-sparing surgery is frequently undertaken by leaving the non-tumorous adnexa in place. If the histology is unknown, the tumor should be removed by unilateral minimal invasive salpingo-oophorectomy. Once final histological results are available, a second surgery can be planned. Staging procedures may then include hysterectomy, bilateral salpingo-oophorectomy, omentectomy, peritoneal biopsies, cytological analysis, appendectomy (critical in mucinous cancer), and systematic pelvic and para-aortic lymph node dissection (which can be omitted in mucinous carcinoma, low-grade serous carcinoma, and low-grade endometrioid) (39, 89).

Fertility-Sparing Surgery

Fertility-preserving surgery can be offered to patients seeking to maintain their fertility who have low-grade stage IA tumors (low-grade serous, endometrioid, mucinous) and some IC1 stage tumors. The recommended approach is unilateral salpingo-oophorectomy with surgical staging, including peritoneal biopsies and cytological analysis (39, 90).

Surgery for Advanced Ovarian Cancer

For AOC, the standard recommended treatment is PDS, provided the patient is fit for surgery and there is a high likelihood of complete cytoreduction. Since low-grade serous carcinoma shows a diminished response to chemotherapy, PDS is the preferred treatment if optimal surgery (< 1cm residual disease) can be achieved. If complete cytoreduction is unlikely or the patient is unfit for surgery, IDS is recommended (39).

Two randomized trials, CHORUS and EORCT, found that NACT with IDS was non-inferior to PDS in terms of both PFS and OS (86, 91). However, neither study could definitively identify a more favourable treatment because of the heterogenous surgical quality across participating sites. NACT followed by IDS can reduce the risk of complications by decreasing the tumor burden and the complexity of the subsequent surgery (92). Preliminary data from the Trial of radical upfront surgical therapy (TRUST) study in AOC showed that PDS conferred a longer PFS, although there was no statistical advantage for OS compared to IDS. These findings support PDS as the treatment of choice in non-frail patients with advanced EOC and good chance of achieving tumor rest=0 (93). The Lymphadenectomy in ovarian neoplasms (LION) trial demonstrated no survival benefit from systematic lymphadenectomy of non-suspicious lymph nodes in patients with advanced disease (94).

The outcome of cytoreductive surgery is classified as: complete cytoreductive surgery (no macroscopically residual disease), optimal cytoreductive surgery (1-10 mm of residual disease), or suboptimal cytoreductive surgery (> 10 mm of residual disease) (87). Studies indicate that ultra-radical surgery increases the rate of complete cytoreductive surgery, and some of these studies have shown an improved OS for those patients (95, 96) Conversely, a study by Falconer et al. reported that while ultra-radical surgery increased the rate of complete resection of all visible tumor, it did not lead to improved survival (97). Ultra-radical surgery is associated with increased postoperative complications, with no difference found between patients undergoing PDS and IDS (98).

Beyond standard procedures, ultra-radical surgery may involve extensive procedures outside of the pelvis and upper abdominal procedures (99, 100). Extensive surgery is often required to achieve macroscopic radicality and includes procedures such as hysterectomy, salpingo-oophorectomy, omentectomy, pelvic peritonectomy, appendectomy, bowel resection, lymphadenectomy, diaphragm stripping, ureteral resection, splenectomy, liver resection, and cholecystectomy. The Aletti surgical complexity score can be used to assess the complexity of the surgery (101).

Table 4. Aletti surgical complexity score (Aletti et al 2007).

Procedure	Points
Hysterectomy and bilateral salpingo-oophorectomy	1
Omentectomy	1
Pelvic lymphadenectomy	1
Paraaortic lymphadenectomy	1
Pelvic peritonectomy	1
Abdominal peritonectomy	1
Small bowel resection	1
Large bowel resection	2
Diaphragm stripping/resection	2
Splenectomy	2
Liver resection	2
Rectosigmoidectomy, anastomosis	3
Complexity score groups	Points
Low Intermediate High	≤3 4-7 ≥8

Postoperative Complications

The risk of postoperative complications within 30 days of surgery increases with intermediate and high surgical complexity scores and low preoperative albumin levels (102). The most common severe complication is pleural effusion, with 4% of AOC patients undergoing surgery requiring pleural fluid drainage (92, 102). Patients undergoing PDS exhibit a higher complication rate compared to those undergoing IDS (92). Increasing age and cardiovascular comorbidity are associated with a higher risk of severe complications (103). Specifically, age ≥ 80 years is associated with a particularly high risk of severe complications (104). Postoperative complications occurring within 30 days are frequently classified using the Clavien-Dindo classification system (105).

Table 5. Clavien-Dindo classification system (Clavien-Dindo et al 2004).

Grade	Definition
I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Acceptable therapeutic regimens are: drugs as antiemetics, antipyretics, analgesics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside
II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included
III	Requiring surgical, endoscopic or radiological intervention
IIIa	Intervention not under general anesthesia
IIIb	Intervention under general anesthesia
IV	Life-threatening complications (including CNS complications) requiring IC/ICU management
IVa	Single organ dysfunction (including dialysis)
IVb	Multi organ dysfunction
V	Death of a patient

Oncological Treatment

Chemotherapy

The standard treatment involves six cycles of intravenous carboplatin (AUC5) and paclitaxel (175mg/m^2) administered every third week, as per Swedish National Guidelines (106, 107). If NACT is used, three cycles are given before surgery, and three cycles complete the treatment after surgery (45). Adjuvant chemotherapy may be omitted in some cases of earliest-stage ovarian cancer; it is not recommended for low-grade serous, low-grade endometrioid, and mucinous ovarian cancer. For other histological subtypes, adjuvant chemotherapy is recommended, contingent on whether the patient has undergone full staging with pelvic and para-aortic lymphadenectomy. If the patient is unfit for surgery or the tumor burden remains too extensive after NACT, they receive palliative chemotherapy (PC) (39). Patients with a poor performance status who are unable to tolerate chemotherapy are given best supportive care (BSC).

Angiogenesis Inhibitors

The vascular endothelial growth factor (VEGF) promotes angiogenesis, which, in turn, facilitates cancer progression and growth. Bevacizumab is a humanized monoclonal antibody targeting VEGF. Studies have shown that Bevacizumab improves PFS and OS in patients with a high risk of progression and in those with FIGO stage IV (108). In Sweden, Bevacizumab is recommended as an addition to standard chemotherapy for patients with EOC FIGO stage IV and stage IIIC with non-radical surgery (45).

Poly (ADP) Ribose Polymerase (PARP) Inhibitors

PARP inhibitors target PARP enzymes, which play an essential role in repairing DNA single-strand breaks. The *BRCA1* and *BRCA2* genes are critical tumor suppressors involved in DNA double-strand break repair via the homologous recombination repair pathway. Cancer cells exhibiting homologous recombinant deficiency (HRD) rely on PARP enzymes for DNA repair (109). Patients with *BRCA1/2* mutations have been shown to achieve a longer PFS when treated with PARP inhibitors after standard chemotherapy for AOC (110). The PAOLA-1 study demonstrated that administering Olaparib combined with Bevacizumab and standard chemotherapy to AOC patients with HRD-mutated tumors significantly increased PFS (111). Maintenance treatment with PARP inhibitors is recommended for patients with HRD mutations (FIGO stage III and IV) who show a complete or partial response to platinum combination therapy (45).

Older Patients and Ovarian Cancer Treatment

Global life expectancy is projected to increase over the next three decades (112). Consequently, the population in high-income countries like Sweden is aging. Life expectancy in Sweden is 85.3 years for women and 82.3 years for men (113). Over 40% of women are aged over 70 years when they receive their ovarian cancer diagnosis (114). A recent study indicated that older patients (defined as age ≥80 years) are less likely to receive standard treatment and face a worse prognosis compared to younger patients. However, when older patients do receive standard treatment, age is no longer a risk factor for worse OS (115). Older patients more frequently undergo less extensive surgery and are less likely to undergo radical cytoreductive surgery (115-117).

Comorbidities, such as respiratory disease and cognitive impairment, are more prevalent among older patients, and these have been associated with an increased rate of complications and mortality after surgery (115, 118). Yet, comorbidities have not been shown to influence the choice of treatment (119). For older patients, specifically aged 70 years or older, the presence of comorbidities and advanced disease stage with a large tumor burden can minimize the chance of radical or optimal resectability. In such cases, NACT with IDS should be considered (39, 120). Patients aged ≥80 years have a higher risk of postoperative complications compared to younger patients and show a better OS when undergoing IDS versus PDS (104). For patients ≥70 years, vulnerability assessment is recommended, including evaluation of nutrition, Eastern Cooperative Oncology Group (ECOG) performance status, comorbidities, medication, and physiological well-being, though this should not delay the start of treatment. It is recommended that older patients be offered

standard treatment; both debulking surgery and chemotherapy whenever possible (39).

Frailty is defined as increased vulnerability caused by a decline in physiological functions in multiple organ systems and a lack of resilience (121). Common manifestations of frailty include exhaustion, weakness, diminished physical activity, and weight loss (122). In ovarian cancer patients, frailty is associated with an increased risk of postoperative severe complications and a poor survival (123). The risk of frailty increases with age, with 45% of patients aged ≥ 80 years being frail (124). Therefore, careful selection of patients for surgical treatment is essential; an ongoing trial evaluating different instruments for assessment of frailty before surgery among AOC patients (125).

Aims

The overall aims of this thesis were threefold: to evaluate the factors that delay the time to diagnosis, to determine how to optimize patients for surgery, and to assess how older patients tolerate surgery for advanced ovarian cancer.

Study I

To evaluate the diagnostic timeline from the first presentation of symptom to a physician (in primary care or specialized care) to the point of reasonable suspicion of ovarian cancer. The secondary aim was to examine the possible role of age, mode of appointment, mode of consultation, histological subtype, CA125 level and place of residence.

Study II

To investigate if the rate of RBC transfusions is reduced after implementation of PBM clinical routines and if the postoperative complication rate is affected. The secondary aim was to evaluate whether the Hb level before chemotherapy can be maintained.

Study III

To assess if preoperative anemia and iron deficiency affect postoperative recovery, including complications, length of hospital stay, and complete administration of chemotherapy. The secondary aim was to examine if iron deficiency can predict a worse outcome compared to patients with no iron deficiency, and if iron infusions close to surgery impact the short-term recovery.

Study IV

To evaluate the surgical tolerance, postoperative outcomes and OS in patients ≥ 70 years compared to younger patients. The secondary aim was to assess the impact of different modes of treatment in patients ≥ 80 years.

Materials and Methods

Study Population

All four studies in this thesis are retrospective cohort studies. The study population consisted of patients with AOC (FIGO stage III and IV) who were treated or referred to Skåne University Hospital Lund between January 2016 and December 2023. Patients seeking health care at a regional hospital or in primary care who have a suspected ovarian malignancy are referred to a tertiary centre. Skåne University Hospital Lund is the tertiary center for gynecological cancer for Södra sjukvårdsregionen (Southern healthcare region), which includes Skåne, Blekinge, and Kronoberg, covering a population of 1,8 million people (126). Study I and IV include patients with all modes of treatment. Study II and III include only patients undergoing PDS or IDS.

Figure 6. Södra sjukvårdsregionen (Southern healthcare region).

Study I

Patients diagnosed with primary AOC between January 1, 2017 and December 31, 2019, having a International Statistical Classification of Disease and Related Health Problems (ICD-10) code of C57.0 malignant neoplasm of fallopian tube, C56.9 malign neoplasm of unspecified ovary, C49.5 malignant neoplasm of connective and soft tissue of pelvis or C76.2 malignant neoplasm of abdomen were included. Data were collected from electronical medical records (Melior) of Region Skåne.

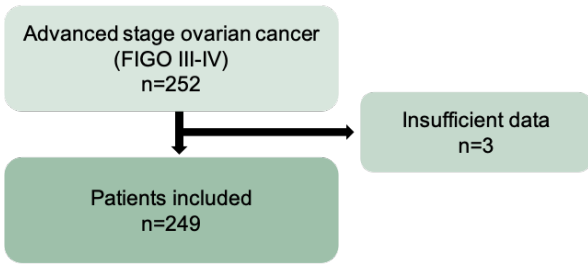


Figure 7. Flow chart of the study population.

Recorded variables included; the site of the first consultation (primary care or specialized care), the time interval between the first consultation with predefined symptoms and reasonable suspicion of ovarian cancer, symptoms at the first consultation, whether the first consultation was an emergency or a planned appointment, age of the patient at diagnosis, date of reasonable suspicion of ovarian cancer, mode of treatment, histological subtypes, CA125 level before diagnosis and place of residence. If the patient was referred the same day from a general practitioner in primary health care to the emergency department, primary health care was recorded as the first consultation. The specialized care group included consultation with a gynecologist in private health care and consultation at the hospital, regardless of the specialty.

The predefined symptoms were modified from the alarm symptoms and findings according to the CPP for ovarian cancer in Sweden 2020. These symptoms included: abdominal/pelvic pain, increased abdominal size/bloating, loss of appetite, urinary urgency, change in bowel habits, respiratory problems/coughing, abnormal/postmenopausal bleeding, venous thromboembolism, or an incidental finding. Included symptoms were new within the last 13 months before first consultation. If the patient presented with more than one symptom, the main symptom that led the patient to seek health care was recorded.

For the statistical analysis, the data were log-transformed as they were skewed and had outliers. A multivariable log-linear regression model was used to evaluate factors that could affect the time interval.

Study II

Patients who underwent omentectomy between January 1, 2016, and December 31, 2021 were identified from the Orbit IT-system and included according to the following criteria: epithelial AOC, including primary peritoneal and fallopian tube cancer, and primary- or interval debulking surgery.

Exclusion criteria were open-close cases, ovarian cancer FIGO stage I and II, and diagnoses other than ovarian cancer. Patients who underwent debulking surgery for ovarian cancer but did not have AOC were also excluded.

The following variables were recorded from electronical medical records: RBC transfusions, operating time, age, estimated blood loss, body mass index, Hb level before surgery and before start of chemotherapy, time from surgery to start of chemotherapy, length of hospital stay, PDS or IDS, FIGO stage, histological subtype, administration of TXA, administration of intravenous iron, complications within 30 days postoperatively, residual tumor, Aletti surgical complexity score, ECOG performance status, and the American Society of Anesthesiologists physical status classification system (127).

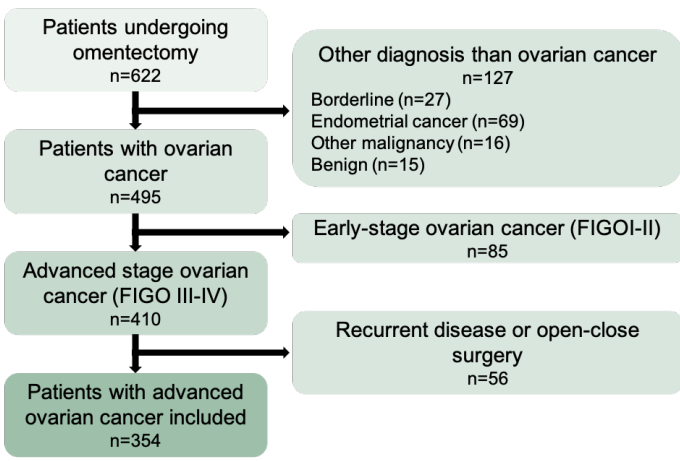


Figure 8. Flow chart of the study population.

Complications were classified according to the CD classification and grouped into no or minor complications (CD 0-2) and severe complications (CD ≥ 3) (105). If a patient had more than one complication, the most severe one was registered. Surgical procedures were classified according to the Aletti surgical complexity score (low, intermediate and high).

PBM clinical routines were gradually implemented at the department. Preoperatively administered intravenous TXA (1000 mg), was introduced in 2016

and became standard before major laparotomies in 2018. Screening for iron deficiency anemia and administration of intravenous iron (1000 mg or 1500 mg of intravenous ferric derisomaltose (Monofer, Pharmacosmos, Denmark)) were introduced at the end of 2019. According to regional guidelines, patients with Hb <130 g/L and iron deficiency, and an expected blood loss of > 500 ml received intravenous iron. Intravenous iron was administered according to the gynecologist's decision, up to 21 days before surgery or while the patients was in the hospital. More restrictive RBC transfusion guidelines (Hb < 70 g/L, or Hb <80 g/L for patients with comorbidities) were implemented gradually during this time period. RBC transfusions occurred either perioperatively or postoperatively while the patient was still in the hospital, and were chosen by the senior consultant responsible for the patient.

For the statistical analysis, the cohort was divided into three consecutive periods: the reference group (2016-2017), 2018-2019, and 2020-2021. Logistic regression was used, both unadjusted and adjusted for age, operating time, Aletti surgical complexity score and ECOG score. To compare Hb level before chemotherapy the model was adjusted for number of days between surgery and chemotherapy and estimated blood loss.

Study III

Included patients with AOC undergoing debulking surgery between January 1, 2020, and December 31, 2023. Exclusion criteria were recurrent disease and open-close surgery. Data were collected from Melior and Orbit. The variables recorded were: Hb before surgery and before the start of chemotherapy, age, preoperative ferritin and TSAT, operating time, RBC transfusions, estimated blood loss, time from surgery to the start of chemotherapy, length of hospital satay, PDS or IDS, FIGO stage, Aletti surgical complexity score, residual disease, histological subtype, complications (CD classification) within 30 days postoperatively, administration of intravenous iron, ECOG, and whether chemotherapy cycles were reduced or complete.

Patients were screened for iron deficiency anemia before surgery. If diagnosed, they were administered intravenous iron (1000 mg or 1500 mg) before surgery, within the first week postoperatively, or both, with a minimum of seven days between administrations. Anemia was defined as Hb <120 g/L and divided into two groups: mild anemia (Hb 100-119 g/L) and moderate to severe anemia (Hb <100). Iron deficiency was defined as TSAT < 0.20. Absolute iron deficiency was defined as ferritin <30 μg/L and functional iron deficiency was defined as ferritin ≥ 30 μg/L and TSAT < 0.20.

The cohort was divided into three group based on the Hb value, and for another analysis, into four groups stratified by both Hb level and TSAT. Descriptive statistic were used to compare the groups. Log linear regression models were performed to compare the rate of severe complications.

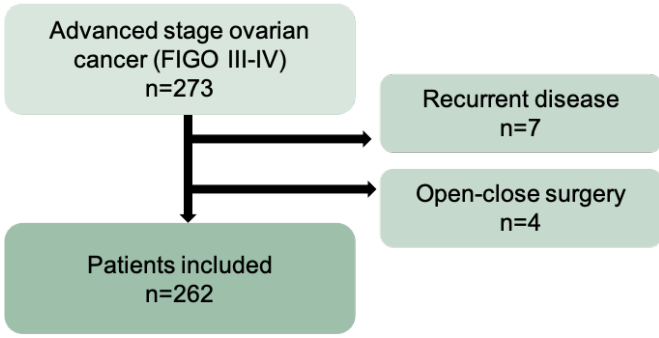


Figure 9. Flow chart of the study population.

Study IV

Patient diagnosed with AOC between January 1, 2018, and December 31, 2023, were included. Treatment recommendations were proposed at a MDT meeting for the majority of patients. The cohort was stratified into four treatment groups: PDS, IDS, PC and BSC. Patients who underwent open-close surgery prior to or after chemotherapy, were categorized in the PC group. Systematic *BRCA* testing, including both somatic and germline mutations, were implemented in 2018. Clinical and patient characteristic retrieved included: age at diagnosis, FIGO stage, histological subtype, ECOG, albumin, CA125 and Hb level before start of treatment, body mass index, social status, *BRCA* mutation, operating time, estimated blood loss, residual tumor, Aletti surgical complexity score, length of hospital stay after surgery, time from surgery to the start of chemotherapy, complications (CD classification) within 30 days, readmission within 30 days after surgery, date of start of treatment, date of death, and whether the patient received all six cycles of chemotherapy or if chemotherapy was reduced. Reduced chemotherapy dose was defined as administering only one of the drugs or dose reductions. Recurrence was defined by cytology/biopsy or by high suspicion on radiology.

The cohort was stratified into three age groups: < 70 years, 70-79 years and ≥ 80 years. OS was calculated from start of treatment to the date of death.

Descriptive statistics were used to compare the three age groups. Kaplan-Meier curves were performed for survival analysis, and survival probabilities were estimated at 12, 24 and 36 months. The log-rank test was performed for statistical

significance. Due to violation of the proportional hazard assumption (crossing of survival curves), Restricted Mean Survival Time (RMST) was calculated at 12, 24, and 36 months. Propensity score matching was performed based on ECOG and age to compare survival between modes of treatment.

Ethical Considerations

All four studies were retrospective non-intervention studies with no impact on the patient's health or treatment. Informed consent was not required. Patient data were anonymous and could not be traced to any individual patient. All data were handled according to the World Medical Association's Declaration of Helsinki 2013. The studies were approved by the Swedish Ethical Review Authority.

Study I

Approved by the Swedish Ethical Review Authority (Dnr 2019-04450).

Study II and III

Approved by the Swedish Ethical Review Authority (Dnr 2021-04223)

Study IV

Approved by the Swedish Ethical Review Authority (Dnr 2025-00586-01)

Results

Study I

A total of 249 patients were included. The median age of women needing a consultation was 72 years. Median age did not differ between patients whose first consultation was in primary care and those in specialized care. Almost two-thirds of patients (66%) had their first consultation with a physician in primary care, and 34% in specialized care. About 50% of all patients had a planned visit.

The median time from first consultation with a physician to reasonable suspicion of cancer was 24 days. The median time interval from first consultation to reasonable suspicion of cancer was 10 days in specialized care versus 41.5 days in primary care, ($p < 0.001$) (Table 6).

Table 6. Days from first consultation to reasonable suspicion of cancer.

	Characteristics	N (%)	Geometric mean	Median (IQR)
Age (years)	< Q1	61 (24.5%)	13.7	15 (4-35)
	Q1-Q3	133 (53.4%)	22.7	29 (9-71)
	>Q3	55 (22.1%)	27.6	37 (10.5-77)
Mode of consultation	Primary care	164 (65.9%)	33.0	41.5 (15.8-85.8)
	Specialized care	85 (34.1%)	8.7	10 (3-23)
Type of consultation	Emergency	116 (46.6%)	12.7	14.5 (4-37)
	Planned	133 (53.4%)	32.4	43 (17-85)

Consultation in specialized care was associated with a 70% decrease in time delay (95% CI -78.8 to -57.4) compared to primary care. Older age (comparing the first to third quartile) was associated with a 54.7% longer time interval (95% CI 16.6-105.3). Emergency consultations were associated with a 52.2% decrease in delay (95% CI -65.9 to -32.9). Almost half of the patients (45%) presented with abdominal or pelvic pain. No significant difference in the time interval was found when comparing the different predefined symptoms.

Study II

There was no difference in patient characteristic between the three time periods. The Hb level before surgery fluctuated between 120 and 123 g/L, and the median age was 68-69 years.

After PBM clinical routines implementation, the percentage of transfused patients decreased from 83% to 52%, ($p < 0.001$). There was a significant decrease in the number of units of RBC transfusions between the reference group and the 2020-2021 group, ($p < 0.001$) (Figure 10).

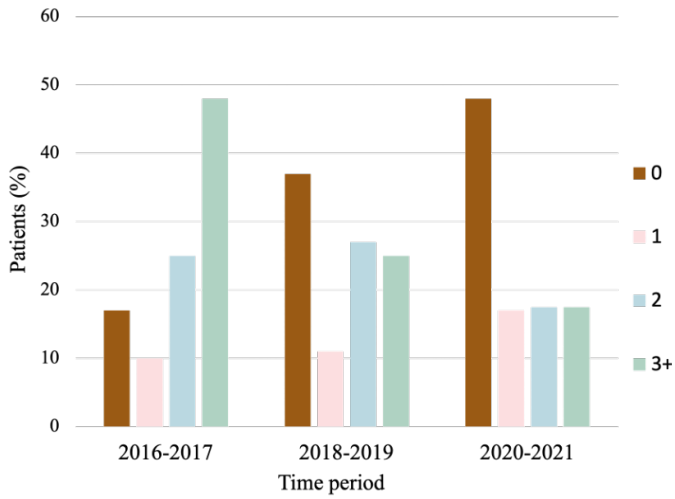


Figure 10. Percentage of patients transfused with units of red blood cells.

Operating time was reduced from a median of 348 minutes to 214 minutes when comparing the reference group and the 2020-2021 group. The estimated blood loss was also significantly reduced. The median length of hospital stay decreased from 8.5 days to 7 days between the reference group and the 2018-2019 group, ($p<0.001$). There was no difference in the Aletti surgical complexity score between the three groups (p 0.167).

The mean Hb level before chemotherapy decreased from 118.9 g/L in the reference group to 115.2 g/L in the 2020-2021 group (p 0.005). This significant decrease remained in an adjusted linear regression model. The unadjusted odds for CD ≥ 3 decreased over the study period (OR 0.55 for 2020-2021 vs reference (95% CI 0.23-0.85)), but this finding was no longer significant in the adjusted model.

Study III

Of the 262 patients, 42% had preoperative anemia, with 8% having moderate to severe anemia (Hb level < 100 g/L). No association was found between severe complications, (CD ≥ 3) and anemia. However, the length of hospital stay was longer among patients with moderate to severe anemia (median 11 days) compared to patients with no anemia or mild anemia, (median 7 days) (p 0.032).

Most patients with iron deficiency had a functional type (97%). Patients with iron deficiency (TSAT <0.20), with or without anemia, were younger (median age 63-65 years) compared to patients with no iron deficiency (median age 69-70 years). Patients with iron deficiency anemia, Hb <120 g/L and TSAT <0.20, were less likely to have radical or optimal surgery; 24% had residual disease (≥ 1 cm after surgery) compared to 6-8% in patient with no anemia or no iron deficiency, (p 0.005) (Table7).

Table 7. Clinical characteristics stratified by anemia and iron deficiency.

	Hb < 120 TSAT < 0.20	**Hb <120 TSAT ≥ 0.20**	**Hb ≥ 120 TSAT <0.20**	**Hb ≥ 120 TSAT ≥ 020**	**p-value**
Age (median) range	63 (44-67)	70 (32-80)	65 (35-85)	69 (18-84)	0.026
Mode of surgery					<0.001
PDS	41 (71%)	6 (13%)	91 (96%)	43 (88%)	
IDS	17 (29%)	41 (87%)	4 (4%)	6 (12%)	
Aletti score					0.026
Low (≤3)	24 (41%)	19 (40%)	24 (25%)	13 (27%)	
Intermediate (4-7)	25 (43%)	24 (51%)	42 (44%)	27 (55%)	
High (≥8)	9 (16%)	4 (9%)	29 (31%)	9 (18%)	
Residual disease					0.005
Radical	33 (57%)	31 (66%)	60 (63%)	40 (82%)	
< 1 cm	11 (19%)	13 (28%)	27 (28%)	6 (12%)	
≥ 1 cm	14 (24%)	3 (6%)	8 (8%)	3 (6%)	
Clavien-Dindo					0.027
0-2	48 (83%)	42 (89%)	69 (73%)	44 (90%)	
3-5	10 (17%)	5 (11%)	26 (27%)	5 (10%)	

PDS: Primary debulking surgery, IDS: Interval debulking surgery, Hb: Hemoglobin, TSAT: Transferrin saturation

Patients with iron deficiency had a higher rate of severe complications (17-27%) compared to 10-11% among patients with no iron deficiency (p 0.027). In an unadjusted logistic regression model, patients with iron deficiency had higher odds risk for CD ≥ 3, with an OR 2.65 (95% CI 1.25-5.62) compared to patient with no iron deficiency. When adjusted for Aletti surgical complexity score, Hb level before surgery, and operating time, this higher risk persisted OR 2.47 (95% CI 1.11-5.50).

A difference was observed between patients undergoing PDS and IDS regarding anemia and iron deficiency. Among PDS patients, 26% had anemia and 73% had iron deficiency; in the IDS group 84% had anemia but only 31% had iron deficiency, ($p<0.001$). All patients undergoing IDS (100%) completed all six cycles of chemotherapy, whereas 91% of patients in the PDS group received all cycles (p 0.006). (Figure 11)

Patients who received intravenous iron had a decrease in Hb from Hb 118 g/L before surgery to Hb 114 g/L before chemotherapy, compared to a decrease from 128 g/L to 118 g/L in patients who did not receive intravenous iron. In this cohort, only 12 patients were administered intravenous iron more than two weeks before surgery.

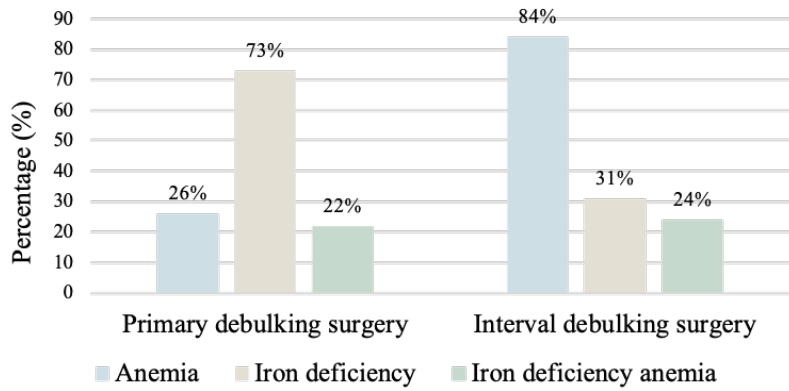


Figure 11. Prevalence of anemia, iron deficiency, and iron deficiency anemia in patients undergoing primary and interval debulking surgery ($p < 0.001$).

Study IV

Of all 485 included patients, 48% were <70 years, 38% were 70-79 years and 14% were ≥ 80 years. Median ages were 58, 75 and 83 years respectively.

The proportion of patients undergoing PDS decreased with age (64% in the youngest group, 49% in the 70-79 years group, decreasing to 23% in the oldest group). PC and BSC increased with age (PC up to 43% and BSC up to 22% in the ≥80 group) ($p < 0.001$).

Of patients who started NACT, 73% of the < 70 years fulfilled the planed IDS, compared to 52% in the 70-79 group and 50% in the oldest group. The majority of NACT patients who did not undergo surgery (63-89%) were due to insufficient response to chemotherapy, where radical or suboptimal surgery was deemed unlikely because of heavy tumor burden.

The rate of achieving complete cytoreductive surgery declined with age; 73% in the youngest group, 61% in the 70-79 group, and 43% in the ≥ 80 group (p 0.026). In patients aged 70-79 years, there was no significant difference in achieving radical surgery between PDS and IDS, 60% and 66% respectively (p 0.823). In patients ≥ 80 years there was a trend towards a higher rate of complete resection for patients undergoing IDS compared to PDS, 63% vs 33 %, but it was not statistically significant (p 0.399). There was no difference in severe complications (CD ≥ 3) across the three age groups (< 70 years 13%, 70-79 years 18% and ≥ 80 13%), (p 0.494) (Table 8).

Table 8. Surgery characteristics stratified by age.

	< 70 years n=201	**70-79 years n=127**	**≥ 80 years n=23**	**p-value**
Operating time (min) median	215 (55-657)	204 (61-620)	140 (90-282)	<0.001
Aletti score				0.074
Low (≤3)	53 (26.4%)	46 (36.2%)	10 (43.5%)	
Intermediate (4-7)	105 (52.2%)	63 (49.6%)	12 (52.2%)	
High (≥8)	43 (21.4%)	18 (14.2%)	1 (4.3%)	
Residual disease				0.026
Radical	146 (72.6%)	78 (61.4%)	10 (43.5%)	
< 1 cm	39 (19.4%)	32 (25.2%)	8 (34.8%)	
≥ 1 cm	16 (8.0%)	17 (13.4%)	5 (21.7%)	
Clavien-Dindo				0.494
0-2	174 (86.6%)	104 (81.9%)	20 (87.0%)	
3-5	27 (13.4%)	23 (18.1%)	3 (13%)	
Complete chemotherapy				0.001
Yes	191 (95.0%)	113 (89.7%)	17 (73.9%)	
No	10 (5.0%)	12 (10.3%)	6 (26.1%)	

Patients ≥ 80 years, had a significantly shorter operating time (140 min) compared to 251 min and 204 min in the younger groups (p <0.001). The extent of the surgery did not differ between the groups (p <0.074). It was less likely for older patients ≥ 80 years to receive all six cycles of chemotherapy (74%) compared to 95% and 90% in the younger cohorts, (p 0.001).

OS decreased with increasing age. Patients < 70 years undergoing PDS or IDS had the highest 36-month survival rates (74% and 61% respectively). In patients aged ≥ 80 years, 36-month survival was 43% for PDS and 48% for IDS, compared to 11% for PC and 0% when receiving BSC.

Table 9. Restricted Mean Survival Time (RMST) by age group and treatment modality at 12, 24 and 36 months.

	Treatment	12 months	24 months	36 months
< 70 years	PDS	11.53	22.33	31.91
	IDS	11.48	21.65	29.95
	PC	7.64	11.50	14.07
	BSC	0.00	0.00	0.00
70-79 years	PDS	11.41	21.68	30.34
	IDS	11.31	20.24	25.67
	PC	8.76	13.10	14.96
	BSC	0.20	0.20	0.20
≥ 80 years	PDS	7.60	13.20	18.80
	IDS	10.50	19.38	25.67
	PC	9.00	11.46	12.75
	BSC	1.57	1.57	1.57

PDS: Primary debulking surgery, IDS: Interval debulking surgery, PC: Palliative chemotherapy, BSC: Best supportive care

Discussion

Study I

Ovarian cancer carries the worst prognosis and the highest mortality rate among gynecological malignancies (1). Symptoms associated with ovarian cancer are non-specific and are sometimes attributed to the normal aging process instead of signaling a malignant disease with an adverse outcome (24, 128).

The results of this study showed that almost half of the patients experienced abdominal or pelvic pain at their first consultation with a physician, and the second most common symptom was increased abdominal size or bloating. Notably, abdominal pain, increased abdominal size, and urinary frequency have been shown to have a low predictive value (25). Studies refute the earlier term “silent killer” as up to 95% of patients have symptoms prior to diagnosis, with more than one third having symptoms for over seven months (129). Even in early-stage ovarian cancer, more than 70% of women experience symptoms prior to diagnosis (26).

Older patients exhibited a significantly longer time interval from the first physician consultation to a reasonable suspicion of cancer. The median time interval was more than twice as long as that in the younger age group. The majority (66%) of patients diagnosed with AOC had their first appointment within primary health care. Consequently, consultation in specialized health care resulted in a significantly shorter time interval to reasonable suspicion of cancer compared to primary care.

Unsurprisingly, the time interval to reasonable suspicion of cancer was significantly shorter when patients initially presented at an emergency visit. This is likely because the more severe symptoms at presentation caused the physician to immediately suspect a malignant disease. However, studies have shown that emergency visits and consultations at the emergency department are associated with a worse prognosis, as these patients more often present with an advanced stage of the disease (130, 131). Correspondingly, patients with poorer survival typically have a shorter time to diagnosis (132). Our results indicated that patient receiving BSC often had a shorter time to diagnosis, which is likely due to more severe symptom leading to a faster referral.

Due to the retrospective nature of the study, we lack information regarding the severity of symptoms at presentation or the time period between the onset of symptoms and the first consultation with health care. Furthermore, there is no difference in the time to diagnosis between Type I and Type II tumors, and the symptoms are similar (133).

The absence of effective screening methods for early ovarian cancer and the fact that most patients are diagnosed at an advanced stage contribute to the severe prognosis. Studies on various screening methods have failed to show a reduction in mortality rate, leading to the current recommendation against screening in the general population (31, 32). While reducing the time to diagnosis after symptoms has not been shown to improve survival or cause a stage shift (132, 134), earlier detection could allow a higher proportion of patients to undergo state-of-the-art treatment with cytoreductive surgery and complete chemotherapy, leading to a better survival at the individual level.

Limitations of this study include not knowing the onset of symptoms or if the patients had contact with another health care profession before consulting a physician. Confounders such as comorbidity and performance status, as well as the relatively small number of patients included, are also limitations. A key strength, however, was that the study included all patients diagnosed with AOC referred to Lund during a three-year time period.

Study II-III

In these cohorts, approximately 50% of patients had anemia before surgery. Moderate to severe anemia was detected in 8% of patients. This finding is comparable to other studies, where 40% of AOC patients have anemia before surgery, and 9% of patients with solid tumors have moderate to severe anemia (65, 72). Patients with ovarian cancer more often have anemia before surgery compared to patients undergoing surgery for benign gynecological conditions or other gynecological malignancies (65). Patients undergoing IDS were more likely to have anemia before surgery compared to those undergoing PDS, a finding consistent with previous studies (66).

Around 60% of patients in the third study had iron deficiency. More than one-third of patients had preoperative iron deficiency without anemia, and the majority of those underwent PDS. Most patients presented with functional iron deficiency, with absolute iron deficiency present in only a small portion, which alignes with previous reports (72).

Interestingly, patients with iron deficiency (with or without anemia) had a higher risk for postoperative severe complications compared to patients without iron

deficiency. Furthermore, patients with iron deficiency and normal Hb levels had the highest rate of severe complications. This suggests that iron deficiency itself might be more strongly associated with postoperative morbidity and complications than anemia alone. Conversely, iron deficiency anemia was associated with a higher risk of residual disease (≥ 10 mm). These findings may indicate a possible correlation between iron deficiency and heavy tumor load. In other words, a higher tumor load might correlate with iron deficiency, which could hold prognostic value concerning resectability. It has long been established that residual tumor after debulking surgery is one of the strongest prognostic factors in ovarian cancer (87).

The PBM clinical routines were implemented gradually, resulting in a significant reduction in estimated blood loss after the introduction of TXA as standard pre-surgical medication, as previously shown (76, 135). Patients undergoing major abdominal surgery who receive RBC transfusions are generally older, have more comorbidities, and undergo longer operating times (136). In our study, however, there was no difference in median age between the three groups. A confounding factor concerning operating time could be the trend towards shorter times following the LION study results, which indicated that systematic lymphadenectomy after debulking surgery was no longer beneficial (94).

The number of patients receiving RBC transfusions decreased throughout the study period. In the reference group, 83% of patients received one or more RBC transfusions, compared to 52% in the last group of the study period. Since this study included only patients with AOC, the transfusion rate may be higher than in other studies that include patients with early-stage ovarian cancer (137). The most substantial decrease was observed following the routine introduction of TXA administration before surgery and when the operating time decreased. The number of units of RBCs transfused per patient also decreased during the study period. The largest reduction was seen in patients transfused with three or more units of RBCs, which decreased from 48% to 17%. Studies have linked perioperative RBC transfusions in ovarian cancer patients undergoing debulking surgery to decreased survival (78, 81). Nevertheless, another study found no decrease in OS and no increased risk of recurrence among ovarian cancer patients receiving RBC transfusions (80). In our study, no significant difference in severe complications was observed, although there was a trend toward fewer complications. Moreover, RBC transfusions are associated with a higher risk of surgical site infections (79).

The median length of hospital stay decreased by one day during the study period. This reduction may be attributed to fewer RBC transfusions, but it could also be influenced by other concurrent factors, such as lower estimated blood loss, shorter operating time, and the tendency towards fewer severe complications. Prolonged length of hospital stay is associated with reduced survival, and RBC transfusions are linked to increased hospital stays (81, 138). The Hb level before the start of

chemotherapy decreased by 1.32 g/L during the implementation of PBM clinical routines, an amount likely lacking clinical significance.

In the third study, half of the patients with anemia received intravenous iron before surgery, but most received it only a few days prior. For optimal response, intravenous iron administration is recommended four weeks before surgery (73). However, receiving intravenous iron 10 days before surgery may still be beneficial (83). The largest increase in Hb, from baseline before surgery to the start of chemotherapy, was seen in patients with moderate to severe anemia. Studies have shown that the most substantial response to intravenous iron occurs in patients with more severe anemia (139, 140).

Postoperative anemia has been shown to increase the risk of morbidity within 90 days after surgery, and increase readmission and frailty within 30 days postoperatively in patients undergoing major abdominal surgery (68, 141). Intravenous iron is also recommended for the treatment of postoperative anemia, and should be initiated no later than before discharge (73).

In our study, patients receiving intravenous iron had a higher rate of severe complications. These patients also had the lowest TSAT levels (an indicator of iron deficiency), which was, in turn, related to complications. Due to the retrospective nature of the study, we cannot determine if these patients were administered iron because of complications or if the complications were casually related to intravenous iron administration. A recent study showed that colorectal cancer patients experienced more mild complications after receiving intravenous iron. However, factors such as missing Hb values and potential selection bias between the groups might hinder the interpretation of these results (142). Conversely, another study showed fewer mild complications and a decrease in postoperative anemia one month after surgery when preoperative anemia was treated with intravenous iron (143). A prospective randomized study is currently underway to evaluate the effect of preoperative intravenous iron in gynecological cancer patients with iron deficiency anemia (144).

The limitations of these studies include a lack of information on whether the patient experienced symptoms of anemia, adverse effects after RBC and intravenous iron administration, and the gynecologist's individual decision to treat anemia, despite local guidelines. Furthermore, data such as Hb before chemotherapy and TSAT before surgery were missing for a few patients in both studies. A major strength of these studies, however, was that all surgeries were performed at a tertiary cancer center by experienced gynecological oncologists.

Study IV

Older patients are less likely to receive the standard treatment for AOC, which includes a combination of cytoreductive surgery and six cycles of platinum and paclitaxel (115, 145). Increasing age is associated with polypharmacy, worse performance status, and more comorbidities (145, 146). We observed that the proportion of patients undergoing cytoreductive surgery decreased with increasing age, with more patients received PC or BSC instead. This trend was especially pronounced among patients aged ≥80 years, where only 35% underwent either PDS or IDS. In this oldest age group, over one-third of patients had ECOG 2 or more, along with a higher proportion of patients having anemia and lower albumin levels compared to the younger groups. There was also a tendency for patients aged 80 or older to be more frequently diagnosed with FIGO stage IV. These factors collectively disadvantage older patients regarding their suitability for surgery compared to younger patients.

In the older group (≥80 years), 21% had more than 1 cm of residual disease after surgery, compared to only 8% in patients younger than 70 years. Patients aged 70-79 years underwent suboptimal surgery (more than 1 cm of residual disease) in 13% of cases. Previous studies have also reported an increased rate of residual disease in older compared to younger patients; specifically, 25% of patients aged ≥ 70 years underwent suboptimal surgery compared to 13% among patients younger than 70 years (117). There was a tendency toward less extensive surgery with increasing age, and patients ≥80 years had a significantly shorter operating time, which aligns with previous findings in patients over 70 years (147).

Patients aged ≥ 80 years appeared to have a lower tolerance for chemotherapy compared to younger patients, as they were less likely to receive all six cycles of chemotherapy after undergoing cytoreductive surgery. Studies have shown that patients over 75 years are less likely to receive all six cycles of chemotherapy, a trend that increases with age (115). Following the decision for NACT, patients aged 70 year or above were less likely to undergo cytoreductive surgery; only 50 % them ultimately underwent IDS. This is comparable to a recent study where 65% of patients aged 70 years or older underwent IDS after receiving NACT (104). The most common reason for not proceeding to IDS after NACT was insufficient response to chemotherapy, where radical or suboptimal surgery was deemed unlikely due to the heavy tumor burden.

There were clear differences in OS based on the treatment mode and age group. Surgery was associated with the longest 36-month survival time across all age groups. However, in patients aged ≥ 80 years, the advantage of IDS over PC was not statistically significant, potentially due to the small sample size. In patients younger than 80 years, PDS and IDS had comparable survival outcomes, with OS being slightly better for those undergoing PDS. These trends were confirmed by the

calculated RMST. Preliminary data from the TRUST study showed a longer PFS in patients who underwent PDS compared to IDS, but no significant difference in OS (93). For patients aged ≥ 80 years, a better OS is reported when undergoing IDS compared to PDS (104). In our study, older patients aged ≥80 years seemed to have a better OS when undergoing IDS compared to PDS, although the results were not statistically significant. The small number of patients included in this group could contribute to this result. Patients undergoing IDS often require less extensive surgery than those undergoing PDS, which may explain why older patients have a better tolerance for IDS. Patients ≥75 years benefit from IDS compared to chemotherapy alone, achieving a better OS (148). Since older patients more often have comorbidities and a worse performance status, comparing these two treatment groups becomes difficult. Therefore, evaluating physical function rather than chronological age is important for selecting the right older patients for surgery.

A limitation of this study was the small number of patients included, particularly in the oldest age group. Furthermore, the short follow-up time limited the possibility of interpreting the survival curves. A strength of the study is that the treatment decisions were made in the majority of cases at an MDT meeting, ensuring clinical relevance and consistency.

Conclusions

- Most patients are referred from primary care with suspicion of advanced ovarian cancer. The timeline from diagnosis is shorter if the patient first consults specialized care.
- Unfortunately, older patients with symptoms who initially seek a physician in primary care can experience a longer delay in the diagnosis of ovarian cancer.
- By implementing clinical guidelines consistent with PBM, RBC transfusions can be reduced without causing any major short-term disadvantage to the patient's recovery. Although hospital stay was reduced by one day, a slight increase in the rate of anemia was also found.
- Iron deficiency anemia is associated with a higher rate of residual disease after surgery for advanced ovarian cancer. Moreover, iron deficiency, regardless of the presence of anemia, is associated with severe postoperative complications. Iron deficiency might therefore be used as a marker for more advanced disease and complex surgical procedures.
- Administration of intravenous iron before or after surgery appears to help maintain the Hb level leading up to the start of chemotherapy.
- Increasing age is associated with a lower likelihood of undergoing cytoreductive surgery, especially among patients aged ≥80 years. With increasing age, patients are less likely to achieve complete cytoreduction, and the likelihood of suboptimal surgery increases.
- Cytoreductive surgery, encompassing both PDS and IDS, is associated with increased survival in patients younger than 80 years. Importantly, patients aged ≥ 80 years can still benefit from IDS.

Future Aspects

Further research should evaluate if other factors are associated with a longer time to diagnosis and if educational programs can successfully shorten the time to diagnosis. Further investigation is needed to determine the impact of preoperative iron deficiency on surgical outcome, as a correlation between iron deficiency and a higher tumor load may exist. A prospective study is currently ongoing to validate the data from study III in a different cohort of ovarian cancer patients. A prospective study is also necessary to evaluate the role of intravenous iron in impacting recovery for advanced ovarian cancer patients undergoing surgery. Finally, further investigation is required to optimize treatment strategies specifically for patients aged 80 years or older.

Acknowledgements

I would like to express my sincere gratitude to the all the patients and everyone who has helped and supported me in completing this thesis.

Assistant Professor Päivi Kannisto, my supervisor, for your invaluable guidance, support and constant encouragement. Thank you for always being available and all the insightful advice.

Susanne Malander, my co-supervisor, for your support, oncological expertise and constructive comments.

Mihaela Asp, my co-supervisor, for all your encouragement and guidance, both in research and in the clinic.

Charlotte Hellsten, head of department, for being a professional and understanding leader.

Alba Plana, for your support and encouragement.

Celine Lönnerfors, for your help with the English language in this thesis.

Colleagues at the Department of Obstetrics and Gynecology, Skåne University Hospital, Lund, for inspiration and for all you have taught me about gynecology.

My co-authors, Tobias Carlsson, Jesper Bengtsson and Sara Alson, for good cooperation.

My mother, for always believing in me.

This thesis was made possible by research grants from Region Skåne, Pharmacosmos A/S and Kronobergs cancerstiftelse.

References

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024;74(3):229-63.
2. Ferlay J EM, Lam F, Laversanne M, Colombet M, Mery K, Pineros M, Znaor A, Soerjomataram I, Bray F. Global Cancer Observatory: Cancer Today, France: International Agenct for Research on Cancer. 2024. Available from: https://gco.iarc.who.int/today.
3. Webb PM, Jordan SJ. Global epidemiology of epithelial ovarian cancer. Nat Rev Clin Oncol. 2024;21(5):389-400.
4. Cancer IAfRo. Estimated number pf new cases from 2022 to 2050, World, Ovart, females, all ages: World Health Organization. 2022 [cited 21 October 2025]. Available from: https://gco.iarc.fr/tomorrow/en/dataviz/isotype?types=0&single_unit=5000&populations=900&group_populations=0&multiple_populations=0&years=2050&cancers=25&sexes=2.
5. Larønningen S AG, Bray F, Dahl-Olsen ED, Engholm G, Ervik M, Friis S, Guðmundsdóttir EM, Gulbrandsen J, Hansen HM, Johannesen TB, Kristensen S, Kønig SM, Lam F, Laversanne M, Lydersen LN, Malila N, Mangrud OM, Miettinen J, Pejicic S, Persson Å, Pettersson D, Skog A, Steig BÁ, Tian H, Aagnes B, Storm HH. NORDCAN: Cancer Incidence, Mortality, Prevalence and Survival in the Nordic Countries, Version 9.5 (19.06.2025). Association of the Nordic Cancer Registries. Cancer Registry of Norway. 2025.
6. Cancerfonden. Statistik äggstockscancer. [9 November 2025]. Available from: https://www.cancerfonden.se/om-cancer/statistik/aggstockscancer.
7. Prat J, Oncology FCoG. Staging classification for cancer of the ovary, fallopian tube, and peritoneum. Int J Gynaecol Obstet. 2014;124(1):1-5.
8. Caruso G, Weroha SJ, Cliby W. Ovarian Cancer: A Review. JAMA. 2025.
9. Torre LA, Trabert B, DeSantis CE, Miller KD, Samimi G, Runowicz CD, et al. Ovarian cancer statistics, 2018. CA Cancer J Clin. 2018;68(4):284-96.
10. Flaum N, Crosbie EJ, Edmondson RJ, Smith MJ, Evans DG. Epithelial ovarian cancer risk: A review of the current genetic landscape. Clin Genet. 2020;97(1):54-63.
11. Hodgson A, Turashvili G. Pathology of Hereditary Breast and Ovarian Cancer. Front Oncol. 2020;10:531790.
12. Pietragalla A, Arcieri M, Marchetti C, Scambia G, Fagotti A. Ovarian cancer predisposition beyond BRCA1 and BRCA2 genes. Int J Gynecol Cancer. 2020;30(11):1803-10.

13. Kuchenbaecker KB, Hopper JL, Barnes DR, Phillips KA, Mooij TM, Roos-Blom MJ, et al. Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers. JAMA. 2017;317(23):2402-16.
14. Hartmann LC, Lindor NM. Risk-Reducing Surgery in Hereditary Breast and Ovarian Cancer. N Engl J Med. 2016;374(24):2404.
15. Hermens M, van Altena AM, Bulten J, van Vliet H, Siebers AG, Bekkers RLM. Increased incidence of ovarian cancer in both endometriosis and adenomyosis. Gynecol Oncol. 2021;162(3):735-40.
16. Simin J, Khodir H, Fornes R, Tamimi RM, Brusselaers N. Association between menopausal hormone therapy use and mortality risk: a Swedish population-based matched cohort study. Acta Oncol. 2022;61(5):632-40.
17. Fournier A, Cairat M, Severi G, Gunter MJ, Rinaldi S, Dossus L. Use of menopausal hormone therapy and ovarian cancer risk in a French cohort study. J Natl Cancer Inst. 2023;115(6):671-9.
18. Jonsson S, Jonsson H, Lundin E, Haggstrom C, Idahl A. Pelvic inflammatory disease and risk of epithelial ovarian cancer: a national population-based case-control study in Sweden. Am J Obstet Gynecol. 2024;230(1):75 e1- e15.
19. World Health Organization IAfRoC. WHO classification of tumours: Female genital tumours. 5 th ed: Lyon: International Agency for Research on Cancer; 2020.
20. Shih Ie M, Kurman RJ. Ovarian tumorigenesis: a proposed model based on morphological and molecular genetic analysis. Am J Pathol. 2004;164(5):1511-8.
21. Kurman RJ, Shih Ie M. The origin and pathogenesis of epithelial ovarian cancer: a proposed unifying theory. Am J Surg Pathol. 2010;34(3):433-43.
22. Kurman RJ, Shih IM. The Dualistic Model of Ovarian Carcinogenesis: Revisited, Revised, and Expanded. Am J Pathol. 2016;186(4):733-47.
23. Bowtell DD. The genesis and evolution of high-grade serous ovarian cancer. Nat Rev Cancer. 2010;10(11):803-8.
24. Goff BA, Mandel LS, Melancon CH, Muntz HG. Frequency of symptoms of ovarian cancer in women presenting to primary care clinics. JAMA. 2004;291(22):2705-12.
25. Hamilton W, Peters TJ, Bankhead C, Sharp D. Risk of ovarian cancer in women with symptoms in primary care: population based case-control study. BMJ. 2009;339:b2998.
26. Chan JK, Tian C, Kesterson JP, Monk BJ, Kapp DS, Davidson B, et al. Symptoms of Women With High-Risk Early-Stage Ovarian Cancer. Obstet Gynecol. 2022;139(2):157-62.
27. Vandborg MP, Edwards K, Kragstrup J, Vedsted P, Hansen DG, Mogensen O. A new method for analyzing diagnostic delay in gynecological cancer. Int J Gynecol Cancer. 2012;22(5):712-7.
28. Baun ML, Jensen H, Falborg AZ, Heje HN, Petersen LK, Vedsted P. Ovarian cancer suspicion, urgent referral and time to diagnosis in Danish general practice: a population-based study. Fam Pract. 2019;36(6):751-7.

29. Buys SS, Partridge E, Black A, Johnson CC, Lamerato L, Isaacs C, et al. Effect of screening on ovarian cancer mortality: the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Randomized Controlled Trial. JAMA. 2011;305(22):2295-303.
30. Menon U, Gentry-Maharaj A, Burnell M, Singh N, Ryan A, Karpinskyj C, et al. Ovarian cancer population screening and mortality after long-term follow-up in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial. Lancet. 2021;397(10290):2182-93.
31. Gonzalez-Martin A, Harter P, Leary A, Lorusso D, Miller RE, Pothuri B, et al. Newly diagnosed and relapsed epithelial ovarian cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2023;34(10):833-48.
32. Sideris M, Jamdade K, Essangri H, Zalawadia S, Oxley SG, Selek K, et al. The Role of Cytoreductive Surgery in Platinum-Resistant Ovarian Cancer (PROC): A Systematic Review. Cancers (Basel). 2025;17(2).
33. Jacobs I, Oram D, Fairbanks J, Turner J, Frost C, Grudzinskas JG. A risk of malignancy index incorporating CA 125, ultrasound and menopausal status for the accurate preoperative diagnosis of ovarian cancer. Br J Obstet Gynaecol. 1990;97(10):922-9.
34. Regionala cancercentrum i samverkan RCC. Standardiserat vårdförlopp äggstockscancer. 2024 [cited 2025 September 28]. Available from: https://kunskapsbanken.cancercentrum.se/diagnoser/aggstockscancer/vardforlopp/#chapter--Ingang-till-standardiserat-vardforlopp.
35. Timmerman D, Planchamp F, Bourne T, Landolfo C, du Bois A, Chiva L, et al. ESGO/ISUOG/IOTA/ESGE Consensus Statement on preoperative diagnosis of ovarian tumors. Ultrasound Obstet Gynecol. 2021;58(1):148-68.
36. Timmerman D, Valentin L, Bourne TH, Collins WP, Verrelst H, Vergote I, et al. Terms, definitions and measurements to describe the sonographic features of adnexal tumors: a consensus opinion from the International Ovarian Tumor Analysis (IOTA) Group. Ultrasound Obstet Gynecol. 2000;16(5):500-5.
37. Fischerova D, Smet C, Scovazzi U, Sousa DN, Hundarova K, Haldorsen IS. Staging by imaging in gynecologic cancer and the role of ultrasound: an update of European joint consensus statements. Int J Gynecol Cancer. 2024;34(3):363-78.
38. Miceli V, Gennarini M, Tomao F, Cupertino A, Lombardo D, Palaia I, et al. Imaging of Peritoneal Carcinomatosis in Advanced Ovarian Cancer: CT, MRI, Radiomic Features and Resectability Criteria. Cancers (Basel). 2023;15(24).
39. Ledermann JA, Matias-Guiu X, Amant F, Concin N, Davidson B, Fotopoulou C, et al. ESGO-ESMO-ESP consensus conference recommendations on ovarian cancer: pathology and molecular biology and early, advanced and recurrent disease. Ann Oncol. 2024;35(3):248-66.
40. Engbersen MP, Van Driel W, Lambregts D, Lahaye M. The role of CT, PET-CT, and MRI in ovarian cancer. Br J Radiol. 2021;94(1125):20210117.
41. Fischerova D, Planchamp F, Alcazar JL, Dundr P, Epstein E, Felix A, et al. ISUOG/ESGO Consensus Statement on ultrasound-guided biopsy in gynecological oncology. Int J Gynecol Cancer. 2025;35(4):101732.

42. Gal AA. The centennial anniversary of the frozen section technique at the Mayo Clinic. Arch Pathol Lab Med. 2005;129(12):1532-5.
43. Vergote I, De Brabanter J, Fyles A, Bertelsen K, Einhorn N, Sevelda P, et al. Prognostic importance of degree of differentiation and cyst rupture in stage I invasive epithelial ovarian carcinoma. Lancet. 2001;357(9251):176-82.
44. Asp M, Peber E, Kannisto P, Masback A, Malander S. Ovarian tumor frozen section, a multidisciplinary affair. Acta Oncol. 2022;61(7):785-92.
45. Regionala cancercentrum i samverkan RCC. Aggstockscancer med epitelial histologi Nationellt vardprogram. 2025 [cited 2025 September 28]. Available from: https://kunskapsbanken.cancercentrum.se/diagnoser/aggstockscancer-epitelial/vardprogram/.
46. Fleurent-Gregoire C, Burgess N, McIsaac DI, Chevalier S, Fiore JF, Jr., Carli F, et al. Towards a common definition of surgical prehabilitation: a scoping review of randomised trials. Br J Anaesth. 2024;133(2):305-15.
47. Scheede-Bergdahl C, Minnella EM, Carli F. Multi-modal prehabilitation: addressing the why, when, what, how, who and where next? Anaesthesia. 2019;74 Suppl 1:20-6.
48. Miralpeix E, Mancebo G, Gayete S, Corcoy M, Sole-Sedeno JM. Role and impact of multimodal prehabilitation for gynecologic oncology patients in an Enhanced Recovery After Surgery (ERAS) program. Int J Gynecol Cancer. 2019;29(8):1235-43.
49. Molenaar CJL, Minnella EM, Coca-Martinez M, Ten Cate DWG, Regis M, Awasthi R, et al. Effect of Multimodal Prehabilitation on Reducing Postoperative Complications and Enhancing Functional Capacity Following Colorectal Cancer Surgery: The PREHAB Randomized Clinical Trial. JAMA Surg. 2023;158(6):572-81.
50. Cho AR, Najafi T, Ramanakumar AV, Ferri L, Spicer J, Najmeh S, et al. The effect of multimodal prehabilitation on postoperative outcomes in lung cancer surgery. J Thorac Cardiovasc Surg. 2025;169(6):1631-44 e2.
51. Skorepa P, Ford KL, Alsuwaylihi A, O'Connor D, Prado CM, Gomez D, et al. The impact of prehabilitation on outcomes in frail and high-risk patients undergoing major abdominal surgery: A systematic review and meta-analysis. Clin Nutr. 2024;43(3):629-48.
52. Dhanis J, Keidan N, Blake D, Rundle S, Strijker D, van Ham M, et al. Prehabilitation to Improve Outcomes of Patients with Gynaecological Cancer: A New Window of Opportunity? Cancers (Basel). 2022;14(14).
53. Sebio-Garcia R, Celada-Castro C, Arguis MJ, Siso M, Torne A, Tena B, et al. Multimodal prehabilitation improves functional capacity in patients with advanced ovarian cancer undergoing cytoreductive surgery. Int J Gynecol Cancer. 2024.
54. Miralpeix E, Sole-Sedeno JM, Rodriguez-Cosmen C, Taus A, Muns MD, Fabrego B, et al. Impact of prehabilitation during neoadjuvant chemotherapy and interval cytoreductive surgery on ovarian cancer patients: a pilot study. World J Surg Oncol. 2022;20(1):46.

55. Diaz-Feijoo B, Agusti-Garcia N, Sebio R, Lopez-Hernandez A, Siso M, Glickman A, et al. Feasibility of a Multimodal Prehabilitation Programme in Patients Undergoing Cytoreductive Surgery for Advanced Ovarian Cancer: A Pilot Study. Cancers (Basel). 2022;14(7).
56. van der Graaff S, Backhuijs TAM, de Kort FP, Lockhorst EW, Smedts HPM, Schreinemakers JMJ, et al. Feasibility and Effects of Implementing Multimodal Prehabilitation Before Cytoreductive Surgery in Patients with Ovarian Cancer: The Gynofit Multicenter Study. Cancers (Basel). 2025;17(9).
57. Nelson G, Altman AD, Nick A, Meyer LA, Ramirez PT, Achtari C, et al. Guidelines for pre- and intra-operative care in gynecologic/oncology surgery: Enhanced Recovery After Surgery (ERAS(R)) Society recommendations--Part I. Gynecol Oncol. 2016;140(2):313-22.
58. Nelson G, Altman AD, Nick A, Meyer LA, Ramirez PT, Achtari C, et al. Guidelines for postoperative care in gynecologic/oncology surgery: Enhanced Recovery After Surgery (ERAS(R)) Society recommendations--Part II. Gynecol Oncol. 2016;140(2):323-32.
59. Sanchez-Iglesias JL, Carbonell-Socias M, Perez-Benavente MA, Monreal Clua S, Manrique-Munoz S, Garcia Gorriz M, et al. PROFAST: A randomised trial implementing enhanced recovery after surgery for highcomplexity advanced ovarian cancer surgery. Eur J Cancer. 2020;136:149-58.
60. Shander A, Hardy JF, Ozawa S, Farmer SL, Hofmann A, Frank SM, et al. A Global Definition of Patient Blood Management. Anesth Analg. 2022;135(3):476-88.
61. Althoff FC, Neb H, Herrmann E, Trentino KM, Vernich L, Fullenbach C, et al. Multimodal Patient Blood Management Program Based on a Three-pillar Strategy: A Systematic Review and Meta-analysis. Ann Surg. 2019;269(5):794-804.
62. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. WHO/NMH/NHD/MNM/11.1. Available from: https://iris.who.int/bitstream/handle/10665/85839/WHO_NMH_NHD_MNM_11.1_eng.pdf.
63. Munoz M, Laso-Morales MJ, Gomez-Ramirez S, Cadellas M, Nunez-Matas MJ, Garcia-Erce JA. Pre-operative haemoglobin levels and iron status in a large multicentre cohort of patients undergoing major elective surgery. Anaesthesia. 2017;72(7):826-34.
64. Maccio A, Madeddu C, Massa D, Mudu MC, Lusso MR, Gramignano G, et al. Hemoglobin levels correlate with interleukin-6 levels in patients with advanced untreated epithelial ovarian cancer: role of inflammation in cancer-related anemia. Blood. 2005;106(1):362-7.
65. Foley OW, Vega B, Roque D, Hinchcliff E, Marcus J, Tanner EJ, et al. Characterization of pre-operative anemia in patients undergoing surgery by a gynecologic oncologist and association with post-operative complications. Int J Gynecol Cancer. 2023.

66. O'Shea A, McCool K, Harrison R, Sampene E, Connor J, Barroilhet L. Neoadjuvant chemotherapy is associated with more anemia and perioperative blood transfusions than primary debulking surgery in women with advanced stage ovarian cancer. Gynecol Oncol. 2018;150(1):19-22.
67. Fowler AJ, Ahmad T, Phull MK, Allard S, Gillies MA, Pearse RM. Meta-analysis of the association between preoperative anaemia and mortality after surgery. Br J Surg. 2015;102(11):1314-24.
68. Myles PS, Richards T, Klein A, Wood EM, Wallace S, Shulman MA, et al. Postoperative anaemia and patient-centred outcomes after major abdominal surgery: a retrospective cohort study. Br J Anaesth. 2022;129(3):346-54.
69. Weber RS, Jabbour N, Martin RC, 2nd. Anemia and transfusions in patients undergoing surgery for cancer. Ann Surg Oncol. 2008;15(1):34-45.
70. Koh JS, Song IC. Functional iron deficiency anemia in patients with cancer. Blood Res. 2024;59(1):26.
71. Shah A, Acheson A, Sinclair RCF. Perioperative iron deficiency anaemia. BJA Educ. 2023;23(10):372-81.
72. Ludwig H, Muldur E, Endler G, Hubl W. Prevalence of iron deficiency across different tumors and its association with poor performance status, disease status and anemia. Ann Oncol. 2013;24(7):1886-92.
73. Shander A, Corwin HL, Meier J, Auerbach M, Bisbe E, Blitz J, et al. Recommendations From the International Consensus Conference on Anemia Management in Surgical Patients (ICCAMS). Ann Surg. 2023;277(4):581-90.
74. Munoz M, Acheson AG, Auerbach M, Besser M, Habler O, Kehlet H, et al. International consensus statement on the peri-operative management of anaemia and iron deficiency. Anaesthesia. 2017;72(2):233-47.
75. Fowler H, Law J, Tham SM, Gunaravi SA, Houghton N, Clifford RE, et al. Impact on blood loss and transfusion rates following administration of tranexamic acid in major oncological abdominal and pelvic surgery: A systematic review and meta-analysis. J Surg Oncol. 2022;126(3):609-21.
76. Yang X, Chai M, Xia L, He Z, Wu X, Zhang J. Intraoperative use of tranexamic acid to reduce blood loss during cytoreductive surgery for advanced ovarian cancer: A randomized controlled clinical trial. Acta Obstet Gynecol Scand. 2023;102(7):950-9.
77. Fotopoulou C, Planchamp F, Aytulu T, Chiva L, Cina A, Ergonul O, et al. European Society of Gynaecological Oncology guidelines for the peri-operative management of advanced ovarian cancer patients undergoing debulking surgery. Int J Gynecol Cancer. 2021;31(9):1199-206.
78. Connor JP, O'Shea A, McCool K, Sampene E, Barroilhet LM. Peri-operative allogeneic blood transfusion is associated with poor overall survival in advanced epithelial ovarian Cancer; potential impact of patient blood management on Cancer outcomes. Gynecol Oncol. 2018;151(2):294-8.

79. Prescott LS, Vergote I, Sun CC, Bodurka DC, Coleman RL. Transfusion use and effect on progression-free, overall survival, and quality of life in upfront treatment of advanced epithelial ovarian cancer: evaluation of the European Organization for Research and Treatment EORTC-55971 Cohort. Int J Gynecol Cancer. 2023;33(1):1-9.
80. Hunsicker O, Gericke S, Graw JA, Krannich A, Boemke W, Meyer O, et al. Transfusion of red blood cells does not impact progression-free and overall survival after surgery for ovarian cancer. Transfusion. 2019;59(12):3589-600.
81. Benyahia S, Avila M, Coughlin E, Mahil A, Riveron A, Luo Y, et al. Impact of Intraoperative Blood Transfusions on Survival Rates in Ovarian Cancer Patients. Cancer Control. 2025;32:10732748251339248.
82. Froessler B, Palm P, Weber I, Hodyl NA, Singh R, Murphy EM. The Important Role for Intravenous Iron in Perioperative Patient Blood Management in Major Abdominal Surgery: A Randomized Controlled Trial. Ann Surg. 2016;264(1):41-6.
83. Neef V, Baumgarten P, Noone S, Piekarski F, Triphaus C, Kleineruschkamp A, et al. The impact of timing of intravenous iron supplementation on preoperative haemoglobin in patients scheduled for major surgery. Blood Transfus. 2022;20(3):188-97.
84. Munoz M, Acheson AG, Bisbe E, Butcher A, Gomez-Ramirez S, Khalafallah AA, et al. An international consensus statement on the management of postoperative anaemia after major surgical procedures. Anaesthesia. 2018;73(11):1418-31.
85. Sinclair RCF, Nadaraja S, Kennedy NA, Wakatsuki M, Bhandari S. Real-world experience of intravenous ferric derisomaltose evaluated through safety and efficacy reporting in the UK. Sci Rep. 2022;12(1):18859.
86. Vergote I, Trope CG, Amant F, Kristensen GB, Ehlen T, Johnson N, et al. Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. N Engl J Med. 2010;363(10):943-53.
87. du Bois A, Reuss A, Pujade-Lauraine E, Harter P, Ray-Coquard I, Pfisterer J. Role of surgical outcome as prognostic factor in advanced epithelial ovarian cancer: a combined exploratory analysis of 3 prospectively randomized phase 3 multicenter trials: by the Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe Ovarialkarzinom (AGO-OVAR) and the Groupe d'Investigateurs Nationaux Pour les Etudes des Cancers de l'Ovaire (GINECO). Cancer. 2009;115(6):1234-44.
88. Chase DM, Mahajan A, Scott DA, Hawkins N, Kalilani L. The impact of varying levels of residual disease following cytoreductive surgery on survival outcomes in patients with ovarian cancer: a meta-analysis. BMC Womens Health. 2024;24(1):179.
89. Minig L, Heitz F, Cibula D, Bakkum-Gamez JN, Germanova A, Dowdy SC, et al. Patterns of Lymph Node Metastases in Apparent Stage I Low-Grade Epithelial Ovarian Cancer: A Multicenter Study. Ann Surg Oncol. 2017;24(9):2720-6.
90. Canlorbe G, Chabbert-Buffet N, Uzan C. Fertility-Sparing Surgery for Ovarian Cancer. J Clin Med. 2021;10(18).

91. Kehoe S, Hook J, Nankivell M, Jayson GC, Kitchener H, Lopes T, et al. Primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer (CHORUS): an open-label, randomised, controlled, non-inferiority trial. Lancet. 2015;386(9990):249-57.
92. Fagotti A, Ferrandina MG, Vizzielli G, Pasciuto T, Fanfani F, Gallotta V, et al. Randomized trial of primary debulking surgery versus neoadjuvant chemotherapy for advanced epithelial ovarian cancer (SCORPION-NCT01461850). Int J Gynecol Cancer. 2020;30(11):1657-64.
93. Mahner S, Heitz F, Salehi S, Reuss A, Guyon F, Du Bois A, et al. TRUST: Trial of radical upfront surgical therapy in advanced ovarian cancer (ENGOT ov33/AGO-OVAR OP7). 2025 [updated Jun 10]. Lba5500-Lba]. Available from: https://ascopubs.org/doi/10.1200/JCO.2025.43.17_suppl.LBA5500.
94. Harter P, Sehouli J, Lorusso D, Reuss A, Vergote I, Marth C, et al. A Randomized Trial of Lymphadenectomy in Patients with Advanced Ovarian Neoplasms. N Engl J Med. 2019;380(9):822-32.
95. Norppa N, Staff S, Helminen M, Auranen A, Saarelainen S. Improved survival after implementation of ultra-radical surgery in advanced epithelial ovarian cancer: Results from a tertiary referral center. Gynecol Oncol. 2022;165(3):478-85.
96. Cummins C, Kumar S, Long J, Balega J, Broadhead T, Duncan T, et al. Investigating the Impact of Ultra-Radical Surgery on Survival in Advanced Ovarian Cancer Using Population-Based Data in a Multicentre UK Study. Cancers (Basel). 2022;14(18).
97. Falconer H, Joneborg U, Krawiec K, Palsdottir K, Bottai M, Salehi S. Ultra-radical upfront surgery does not improve survival in women with advanced epithelial ovarian cancer; a natural experiment in a complete population. Gynecol Oncol. 2020;159(1):58-65.
98. Kuusela K, Norppa N, Auranen A, Saarelainen S. Maximal surgical effort increases the risk of postoperative complications in the treatment of advanced ovarian cancer. Eur J Surg Oncol. 2022;48(12):2525-30.
99. Aletti GD, Dowdy SC, Gostout BS, Jones MB, Stanhope CR, Wilson TO, et al. Aggressive surgical effort and improved survival in advanced-stage ovarian cancer. Obstet Gynecol. 2006;107(1):77-85.
100. Chi DS, Eisenhauer EL, Zivanovic O, Sonoda Y, Abu-Rustum NR, Levine DA, et al. Improved progression-free and overall survival in advanced ovarian cancer as a result of a change in surgical paradigm. Gynecol Oncol. 2009;114(1):26-31.
101. Aletti GD, Dowdy SC, Podratz KC, Cliby WA. Relationship among surgical complexity, short-term morbidity, and overall survival in primary surgery for advanced ovarian cancer. Am J Obstet Gynecol. 2007;197(6):676 e1-7.
102. Palmqvist C, Michaelsson H, Staf C, Johansson M, Albertsson P, Dahm-Kahler P. Complications after advanced ovarian cancer surgery-A population-based cohort study. Acta Obstet Gynecol Scand. 2022;101(7):747-57.

103. Kengsakul M, Nieuwenhuyzen-de Boer GM, Udomkarnjananun S, Kerr SJ, van Doorn HC, van Beekhuizen HJ. Factors Predicting 30-Day Grade IIIa-V Clavien-Dindo Classification Complications and Delayed Chemotherapy Initiation after Cytoreductive Surgery for Advanced-Stage Ovarian Cancer: A Prospective Cohort Study. Cancers (Basel). 2022;14(17).
104. Piedimonte S, Bernardini MQ, May T, Cybulska P, Ferguson SE, Laframboise S, et al. Treatment outcomes and predictive factors in patients >/=70 years old with advanced ovarian cancer. J Surg Oncol. 2022;125(4):736-46.
105. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240(2):205-13.
106. McGuire WP, Hoskins WJ, Brady MF, Kucera PR, Partridge EE, Look KY, et al. Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. N Engl J Med. 1996;334(1):1-6.
107. Piccart MJ, Bertelsen K, James K, Cassidy J, Mangioni C, Simonsen E, et al. Randomized intergroup trial of cisplatin-paclitaxel versus cisplatin-cyclophosphamide in women with advanced epithelial ovarian cancer: three-year results. J Natl Cancer Inst. 2000;92(9):699-708.
108. Colombo N, Sessa C, Bois AD, Ledermann J, McCluggage WG, McNeish I, et al. ESMO-ESGO consensus conference recommendations on ovarian cancer: pathology and molecular biology, early and advanced stages, borderline tumours and recurrent disease. Int J Gynecol Cancer. 2019.
109. Jiang X, Li X, Li W, Bai H, Zhang Z. PARP inhibitors in ovarian cancer: Sensitivity prediction and resistance mechanisms. J Cell Mol Med. 2019;23(4):2303-13.
110. Banerjee S, Moore KN, Colombo N, Scambia G, Kim BG, Oaknin A, et al. Maintenance olaparib for patients with newly diagnosed advanced ovarian cancer and a BRCA mutation (SOLO1/GOG 3004): 5-year follow-up of a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2021;22(12):1721-31.
111. Ray-Coquard I, Pautier P, Pignata S, Perol D, Gonzalez-Martin A, Berger R, et al. Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer. N Engl J Med. 2019;381(25):2416-28.
112. Wise J. Global life expectancy to increase by almost five years by 2050, study predicts. BMJ. 2024;385:q1126.
113. Sweden SCB. Population Projections. 2025. Available from: https://www.scb.se/hitta-statistik/sverige-i-siffror/manniskorna-i-sverige/medellivslangd-i-sverige/.
114. Ekmann-Gade AW, Schnack TH, Seibaek L, Noer MC, Hogdall C. Impact of surgery and chemotherapy timing on outcomes in older versus younger epithelial ovarian cancer patients: A nationwide Danish cohort study. J Geriatr Oncol. 2023;14(1):101359.
115. Dumas L, Bowen R, Butler J, Banerjee S. Under-Treatment of Older Patients with Newly Diagnosed Epithelial Ovarian Cancer Remains an Issue. Cancers (Basel). 2021;13(5).

116. Joueidi Y, Dion L, Bendifallah S, Mimoun C, Bricou A, Nyangoh Timoh K, et al. Management and Survival of Elderly and Very Elderly Patients with Ovarian Cancer: An Age-Stratified Study of 1123 Women from the FRANCOGYN Group. J Clin Med. 2020;9(5).
117. Mallen A, Todd S, Robertson SE, Kim J, Sehovic M, Wenham RM, et al. Impact of age, comorbidity, and treatment characteristics on survival in older women with advanced high grade epithelial ovarian cancer. Gynecol Oncol. 2021;161(3):693-9.
118. Tortorella L, Vizzielli G, Fusco D, Cho WC, Bernabei R, Scambia G, et al. Ovarian Cancer Management in the Oldest Old: Improving Outcomes and Tailoring Treatments. Aging Dis. 2017;8(5):677-84.
119. Noer MC, Sperling CD, Ottesen B, Antonsen SL, Christensen IJ, Hogdall C. Ovarian Cancer and Comorbidity: Is Poor Survival Explained by Choice of Primary Treatment or System Delay? Int J Gynecol Cancer. 2017;27(6):1123-33.
120. Rousseau F, Ranchon F, Bardin C, Bakrin N, Lavoue V, Bengrine-Lefevre L, et al. Ovarian cancer in the older patient: where are we now? What to do next? Ther Adv Med Oncol. 2023;15:17588359231192397.
121. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. Lancet. 2013;381(9868):752-62.
122. Kim DH, Rockwood K. Frailty in Older Adults. N Engl J Med. 2024;391(6):538-48.
123. Inci MG, Anders L, Woopen H, Richter R, Guzel D, Armbrust R, et al. Frailty Index for prediction of surgical outcome in ovarian cancer: Results of a prospective study. Gynecol Oncol. 2021;161(2):396-401.
124. Hewitt J, Carter B, McCarthy K, Pearce L, Law J, Wilson FV, et al. Frailty predicts mortality in all emergency surgical admissions regardless of age. An observational study. Age Ageing. 2019;48(3):388-94.
125. Hunde D, Ekerstad N, Asp M, Kannisto P, Wedin M, Palmqvist C, et al. Determining the effect of frailty on survival in advanced ovarian cancer: study protocol for a prospective multicentre national cohort study (FOLERO). Acta Oncol. 2025;64:208-13.
126. SCB . Befolkningsstatistik. 2025 [cited 2025 November 7]. Available from: https://www.scb.se/hitta-statistik/statistik-efter-amne/befolkning-och-levnadsforhallanden/befolkningens-sammansattning-och-utveckling/befolkningsstatistik/pong/tabell-och-diagram/folkmangd-och-befolkningsforandringar---manad-kvartal-och-halvar/folkmangd-och-befolkningsforandringar---kvartal-2-2025/.
127. Doyle DJ, Hendrix JM, Garmon EH. American Society of Anesthesiologists Classification. StatPearls. Treasure Island (FL)2023.
128. Lawson-Michod KA, Watt MH, Grieshober L, Green SE, Karabegovic L, Derzon S, et al. Pathways to ovarian cancer diagnosis: a qualitative study. BMC Womens Health. 2022;22(1):430.
129. Goff BA, Mandel L, Muntz HG, Melancon CH. Ovarian carcinoma diagnosis. Cancer. 2000;89(10):2068-75.

130. Altman AD, Lambert P, Love AJ, Turner D, Lotocki R, Dean E, et al. Examining the Effects of Time to Diagnosis, Income, Symptoms, and Incidental Detection on Overall Survival in Epithelial Ovarian Cancer: Manitoba Ovarian Cancer Outcomes (MOCO) Study Group. Int J Gynecol Cancer. 2017;27(8):1637-44.
131. Athey RA, Macdonald MC, Jha S. Stage of ovarian cancer at diagnosis. Does presentation as an emergency make a difference? Eur J Obstet Gynecol Reprod Biol. 2021;261:7-11.
132. Nagle CM, Francis JE, Nelson AE, Zorbas H, Luxford K, de Fazio A, et al. Reducing time to diagnosis does not improve outcomes for women with symptomatic ovarian cancer: a report from the Australian Ovarian Cancer Study Group. J Clin Oncol. 2011;29(16):2253-8.
133. Lim A, Mesher D, Gentry-Maharaj A, Balogun N, Widschwendter M, Jacobs I, et al. Time to diagnosis of Type I or II invasive epithelial ovarian cancers: a multicentre observational study using patient questionnaire and primary care records. BJOG. 2016;123(6):1012-20.
134. Dilley J, Burnell M, Gentry-Maharaj A, Ryan A, Neophytou C, Apostolidou S, et al. Ovarian cancer symptoms, routes to diagnosis and survival - Population cohort study in the 'no screen' arm of the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). Gynecol Oncol. 2020;158(2):316-22.
135. Lundin ES, Johansson T, Zachrisson H, Leandersson U, Backman F, Falknas L, et al. Single-dose tranexamic acid in advanced ovarian cancer surgery reduces blood loss and transfusions: double-blind placebo-controlled randomized multicenter study. Acta Obstet Gynecol Scand. 2014;93(4):335-44.
136. Morris FJD, Fung YL, Craswell A, Chew MS. Outcomes following perioperative red blood cell transfusion in patients undergoing elective major abdominal surgery: a systematic review and meta-analysis. Br J Anaesth. 2023;131(6):1002-13.
137. Wallace SK, Halverson JW, Jankowski CJ, DeJong SR, Weaver AL, Weinhold MR, et al. Optimizing Blood Transfusion Practices Through Bundled Intervention Implementation in Patients With Gynecologic Cancer Undergoing Laparotomy. Obstet Gynecol. 2018;131(5):891-8.
138. Zhang H, Wu X, Xu Z, Sun Z, Zhu M, Chen W, et al. Impact of perioperative red blood cell transfusion on postoperative recovery and long-term outcome in patients undergoing surgery for ovarian cancer: A propensity score-matched analysis. Gynecol Oncol. 2020;156(2):439-45.
139. Bojesen RD, Eriksen JR, Vogelsang RP, Grube C, Forman JL, Gogenur I. The dynamic effects of preoperative intravenous iron in anaemic patients undergoing surgery for colorectal cancer. Colorectal Dis. 2021;23(10):2550-8.
140. Barsballe KEB, Bundgaard-Nielsen M, Ruhnau B, Hillingsoe JG, Aasvang EK, Jans O. Efficacy of a pre-operative anaemia clinic in patients undergoing elective abdominal cancer surgery. Acta Anaesthesiol Scand. 2024;68(10):1338-46.
141. Macpherson KJ, Collaborative POI. Postoperative anaemia increases unplanned readmission: an international prospective cohort study of patients undergoing major abdominal surgery. Br J Surg. 2024;111(7).

142. Ploug M, Kroijer R, Qvist N, Knudsen T. Preoperative Intravenous Iron Treatment in Colorectal Cancer: Experience From Clinical Practice. J Surg Res. 2022;277:37-43.
143. Kangaspunta M, Mäkijärvi J, Koskensalo S, Kokkola A, Arkkila P, Scheinin T, et al. Preoperative intravenous iron treatment reduces postoperative complications and postoperative anemia in preoperatively anemic patients with colon carcinoma. Int J Colorectal Dis. 2022;37(2):449-55.
144. Bisch SP, Woo L, Ljungqvist O, Nelson G. Ferric derisomaltose and Outcomes in the Recovery of Gynecologic oncology: ERAS (Enhanced Recovery After Surgery) (FORGE) - a protocol for a pilot randomised double-blinded parallel-group placebo-controlled study of the feasibility and efficacy of intravenous ferric derisomaltose to correct preoperative iron-deficiency anaemia in patients undergoing gynaecological oncology surgery. BMJ Open. 2023;13(11):e074649.
145. Liontos M, Papatheodoridi A, Andrikopoulou A, Thomakos N, Haidopoulos D, Rodolakis A, et al. Management of the Elderly Patients with High-Grade Serous Ovarian Cancer in the REAL-WORLD Setting. Curr Oncol. 2021;28(2):1143-52.
146. van Walree IC, van Soolingen NJ, Hamaker ME, Smorenburg CH, Louwers JA, van Huis-Tanja LH. Treatment decision-making in elderly women with ovarian cancer: an age-based comparison. Int J Gynecol Cancer. 2019;29(1):158-65.
147. Chereau E, Ballester M, Selle F, Rouzier R, Darai E. Ovarian cancer in the elderly: impact of surgery on morbidity and survival. Eur J Surg Oncol. 2011;37(6):537-42.
148. Klein DA, Mann AK, Freeman AH, Liao CI, Kapp DS, Chan JK. Chemotherapy alone for patients 75 years and older with epithelial ovarian cancer-is interval cytoreductive surgery still needed? Am J Obstet Gynecol. 2020;222(2):170 e1- e11.