Advanced Ovarian Cancer. A multimodal diagnostic approach to predict outcome

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LUND UNIVERSITY

DOCTORAL DISSERTATION

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Advanced Ovarian Cancer (AOC) - A multimodal diagnostic approach to predicting outcome

Primary debulking surgery (PDS) followed by platinum-based chemotherapy is the standard of care for advanced ovarian cancer (AOC). Characterization of the tumor type and its spread before initial intervention can select more effective therapeutic approaches for each patient. Histotype-specific and/or stage-dependent treatment options are needed, in combination with a patient's characteristics such as age, comorbidity, and personal or family wishes.

The overall aims of this thesis were to evaluate diagnostic tools along the diagnostic pathway, from the preoperative investigation to the intraoperative stage, and to investigate how an accurate diagnosis could predict surgical outcome and ultimate survival in patients with advanced ovarian cancer.

Study I: A retrospective population-based review was conducted of 328 biopsies on 309 patients, in order to assess the adequacy, accuracy and safety of tru-cut biopsy in gynecological malignancies from the perspective of a daily clinical practice. The tru-cut biopsy was shown to be a reliable and safe diagnostic method, with adequacy of 86.3%, accuracy of 97.5% and a complication rate of 1.3%. The adequacy of tru-cut biopsy depends on the site of the tissue sample, indications for the biopsy and the experience of the operator.

Study II: A single-center, retrospective population-based study was conducted on 358 patients, to evaluate the reliability of intraoperative frozen section(FS) diagnosis for planning the treatment of patients with suspected ovarian cancer (OC) from a multidisciplinary perspective. Prevalence, sensitivity, specificity, positive predictive value and negative predictive value for invasive malignancies on FS were 54.0%, 88.1%, 98.8%, 98.9% and 87.6% respectively. Malignancy was observed to be underestimated, but overestimation of benign or borderline tumors was rare. Borderline-related tumors were more likely to be incorrectly graded by FS. Despite diagnose difficulties in some of the cases, the intraoperative communication between specialists mostly resulted in adequate treatment decision, which reduced the risk for reoperation and secondary delay in chemotherapy.

*Studies III and IV***:** A single-center, retrospective population-based study was conducted on 118 patients with AOC, to determine whether the peritoneal cancer index (PCI) and the quantity of ascites visualized by computed tomography (CT) could assess the extent of the tumor (S-PCI) and residual disease (RD) for AOC patients treated with PDS. Furthermore, in study IV, the impact of the tumor extent on survival was examined. CT-PCI correlated well with S-PCI and the risk of RD, with a cut-off of 21 for CT-PCI (0.715, p = 0.000). The risk of RD was 3.5 times higher when the quantity of ascites on CT (CT-ascites) was estimated to be above 1000ml. Regardless of the completeness of cytoreductive surgery or the complication rate, the extent of the tumor at the beginning of surgery seemed to affect OS in patients with AOC. PCI above 18.5 doubled the risk of dying of the disease. CT-PCI seemed to play a prognostic role for PFS, but its prognostic role for OS is still to be investigated.

Conclusions: The existing diagnostic methods are reliable, with high diagnostic performance when carried out by highly trained specialists. The preoperative CT is accessible and can be used by an experienced radiologist as a single technique in selecting patients as candidates for PDS. The complete removal of the tumor is a very important prognostic factor in AOC, but patient's status and tumor biology are important factors to take into account in the decision-making on a treatment plan. This thesis sustain the idea that centralization of cancer care to tertiary centres, improve health care, and possible the outcome, in patients with AOC.

Key words: Advanced ovarian cancer, multidisciplinary, tru-cut biopsy, frozen section, peritoneal cancer index, CT, primary debulking surgery, cytoreductive surgery, survival

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To Mattias, Sara and Tomas

If we knew what it was, we were doing, it would not be called research, would it? Albert Einstein

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Thesis as a glance

Study	Title	Aim	Results	Conclusion
I	Tru-cut biopsy in gynecological cancer: adequacy, accuracy, safety and clinical applicability– a single-center experience.	The aim of this study was to assess the adequacy, accuracy and safety of the method from a daily clinical practice perspective.	Adequacy was 80.8% when performed by a gynecological oncologist and 93.5% when performed by a gynecologist with subspeciality in ultrasound diagnosis. Sampling of the pelvic masses was inferior to metastatic lesions. Accuracy was 96.9%, and the complication rate was 1.3%.	Tru-cut biopsy in gynecological cancer is a safe procedure where accuracy depends on the operator and the site of biopsy.
II	Ovarian tumor frozen section, a multidisciplinary affair	To assess the reliability of intraoperative frozen section (FS) diagnosis in patients with suspected OC from a multidisciplinary perspective. The secondary aim of this study was to investigate the clinical consequences of reclassification and multidisciplinary management of the therapy plan.	Out of a total of 358 patients, 187 were included in the FS group. Overall accuracy was 89.8%. Prevalence, sensitivity, specificity, positive predictive value and negative predictive value for invasive malignancies on FS were 54.0%, 98.8%, 98.9% and 87.6% respectively.	FS was shown to be very reliable in diagnosing invasive malignancies and benign pathology, but less so in tumors involving borderline tumors In both intraoperative decision-making and postoperative patient care, communication between the surgeon, medical oncologist and pathologist is extremely important.
III	The role of computed tomography in the assessment of tumour extent and the risk of residual disease after upfront surgery in advanced ovarian cancer (AOC)	To determine whether the peritoneal cancer index (PCI), the quantity of ascites and the presence of cardiophrenic nodes (CPLNs) visualized by computed tomography (CT) could assess the extent of the tumor (S-PCI) and residual disease (RD) in advanced ovarian cancer (AOC) patients treated with upfront surgery.	A good correlation was found between CT-PCI and S-PCI. CT-PCI was related to RD with a cut-off of 21 for CT-PCI. The quantity of ascites was positively correlated with the extent of the tumor and RD. Patients with CT-ascites>1000ml were 3.5 times more likely to have RD at the end of surgery.	CT seems to be a reliable tool for assessing the extent of the disease in advanced ovarian cancer. Large volumes of ascites and higher CT-PCI estimated on CT predicted the surgical outcome, expressed as RD of any size.
IV	Prognostic Value of Peritoneal Cancer Index After Complete Cytoreductive Surgery in Advanced Ovarian Cancer	To examine whether the extent of the tumor expressed as PCI affects progression-free survival (PFS) and overall survival (OS) in AOC patients treated with upfront surgery.	S-PCI correlated with both OS and PFS. The risk of dying from the disease was twice as high for patients exhibiting high S-PCI (≥18.5). In crude data, CT-PCI correlated with OS but this was not sustained in multivariate analyses. The presence of RD increased the risk of dying by twofold. No difference in major complications was noted between patients exhibiting S-PCI below and above 18.5.	Regardless of the completeness of cytoreductive surgery or complication rate, the extent of the tumor at the beginning of surgery seems to affect OS in patients with AOC. PCI above 18.5 doubled the risk of dying of the disease. CT-PCI seemed to play a prognostic role for PFS, but its prognostic role for OS is still to be investigated.

Original Papers

This thesis is based on the following papers which will be referred to in the text by Roman numerals. The papers appear as appendices at the end of the thesis.

I. **Asp M**, Mockute I, Malander S, Måsbäck A, Liuba K, Kannisto P. Tru-cut biopsy in gynecological cancer: adequacy, accuracy, safety and clinical applicability. Manuscript unpublished.

II. **Asp M**, Peber E, Kannisto P, Måsbäck A, Malander S. Ovarian tumor frozen section, a multidisciplinary affair. *Acta Oncologica*. Jul; 61(7):785-792

III. **Asp M**, Malander S, Wallengren N-O, Pudaric S, Bengtsson J, Sartor H, Kannisto P. The role of computed tomography in the assessment of tumor extent and the risk of residual disease after upfront surgery in advanced ovarian cancer (AOC). *Archives of Gynecology and Obstetrics*. 2022 Oct;306(4):1235-1243

IV. **Asp M**, Malander S, Bengtsson J, Sartor H, Kannisto P. Prognostic Value of Peritoneal Cancer Index After Complete Cytoreductive Surgery in Advanced Ovarian Cancer 2022 may 1, I: *Anticancer research*. 2022 May; 42(5):2541-2551

Populärvetenskaplig sammanfattning

Globalt sett är äggstockscancer den sjunde vanligaste cancerformen hos kvinnor. Ca 313 000 kvinnor insjuknar årligen, varav drygt 207 000 dör till följd av sin sjukdom. I Sverige insjuknar årligen cirka 700 kvinnor.

Sjukdomen ger vaga symtom . Över 70 % av fallen upptäcks därför i avancerade stadier, det vill säga när cancern har spridit sig in i bukhålan.

Behandlingen är i första hand kirurgisk. Äggstockar, äggledare, livmoder och tarmkäx, samt så mycket som möjligt av tumören avlägsnas. I avancerade stadier så behöver kompletterande behandling med cellhämmande läkemedel (kemoterapi) ges utöver den kirurgiska. 5-års överlevnaden för hela patientgruppen (alla stadier) ligger strax under 50%.

Radikal kirurgi innebär att all synlig tumör avlägsnas och är det bästa för patientens möjlighet att överleva sin sjukdom. I vissa fall, där patienten har stor tumörbörda, så måste man börja med cellhämmande behandling och operera efter att behandlingen har krympt tumörbördan. Man kallar tekniken för fördröjd primärkirurgi eller intervallkirurgi. Bedömningen avseende vilken typ av behandlingsstrategi man skall välja görs multidisciplinärt, dvs läkare från flera olika discipliner (radiologi, patologi, gynekologi, gynekologisk onkologi gör en sammanvägd bedömning av patientens allmäntillstånd och tumörresektabilitet, d.v.s. möjligheten att kunna ta bort all synlig tumör. Resektabiliteten är beroende av hur stor tumörbördan är samt var tumörerna sitter. Tumörspridningen i bukhålan bedöms preoperativt med hjälp av datortomografi och klinisk undersökning samt kirurgiskt, dvs under själva operationen.

När man bedömer att patientens allmäntillstånd inte tillåter en extensiv kirurgi eller att tumören är så pass spridd att en radikal kirurgi är svårt att uppnå, så är patienten kandidat till preoperativ kemoterapi följt av intervallkirurgi. Innan uppstart av kemoterapi så behövs ett vävnadsprov från patientens tumör, för att kunna bekräfta eller förkasta den misstänkta diagnosen, så att rätt beslut tas avseende val av kemoterapi. Vid primärkirurgi, finns det möjlighet för att få vävnadsprov under själva operationen. En av målsättningarna i avhandlingen var att undersöka om det preoperativa och intraoperativa vävnadsprovet är pålitligt och om behandlingen kan planeras baserat på provet.

Ytterligare en målsättning var att undersöka hur tillförlitlig datortomografi är för att utvärdera tumörspridning och förutse om radikal kirurgi är möjlig att genomföra samt värdera patienternas överlevnad och om det finns skillnader i överlevnad med patienter som har mycket tumör.

Studie I analyserar om det preoperativa vävnadsprovet är pålitligt och säkert för patienten. Hos patienter som på grund av nedsatt allmäntillstånd, eller spridd sjukdom, inte kan genomgå primär kirurgi, är kemoterapi den första behandlingen. Diagnosen behöver bekräftas med vävnadsprov innan uppstart av behandling. Även i fall där kirurgi är möjlig som första behandling men tumörursprunget inte är känt, så behövs ett

vävnadsprov. Detta prov tas med hjälp av mellannålsbiopsi. Säkerheten och pålitligheten i gynekologisk cancer är sparsamt utredd.

Studien kunde påvisa en hög tillförlitlighet när biopsitagningen utfördes av specialiserade läkare, med stor erfarenhet.

Studie II undersökte om det intraoperativa vävnadsprovet är tillräckligt pålitligt för att hjälpa kirurgen att fatta beslut om kirurgins omfattning under tiden som patienten opereras samt om onkologisk behandling kan startas baserat på det intraoperativa vävnadsprovet. 385 patienter ingick i studien. Studien kunde påvisa god pålitlighet avseende urskiljning av elakartade från godartade tumörer. Ovanliga tumörer kan ställa till svårigheter för diagnosen. Studien undersökte även om kommunikation och samarbete mellan olika läkarspecialiteter skulle kunna minska risken för att patienten blir överbehandlad eller underbehandlad i de svåra fallen.

Studie III undersökte tumörbördan inför kirurgi med hjälp av datortomografi, beräknad med en slags numerisk skala som kallas för peritonealt cancer index (PCI), därefter jämfördes den med den intraoperativa beskrivningen av PCI. Studien inkluderade 118 patienter som hade genomgått primär kirurgi för avancerad äggstockscancer. Ett flertal olika parametrar bedömdes: CT-PCI, ascites (frivätska i bukhåla), tumör markörer och lymfkörtlar. Resultaten visade att den preoperativa PCI-bedömningen av tumörspridningen stämde väl överens med den intraoperativa PCI-bedömningen. Datortomografi är en pålitlig undersökningsmetod i den preoperativa bedömningen av vilka patienter som kan opereras primärt.

Studie IV undersökte om den primära tumörbördan kan påverka överlevnaden trots radikal kirurgi, och om en faktor som stor kirurgi med konsekutiva komplikationer kan bidra till en försämrad överlevnad. Samma patientgrupp som i studie III följdes upp och analyserades. Resultatet visade att patienter med kvarvarande tumör efter kirurgi hade sämre överlevnad. Dessutom så påvisade studien att patienter med högt PCI hade, trots radikal kirurgi, dubbelt så stor risk att dö i sin sjukdom.

Sumar pe românește

Cancerul ovarian este la nivel global, a şaptea formă de cancer la femei şi a opta cauză de deces cauzat de cancer. În fiecare an, 313 000 de femei se îmbolnavesc şi aproximativ 207 000 femei mor ca urmare a cancerului ovarian. În Suedia, circa 696 femei suferă de această formă de cancer, ceea ce reprezintă aproximativ 3 % din cancerul la femei. În Romania,1909 femei se îmbolnavesc şi aproximativ 1121 decedează ca urmare a cancerului ovarian în fiecare an.

Cancerul ovarian este deobicei detectat în forme avansate, mai mult de 70 % din cazuri sunt diagnosticate după ce boala s-a răspândit în toată cavitatea abdominală sau/şi torax, ceea ce defineşte cancerul ovarian avansat, stadium III şi IV.

Tratamentul cancerului ovarian este chirurgical în stadii incipiente. În stadii avansate tratamentul standard al cancerului ovarian este chirurgical urmat de chimioterapie adjuvantă. Scopul chirurgiei este de a înlatura toate focarele tumorale vizibile, ceea ce se numeşte chirurgie radicală. Radicalitatea chirurgicală, definită ca zero tumori residuale, este cel mai puternic factor prognostic pt supravieţuire.

In anumite cazuri, când starea de sănătate a pacientei nu permite sau extinderea tumorală este prea amblă, se apelează la chimioterapie preoperatorie, în scopul de a câstiga timp pentru rehabilitarea preoperatorie a pacientei sau/şi pentru a micşora cantitatea tumorală, si a face posibilă intervenţia chirurgicală secundară.

Alegerea pacientelor care pot fi candidate pentru chirurgie primară sau pentru chimioterapie primară urmată de chirurgie secundară, este o decizie dificilă, care este luată in cadrul conferinţelor multidisciplinare săptămânale. Conferinţele sunt compuse din specialişti oncologi, radiologi, patologi şi ginecologi cu subspecialitate in chirurgia tumorală ginecologică. Chirurgia cancerului avansat ovarian, este o chirurgie extensivă cu multe riscuri, motiv pentru care pacienta trebuie să aibă o stare generală care permite o astfel de intervenţie. Dacă starea de sănatate a pacientei permite o astfel de intervenţie, se apreciază mai apoi, dacă cancerul poate fi extirpat in totalitate.

Această lucrare se focusează pe diagnosticul cancerului avansat ovarian şi inbunataţirea metodelor şi instrumentelor diagnostice folosite in selecţia tratamentului, individualizat pentru fiecare caz în parte. Diagnosticul cancerului ovarian avansat implică un diagnostic histopatlogic şi unul imagistic.

Prima parte a acestei lucrari se focusează pe diagnosticul histopatologic al cancerului ovarian avansat. În cazurile în care diagnosticul este neclar în ceea ce priveşte originea tumorii sau în cazurile inoperabile, este nevoie de o probă de ţesut tumoral pentru analiza histopatologică. Această probă se face cu ajutorul biopsiei cu ac gros sau tru-cut biopsy. În prima lucrare am analizat peste 300 cazuri de biopsii cu ac gros, in vederea aprecierii credibilitaţii si siguranţei acestei metode.

Rezultatele arată ca această metodă poate fi folosită cu incredere dacă este facută si analizată de specialisti cu competenţa in domeniu.

Diagnosticul histopatologic poate fi realizat şi intraoperativ, ceea ce se numeşte exament histopatologic extemporaneu. Acest tip de diagnostic se foloseşte în cazurile fară diagnostic histopatologic preoperativ, cu scopul de a adapta intervenţia chirurgicală la tipul de tumoare. Această examinare este de mare folos în cazurile incipiente, dictand extensivitatea intervenţiei chirurgicale, dar şi in cazurile de cancer avansat, dând posibilitatea informarii şi planificarii rapide a chimioterapiei postoperatorii. Rezultatele arată că examenul extemporaneu are o capacitate foarte bună de diagnosticare a tumorilor maligne, şi mici neajunsuri in diagosticarea tumorilor borderline (o forma neinvaziva a cancerului ovarian).

In adoua parte a acestei lucrari, ne-am focusat pe a investiga dacă metodele convenţionale de diagnostic a extinderii tumorale sunt suficient de bune pentru a alege pacientele candidate pentru chirurgie primară. Computer tomograful (CT) este folosit ca rutină în Suedia, pentru a face aceste estimari. Cantitatea de tumori, numite carcinomatoza, in cavitatea abdominală, se estimează cu ajutorul unui idex numit index de carcinoză peritoneală (PCI), care sumează carcinomatoza în diferite regiuni ale abdomenului. In a treia lucrare am comparat parametrii masuraţi pe computer-tomograful făcut preoperativ cu aceiaşi parametri masuraţi intraoperativ. Rezultatele arată că CT-ul e un instrument capabil să aprecieze extinderea tumorală şi să predicteze dacă chirurgia va fi radicală sau nu. Aceste rezultate sunt de mare valoare pentru clinicieni în procesul decizional. În a patra lucrare, am pornit de la date cunoscute, şi anume că supravieţuirea este mult mai buna în cazul pacientelor operate radical. Am vrut să investigăm dacă, deşi rezultatul chirurgical e acelaşi, adică radicalitate completă, fară tumori reziduale vizibile, cantitatea de carcinomatoza la începutul intervenţiei chirurgicale afectează supravieţuirea pacientelor cu cancer ovarian avansat. Rezultatele arată ca deşi pacientele au fost operate radical, pacientele care iniţial au avut carcinomatoză mult mai extinsă, au o supravieţuire de doua ori mai scazută. Aceast rezultat este înca o dovadă că biologia tumorală e importantă, indifferent de efortul chirurgical.

Credem că rezultatele studiilor noastre au o mare aplicabilitate clinica si ştiintifica, stând la baza altor studii asemanatoare, in scopul de a inbunataţi diagnosticul cancerului ovarian. Un diagnostic cat mai correct al tipului şi stadiului cancerului ovarian, rezultă în alegerea unui tratament adecvat, şi prin urmare o inbunataţire a prognosticului acestei boli.

Abstract

Background:

Around 700 patients are diagnosed with epithelial ovarian cancer (EOC) in Sweden each year, making OC the eighth most common female cancer. Due to the late-stage at first diagnose, the prognosis of EOC is poor, with a five-year survival rate of 49%. Primary debulking surgery (PDS) followed by platinum-based postoperative chemotherapy is the standard of care for advanced ovarian cancer (AOC). In cases where surgery is not primarily possible, patients receive neoadjuvant chemotherapy followed by interval debulking surgery (IDS). Also the extent of surgery depends on the histopathological type and spread of the tumor. In cases where PDS is not the primary therapeutic choice, it is necessary to characterize the type of tumor in order to develop a plan for chemotherapy. The extent of the abdominal tumor must be well characterized preoperatively in order to plan surgery effectively and achieve maximal radicality. One way of characterizing the extent of the tumor involves the surgeon quantifying it numerically in the peritoneal cavity, using what is known as the peritoneal cancer index (PCI). The full therapy plan is a complex process involving a multidisciplinary approach which includes oncologists, radiologists, pathologists and gynecologists. The centralization of cancer care to tertiary centers has resulted in highly specialized pathology, radiology, oncology and surgical departments, and has improved outcomes and survival rates.

The overall aim of this thesis was to analyze preoperative and perioperative methods of diagnosis from a multidisciplinary perspective, in order to improve the therapy plan which is crucial for patient's with AOC

Aims of the studies

Study I: To assess the adequacy, accuracy and safety of tru-cut biopsy in diagnosing gynecological cancer.

Study II: To assess the reliability of intraoperative frozen section (FS) diagnosis in patients with suspected OC from a multidisciplinary perspective. The secondary aim of this study was to investigate the clinical consequences of reclassification and multidisciplinary management of the therapy plan.

Study III: To determine whether the peritoneal cancer index (PCI), the quantity of ascites and the presence of cardiophrenic nodes (CPLNs) visualized by CT could assess the extent of the tumor (S-PCI) and residual disease (RD) in advanced ovarian cancer (AOC) patients treated with upfront surgery.

Study IV: To examine whether the extent of the tumor, expressed as PCI, affects progression-free survival (PFS) and overall survival (OS) in AOC patients treated with upfront surgery.

Materials and methods

Study I: A retrospective population-based review was conducted of 328 biopsies performed on 309 patients. The main indications for tru-cut biopsies were diagnosis of new tumors, metastatic disease in non-gynecological tumors and suspected recurrences.

Study II: A single-center, retrospective population-based study of 358 patients who had undergone surgery for suspected OC between 2018 and 2020. Histopathological outcomes were classified as benign, borderline or malignant. The final histopathology report was the gold standard, and FS diagnosis was carried out through as the diagnostic test.

Study III: A study of 118 AOC patients treated for AOC between January 2016 and December 2018 at Skåne University Hospital, Lund, Sweden. The relationship between CT-PCI and S-PCI was analyzed. The patients were stratified by complete cytoreductive surgery (CCS) with no RD or non-CCS with RD of any magnitude. The quantity of ascites on CT (CT-ascites), CA-125 and the presence of radiologically enlarged CPLNs (CT-CPLN) were analyzed for their impact on estimating RD.

Study IV: The same study population as in Study III was subjected to survival analyses. The following clinicopathological characteristics were analyzed: age, ECOG score, International Federation of Gynecology and Obstetrics (FIGO) stage, CA-125, RD, preoperative imaging (CT-PCI) and macroscopic visualization at the start of surgery (S-PCI). Complications were analyzed using Clavien-Dindo classification, and their effect on survival was investigated using Cox regression, Kaplan-Meier and receiver operating curves (ROC).

Results and conclusion

Study I: In total, 300 biopsies were identified as tru-cut. The overall adequacy was 86.3%, varying between 80.8% and 93.5% when performed by a gynecological oncologist or a gynecologist with a subspecialty in ultrasound diagnosis respectively. Sampling of a pelvic mass had lower adequacy (81.6%) than sampling of omentum (93.9%) or carcinomatosis (91.5%). Overall accuracy was 98.1%, and the complication rate was 1.3%.

- Tru-cut biopsy in gynecological cancer is a safe diagnostic procedure, where adequacy depends on the operator, indication and the site of biopsy.

Study II: Out of a total of 358 patients, 187 were included in the FS group. Overall accuracy was 89.8%. Prevalence, sensitivity, specificity, positive predictive value and negative predictive value for invasive malignancies on FS were 54.0%, 88.1%, 98.8%, 98.9% and 87.6% respectively. Borderline-related tumors and rare tumor types, were more likely to be incorrectly graded by FS.

- FS is a reliable method for helping to ensure appropriate surgery and for planning oncological treatment planning. FS was shown to be extremely reliable in diagnosing invasive malignancies and benign pathology. For both intraoperative decision-making and postoperative patient care, communication between the surgeon, medical oncologist and pathologist was extremely important.

Study III: We found a good correlation between CT-PCI and S-PCI (0.397; 95% CI 0.252-0.541; $p < 0.001$). The quantity of ascites was positively correlated with the extent of the tumor in both the crude and adjusted data (for ascites volume > 1000ml: 4.390 (95% CI 1.027–7.753) $p < 0.038$). CT-PCI was related to RD (OR 1.069 (1.009-1.131), $p < 0.023$) with a cut-off of 21 for CT-PCI (0.715, $p = 0.00$). RD was predicted preoperatively by CT-ascites above 1000ml (OR 3.510 (1.298-9.491) $p < 0.013$).

- CT seems to be a reliable tool for assessing the extent of the disease in advanced ovarian cancer. Large volumes of ascites and higher CT-PCI estimated on CT, predicted the surgical outcome, expressed as RD of any magnitude.

Study IV: S-PCI correlated with both OS (1.067, (1.018-1.119); $p<0.007$) and PFS. The risk of dying of the disease was twice as high for patients exhibiting high S-PCI (≥18.5), adjusted for age, performance status and RD (HR=2.070, 95%CI=1.061-4.038; $p=0.033$), as for those with a lower PCI score (<18.5). In crude data, CT-PCI correlated with OS (1.037, 95%CI=1.005-1.071, $p=0.025$), but this was not sustained in multivariate analyses. The presence of RD of any magnitude at the end of surgery increased the risk of dying by twofold (2.177, 95% CI=1.235-3.838, $p=0.007$). No difference in major complications was noted between the patients exhibiting S-PCI below and above 18.5.

- Regardless of the completeness of cytoreductive surgery or the complication rate, the extent of the tumor at the beginning of surgery seemed to affect OS in patients with AOC. PCI above 18.5 doubled the risk of dying of the disease. CT-PCI seemed to play a prognostic role for PFS, but its prognostic role for OS is still to be investigated.

List of abbreviations

AOC	Advanced Ovarian Cancer
ASR	Age-standardized incidence rate
AUC	Area under the curve
BOT	Borderline tumors
CCC	Clear cell cancer
CCS	Complete Cytoreductive surgery
CD	Clavien-Dindo classification
CNS	Central nervous system
CPLN	Cardiophrenic lymph nodes
CT	Computed tomography
CT-PCI	Computed tomography peritoneal cancer index
DFS	Disease free survival
ECOG	Eastern Cooperative Oncology Group
EOC	Epithelial ovarian cancer
FIGO	International Federation of Gynecology and Obstetrics
FS	Frozen section
HBOC	Hereditary breast and ovarian cancer
HE4	Human epididymis hormone
HDI	Human development index
HGSC	High-grade serous cancer
HR	Hazard ratio
HRD	Homologous recombination defect
HRT	Hormonal replacement therapy
LGSC	Low-grade serous cancer
LR	Likelihood ratio
IDS	Interval debulking surgery
MC	Mucinous cancer
MHT	Menopausal hormonal therapy
NACT	Neoadjuvant chemotherapy
OS	Overall survival
PARP	Poly (ADP-ribose) polymerase
PCI	Peritoneal cancer index
PDS	Primary debulking surgery
PFS	Progression-free survival
PPV	Positive predictive value
RD	Residual disease
SCS	Surgery complexity score
S-PCI	Surgical peritoneal cancer index
STIC	Serous tubal intraepithelial carcinoma
WHO	World Health Organization

Introduction

Epithelial ovarian cancer (EOC) has the highest mortality rate of any gynecological malignancy, with a five-year survival rate below 45% (Jessmon et al. 2017; Dahm-Kähler et al. 2017). More than 70% of OC cases are diagnosed in the advanced stages, with carcinomatosis in the abdominal cavity (Siegel et al. 2015). PDS followed by adjuvant chemotherapy is the standard of care for EOC (Piver 2006). Since CCS with no residual disease is the strongest prognostic factor, the characteristics and extent of the tumor must be well described both preoperatively and intraoperatively, in order to achieve the best surgical result.

The characteristics of the tumor are visualized through ultrasound and defined histopathologically. The histopathological diagnosis can be made preoperatively by tru-cut biopsy and perioperatively by frozen section. The extent of the tumor can be quantified numerically using the PCI (Peritoneal Cancer Index). This can be carried out preoperatively on the CT scan (CT-PCI) or by the surgeon, using surgical PCI (S-PCI) (Sugarbaker, 1995, Sugarbaker, 1999 #2017).

In Sweden, the treatment plan for patients with Advanced Ovarian Cancer (AOC) is conducted in accordance with national guidelines and discussed in a multidisciplinary team composed of surgeons, medical oncologists, pathologists, radiologists and ultrasound specialists.

This thesis focused on evaluating the extent of the tumor preoperatively, where CT was used to select patients as candidates for upfront surgery. In addition, we analyzed the prognostic factor of the extent of the tumor on survival. Furthermore, the accuracy and adequacy of histopathological diagnosis methods were investigated, as well as their applicability to daily clinical practice.

Background

Advanced Ovarian Cancer

Epidemiology and etiology

Ovarian cancer is the seventh most common cancer in women and the eighth most common cause of cancer deaths worldwide (Webb and Jordan 2017). More than 314,000 new cases of ovarian cancer and 207,000 deaths occurred in 2020 (International 2021). There are geographic variations in incidence rates. European countries with a very high human development index (HDI) have the highest rates, while low rates were found in African countries with a lower HDI. Comparable mortality rates were observed across the four-tier HDI. The age-standardized incidence rate (ASR) is declining in North America and Northern Europe, while in other parts of the world the incidence is increasing. Estimations for 2040 indicate approximately 100% increase in new ovarian cancer cases and deaths in low-HDI countries, compared to 20% to 30% in very high HDI countries (Cabasag et al. 2022a).

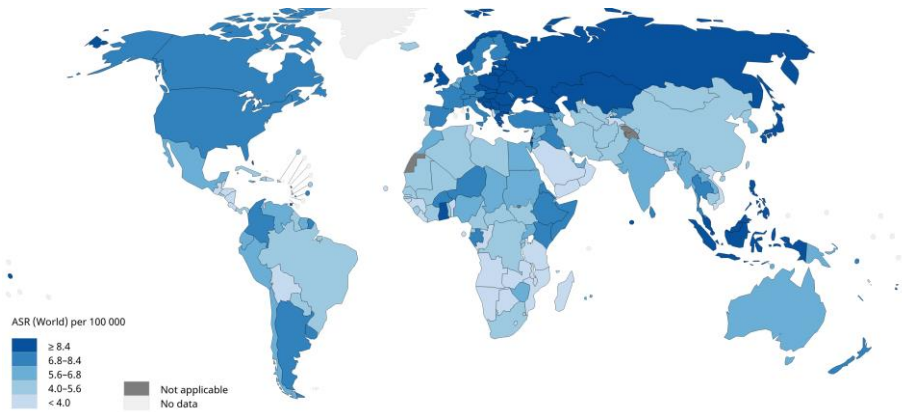

Figure 1. Estimated age-standardized incidence rates (worldwide) in 2020 for ovarian cancer in females of all ages. Data source: GLOBOCAN 2020. Graph production: IARC (http://larc.fr/today) World Health Organization

Risk and protective factors

EOC has a hereditary background in 15% to 25% of cases. The most common mutation involves the *BRCA1* and *BRCA2* tumor-suppressor genes which characterize hereditary breast and ovarian cancers (HBOC) (Hodgson and Turashvili 2020). Mutations in a variety of other genes characterizes other hereditary ovarian cancers such as Lynch syndrome (mismatch repair genes), Li-Fraumeni syndrome (*TP53*), *STK11* in Peutz-Jeghers syndrome (*STK1*1) and mutations in *CHEK2, RAD51, BRIP1 and PALB2* (Pietragalla et al. 2020).

Early menarche and late menopause are described as risk factors for OC (Pelucchi et al. 2007). The risk of OC increases with the number of periods of menstruation in life, suggesting that ovulation is involved in ovarian carcinogenesis. Repetitive trauma to the ovarian surface epithelium, and exposure to follicular liquid, rich in estrogen, contribute to neoplasia-inducing theory (Townsend et al. 2021). Parity has also been described as a risk factor, due to a consistent inverse relation between parity and OC (La Vecchia 2017). However, a more recent study investigating the impact of reproductive history on ovarian cancer prognosis, noted a reduction of cancer-specific mortality among parous women diagnosed with germ cell tumors, but found no association between parity and survival in epithelial ovarian cancer was found (Sköld et al. 2022).

Endometriosis is described as a risk factor for clear cell and endometrioid cancers (Králíčková et al. 2020; Kvaskoff et al. 2021). Pelvic inflammatory disease, use of menopausal hormonal therapy (MHT), infertility and the use of assisted reproductive methods are also described as risk factors (Liu et al. 2019; Paavonen et al. 2021; Spaan et al. 2021). In terms of women treated for infertility, the risk is slightly higher in nulliparous women than in multiparous ones, and seems to be higher for borderline ovarian tumors (Rizzuto et al. 2019).

Lifestyle has an impact on OC risk, and obesity is related to borderline tumors, as well as invasive endometrioid and mucinous cancer. Obesity does not increase the risk of HGSC, and it is therefore highly unlikely that reducing BMI will lead to decreased mortality from OC (Olsen et al. 2013). Smoking has been associated with an increased risk of mucinous cancer and a decreased risk of clear cell and endometrioid cancers (31). There is no evidence of any association between alcohol consumption and OC (31). Although lifestyle seems to play a modest role as a risk factor, it may improve survival rates in ovarian cancer patients along with physical activity and nutrition (El-Sherif et al. 2021).

Breast feeding and contraceptives have been described as protective factors, and a reduction in risk is correlated with duration of breastfeeding and the length of time contraceptives are used (Bosetti et al. 2002). The use of contraceptives could be

controversial in BRCA mutation carriers due to their protective role in OC, but could carry an increased risk of breast cancer (Huber et al. 2020).

Symptoms and diagnosis

The symptomatology of ovarian cancers is mainly diffuse and unspecific, such as abdominal swelling, diffuse pain, indigestion, alteration in bowel habits, non-specific urinary symptoms, and fatigue. These are often wrongly attributed to benign causes such as menstruation, menopause, stress and irritable bowel syndrome. All this contributes to late diagnoses (Goff et al. 2004). Many screening methods have been and continue to be investigated, but at this point, screening of the general population at average risk has shown a minimal impact on mortality and is not recommended. False-positive results are a significant issue with present technology, and more research is required before a screening strategy can be recommended (Gupta et al. 2019).

Due to the lack of effective screening methods, consistent efforts are made to improve the initial care of patients with suspected ovarian cancer. In 2015, a standardized ovarian cancer care pathway was initiated in Sweden, facilitating a fast-track procedure from primary care to gynecologist (within 10 days) for patients with suspected OC. If the suspicion is sustained, patients are referred to a tertiary ovarian cancer care center. The lead time to surgical treatment or oncological treatment is 24 days and 22 days respectively. CA-125 and ultrasound of the pelvis and abdomen are included in the diagnostic strategy. A Risk of Malignancy Index (RMI) is calculated, based on ultrasound, CA-125 and menopause status (Jacobs et al. 1990). The need for ultrasound makes it difficult to use the RMI algorithm in primary care.

The risk of ovarian malignancy algorithm (ROMA) was introduced in 2009, and includes CA125, HE 4 and menopause status. The absence of ultrasound makes it possible to use the algorithm in primary care (Moore et al. 2009).

Diagnostic imaging

Ultrasound

Transvaginal ultrasound examination is the standard first-line imaging form of investigation for assessing adnexal pathology. To homogenize and standardize quality evaluation of ultrasonography, a consensus on terminology and definition was presented by the International Ovarian Tumors Analysis (IOTA) group in 2000 (Timmerman et al. 2000). Besides the describing of the tumors characteristics, ultrasound has begun to be used in assessing the pelvic and abdominal spread of AOC cancer (Weinberger et al. 2016; Fischerova et al. 2017).

Computed tomography (CT)

CT is the most common diagnostic tool used in routine clinical practice for assessing the extent of spread of the tumor in the abdominal cavity and its dissemination outside the abdomen (Sahdev 2016). CT scans have the advantage of being easily accessible. They are effective in terms of time and yield high-quality images. However, disadvantages include the need for exposure to radiation. The use of contrast could also be considered a disadvantage, especially in patients with impaired kidney function (Caraiani et al. 2019).

Magnetic resonance images (MRI)

MRIs have the advantage of being able to assess both morphological and functional characteristics of tumors, differentiating between benign, borderline and malign tumors, and absence of ionizing radiation (Medeiros et al. 2011). Several reports suggest that, in combination with CT, they can assess the presence of peritoneal carcinomatosis accurately, especially when performed by an experienced radiologist (Dohan et al. 2017). MRI has the disadvantage of being susceptible to various artifacts such as high exanimated volume, which can affect the quality of the image and reduced accessibility.

Positron emission tomography-computed tomography (PET/CT)

PET-CT may be useful in differentiating borderline and benign tumors from malignant tumors, but it can be false negative due to the lower fluorodeoxyglucose uptake in clear cell and mucinous invasive subtypes (Tanizaki et al. 2014). PET/CT can play a role in diagnosing lymph-node metastases. However, its role in appreciating peritoneal carcinomatosis may be limited, especially on the bowel and mesenteric serosa, as it has a resolution limit of 4mm, corresponding to detection of tumors with a volume of 0.2ml (7mm diameter) (Erdi 2012).

Positron emission tomography-magnetic resonance imaging (PET/MRI)

Fused PET/MRI is a combination of MRI and PET in a single scanner. This method has the advantage of combining morphological information from the CT/PET with functional information with diffusion-weighted imaging (DWI) on MRI (Rosenkrantz et al. 2016). A recently published study suggests that FDG PET/MRI could be superior to DW-MRI in terms of estimating the total spread of carcinomatosis in gynecological cancer (Jónsdóttir et al. 2021). The greatest disadvantage of the method is its accessibility, as most cancer centers do not have access to PET/MRI.

Histopathology and Staging

Ovarian cancer is a heterogeneous disease involving different types of tumor with a variety of clinicopathological features and behavior. It is categorized as epithelial ovarian cancer (EOC), accounting for about 90% of all cases, and non-epithelial cancer (germ cells and sex cord-stromal tumors), which constitutes the remaining 10% (Webb and Jordan 2017). This thesis focuses mainly on EOC.

Epithelial ovarian carcinoma

EOC is classified into two groups, type I and type II. These progress along two different tumorigenic pathways (Kurman and Shih Ie 2016).

Table 1. Features of the five major subtypes of EOC (SC: serous carcinoma, MC: mucinous carcinoma, EC: endometroid carcinoma, CCC:clear cell carcinoma, STIC: serous tumal intraephithelial neoplasia, ER: estrogen receptor, PR: progesteron receptor) (Kurman and Shih Ie 2016; Kossaï et al. 2018)

	Low-grade SC	**High-grade SC**	**MC**	**EC**	**CCC**
Frequency	<5%	70%	2-3%	10%	5-10%
Origin	Low-grade malignant potential lesion	STIC	Borderline mucinous lesion	Endometriosis	Endometriosis
Immuno-phenotype	CK+, WT1+, ER+	CK+, CK20, PAX8+, WT1+	CK+, CK20-, ER-, PR-, WT1-	CK+, PAX8+, CK20-, WT1-	NapsinA+, WT-, p53-, ER-
Molecular abnormalities	KRAS, BRAF	TP53, BRCA1/2	KRAS, HER 2	ARID1A, PTEN	ARID1A, PIK3CA
Prognosis	intermediate	poor	good	favorable	intermediate

Type I EOC includes low-grade serous carcinoma (LGSC), mucinous carcinoma (MC), endometrioid carcinoma (EC) and clear cell cancer (CCC). These are considered to be well-differentiated tumors of a low-grade type. Especially LGS and MC are thought to arise from borderline tumors, which will be addressed as borderline-related tumors in this paper. EC and CCC can emerge from endometriosis, which will be addressed in this paper as endometriosis-related tumors (Wiegand et al. 2010; Kobayashi et al. 2009). These tumors exhibit somatic mutations of *KRAS*, *BRAF*, *ERBB2*, *PTEN*, *PIK3CA*, *ARID1A* and *CTNNB1*, and in the DNA mismatch repair (MMR) genes, and mainly lack *TP53* mutations. They are slow-growing and genetically stable, and are often diagnosed at an early stage, generally with good prognosis. The prognosis of type I has been described as heterogenic, and MC and CCC have a worse outcome than the other subtypes in the group, especially in association with higher stages. However, in advanced stages, the prognosis is poor, and comparable to type II EOC (Braicu et al. 2011).

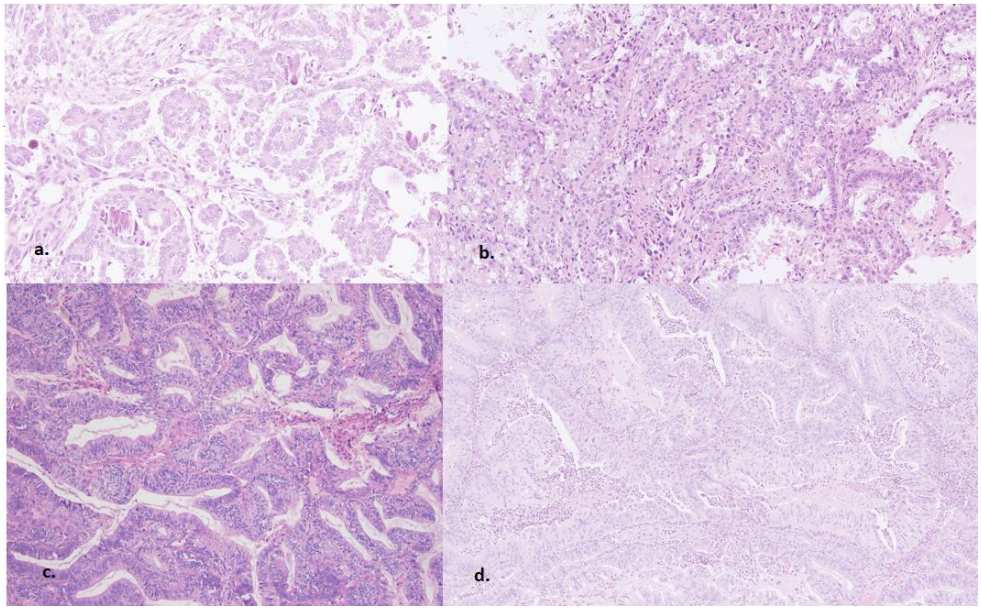

Figure 2. Histopathology type I EOC: a) Low-grade serous ovarian carcinoma, b) Clear cell ovarian carcinoma, c) Endometrioid ovarian carcinoma, d) Mucinous ovarian carcinoma (©Anna Måsbäck 2022)

Type II EOC includes high-grade serous cancer (HGSC), undifferentiated carcinoma and carcinosarcoma. These tumors evolve from serous tubal intraepithelial neoplasia (STIC), and spread rapidly to the ovary and peritoneum. They are diagnosed in the late stages and have a poor prognosis (Medeiros et al. 2006; Kindelberger et al. 2007; van der Ploeg et al. 2022). Type II EOC has high chromosomal instability, showing frequent/recurrent mutations in specific oncogenes such as mutation of *TP53*, which is pathognomonic. It is common with homologous recombination defects such as *BRCA* 1/2 (Vang et al. 2009; Kurman and Shih Ie 2016).

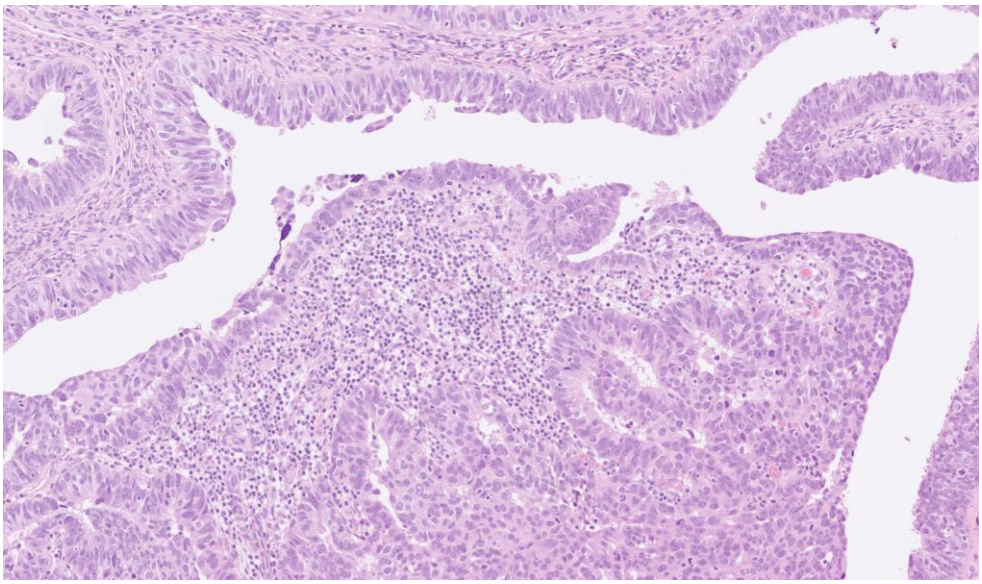

Figure 3. Histopathology type II EOC: High-grade serous ovarian carcinoma (©Anna Måsbäck 2022)

Non-epithelial ovarian cancer

These tumors represent 10-15% of all ovarian cancers. They include a variety of tumors of sex cord-stromal cell and germ-cell origin, as well as extremely rare types of ovarian cancer of mesenchymal origin (Boussios et al. 2016). Usually, non-epithelial ovarian cancer is found at an early age, in some cases with an aggressive, rapidly evolving pattern.

When the ovarian cancer diagnosis is settled, the majority of patients are in advanced stages (III and IV according to the advanced Federation of Gynecology and Obstetrics (FIGO) classification system) (Prat 2014).

Table 2. FIGO classification system (Prat 2014)

Stage I: Tumor confined to ovaries or fallopian tube(s) T1-N0-M0
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 T1a-N0-M0
IB: Tumor limited to both ovaries (capsules intact) or fallopian tubes; no tumor on ovarian or fallopian tube surface; no malignant cells in the ascites or peritoneal washing T1b-N0-M0
IC: Tumor limited to one or both ovaries or fallopian tubes, with any of the following:
IC1: Surgical spill T1c1-N0-M0
IC2: Capsule ruptured before surgery or tumor on ovarian or fallopian tube surface T1c2-N0-M0
IC3: Malignant cells in the ascites or peritoneal washings T1c3-N0-M0
Stage II: Tumor involves 1 or both ovaries or fallopian tubes with pelvic extension (below pelvic brim) or primary peritoneal cancer T2-N0-M0
IIA: Extension and/or implants on uterus and/or fallopian tubes and/or ovaries T2a-N0-M0
IIB: Extension to other pelvic intraperitoneal tissues T2b-N0-M0
Stage III: Tumor involves 1 or both ovaries or fallopian tubes, or primary peritoneal cancer, with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes T1/T2-N1-M0
IIIA1: Positive retroperitoneal lymph nodes only (cytologically or histologically proven):
IIIA1(i) Metastasis up to 10mm in greatest dimension
IIIA1(ii) Metastasis more than 10mm in greatest dimension
IIIA2: Microscopic extrapelvic (above the pelvic brim) peritoneal involvement with or without positive retroperitoneal lymph nodes T3a2-N0/N1-M0
IIIB: Macroscopic peritoneal metastasis beyond the pelvis up to 2cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes T3b-N0/N1-M0
IIIC: Macroscopic peritoneal metastasis beyond the pelvis more than 2cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes (includes extension of tumor to capsule of liver and spleen without parenchymal involvement of either organ) T3c-N0/N1-M0
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 the abdominal cavity) Any T, any N, M1

Histopathological Diagnosis

True-cut Biopsy

In cases where the histology of the tumor is uncertain (recurrence, metastasis, non-genital origin), or in cases where primary surgery is not possible due to poor performance status of the patient or extensive spreading of the tumor, it is necessary to obtain a tissue sample prior to planning treatment (Timmerman et al. 2021b). A number of methods can be used for this, such as fine-needle aspiration, tru-cut biopsy and laparoscopy.

The fine-needle aspiration technique is mini-invasive, but produces a cytological rather than histological evaluation (Malmström 1997). A laparoscopy is relatively mini-invasive, but requires general anesthesia which might be problematic in patients with poor performance status and extensive comorbidity (Fagotti et al. 2008; Vizzielli et al. 2014). On the other hand, a tru-cut biopsy provides samples with preserved tissue architecture, allowing comprehensive histological evaluation including immunohistochemistry, without the need for general anesthesia (Fischerova et al. 2008).

Ultrasound-guided sampling methods, which are flexible in terms of whether a transabdominal, transvaginal or transrectal approach is used, are accessible and of low cost compared to guidance by computed tomography (CT) or magnetic resonance (MR) guidance (Chojniak et al. 2006; Matsui et al. 2019).

Tru-cut biopsy is a highly sensitive method, with accuracy ranging from 76% to 99%, and a low complication rate involving mainly minor complications, varying between 1.1% and 4.8% (Zikan et al. 2010; Verschuere et al. 2021).

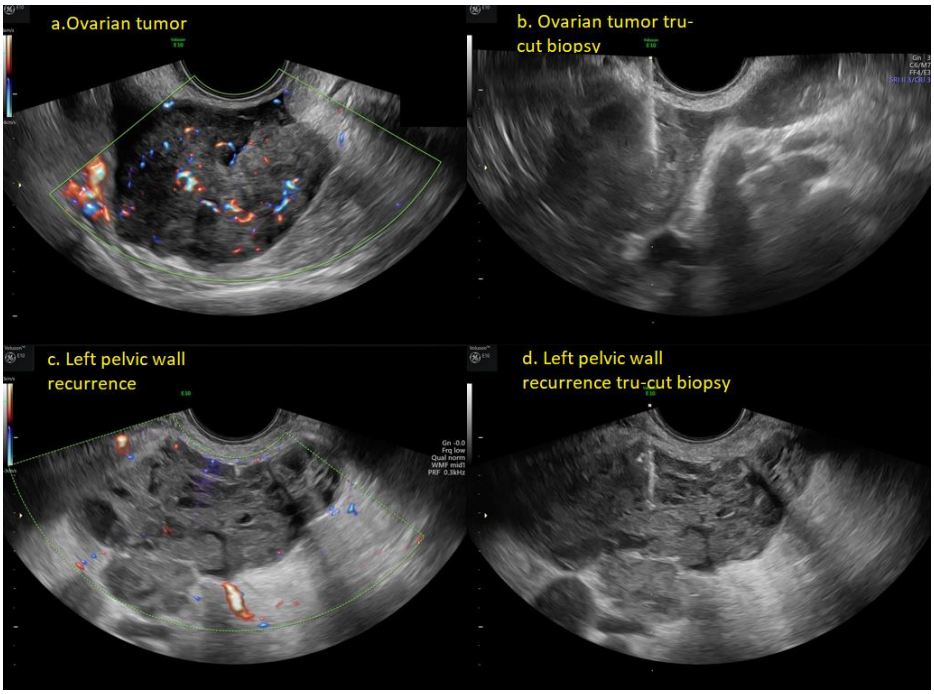

Figure 4. Ultrasound-guided biopsy: a) Ovarian tumor, b) Transvaginal ultrasound-guided tru-cut biopsy, c) Left pelvic wall recurrent ovarian cancer, d) Transabdominal ultrasound-guided tru-cut biopsy. © Karina Liuba picture database, with patient's consent.

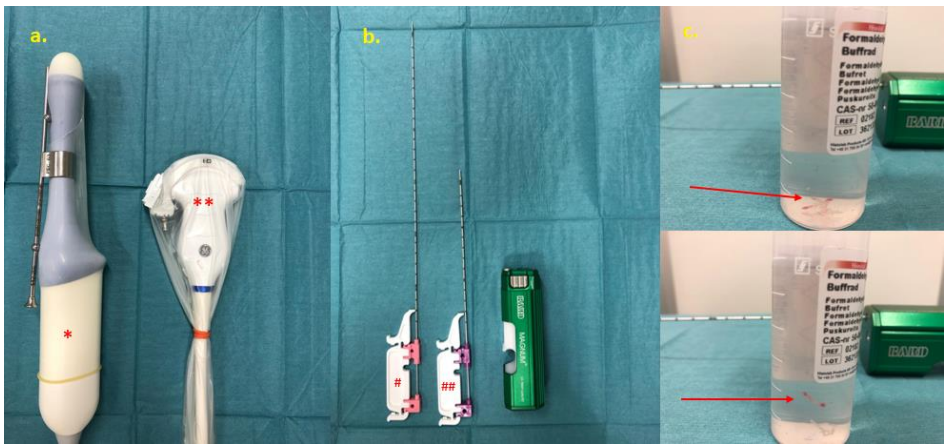

Figure 5. a) Transvaginal RIC5–9–D (*) and transabdominal C2-9–D curvilinear (**) probes prepared with protective cover and probe guide, b) Bard® Magnum® Ref MG1522 tru-cut core biopsy instrument and 18G 30cm needle for transvaginal (#) respectively, 16G 20cm needle for transabdominal (##) sampling, c) Formalin sample tissue © Karina Liuba picture database.

Frozen Section (FS)

Intraoperative histopathological diagnosis through FS is used to guide surgeons in choosing the correct surgical procedure. The tumor sample can be examined rapidly by the pathologist, and add information to guide the surgeon while the patient is still under anesthesia (Gal 2005).

FS is mostly used in early stages, when preoperative histopathological diagnosis, such as tru-cut, has to be avoided due to the risk of dissemination following a preoperative risk of cyst rupture (Vergote et al. 2001). FS is particularly important in young patients when there is a desire to preserve fertility. However, FS has become important in more advanced stages too, facilitating a rapid diagnosis and prompt postoperative chemotherapy with positive effect on survival (Larsen and Blaakaer 2009). Another important aspect of FS diagnosis is that it improves the chances of giving correct information to patients and delivering an individualized therapy plan immediately after surgery.

FS has been described as having overall sensitivity of 90.0% and sensibility of 99.5% in terms of correctly differentiating malignant tumors from benign and borderline tumors (Ratnavelu et al. 2016). The diagnostic capability of FS is influenced by the pathologist, the surgeon and the type of tumor. When a pathologist specialized in gynecological pathology performs FS, its accuracy improves (Bige et al. 2011). The surgeon's knowledge of macroscopic characteristics of tumors is important while sampling the most representative tissue, and intraoperative communication between the different specialists affects the quality of FS. It gives accurate results for malignant (99%) and benign (94%) tumors, making it reliable in correctly identifying invasive malignancies and ruling out benign pathology. However, its reliability decreases for borderline tumors (73%) (Ratnavelu et al. 2016; Asp et al. 2022c).

Peritoneal Cancer Index (PCI)

Since the only way to improve the prognosis for patients with AOC is successful surgery, the extent of the tumor within and outside the abdominal cavity must be well characterized to achieve maximum radicality. Sugarbaker first described a way of characterizing the extent of tumor spread for colorectal cancer and mesothelioma. The surgeon described the extent of the tumor in the abdominal cavity as an intraoperative numerical quantification (Jacquet and Sugarbaker 1996; Sugarbaker 1999).

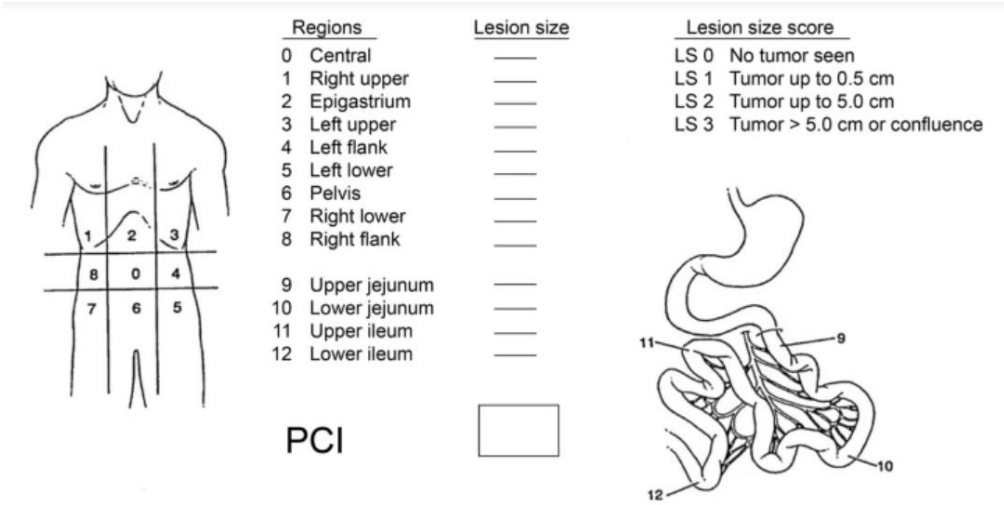

Figure 6. Sugarbaker peritoneal cancer index (Harmon and Sugarbaker 2005), Copyright ©2005, Harmon and Sugarbaker; licensee BioMed Central Ltd. Reprinted with permission from Springer.

Scoring was based on two components: the distribution and size of tumors. The abdominal cavity was divided into 13 regions, which were assessed for tumor content and scored from 0 to 3 depending on the size of the tumor: 0 points indicated no visible tumor, and 1, 2 or 3 points indicated lesions with maximum diameters of 0.5, 5.0 or > 5cm respectively, or confluent lesions producing a final score between 1 and 39.

In colorectal cancer, a cut-off value of 20 was described. Above this cut-off, surgery was not recommended (Simkens et al. 2017).

OS is also strongly correlated with PCI in colorectal cancer (Faron et al. 2016). In ovarian cancer, the clinical implication and its effect on survival is still disputed, with differential results.

In previous studies, different cut-off values of total PCI have been investigated in order to predict the result of surgery (Table 10). Because some anatomical regions are more difficult to reach surgically, such as the small bowel, hepatoduodenal ligaments and infiltrating carcinomatosis in the mesenteric root, and the fact that they leave the patient with residual disease, these specific regions on the PCI scoring area were investigated as predictive of surgical outcome (Rosendahl et al. 2018).

PCI can be assessed intraoperatively by laparotomy or mini-invasive surgery, by laparoscopy alone, or preoperatively using imaging methods such as ultrasound, CT, MRI and PET-CT.

This paper uses the term surgical PCI (S-PCI) to describe intraoperative assessment of PCI, and CT-PCI to describe preoperative, radiological assessment of PCI.

Surgical PCI (S-PCI)

Laparotomy is considered the most accurate way of assessing tumor spread to determine whether radical surgery is possible. As laparotomy is very invasive, less invasive methods have been widely investigated, and results depend on institutional experience and traditions (Liu et al. 2009; Ahmed et al. 2019). A laparoscopic predictive model for optimal cytoreductive surgery was described by Fagotti, with overall accuracy of 85% (Fagotti et al. 2008). However, there were difficulties in assessing bowel carcinomatosis, stomach infiltration and the hepatic hilum, which were not included in the scoring system, yet all these areas are extremely important in evaluating tumor resectability. The time between the laparoscopic assessment and final laparotomy was also described as an important factor. The final PCI score was underestimated by laparoscopy, and the difference increased with the time lapse between surgical interventions. An ideal time interval of 10 days was described between the diagnostic laparoscopy and final laparotomy (Angeles et al. 2021; Yurttas et al. 2022). Port site metastases due to evacuation of all gases and fluids from the peritoneal space through the trocars port, which then contaminates the tissue surrounding the port site with intraperitoneal cancer cells, have been a concern from the very beginning in terms of laparoscopy in colorectal cancer (Wexner and Cohen 1995). In ovarian cancer, a rate of port site metastases of 47% was described with no impact on overall survival, but with significantly more wound-healing disorders and higher postoperative morbidity (Ataseven et al. 2016).

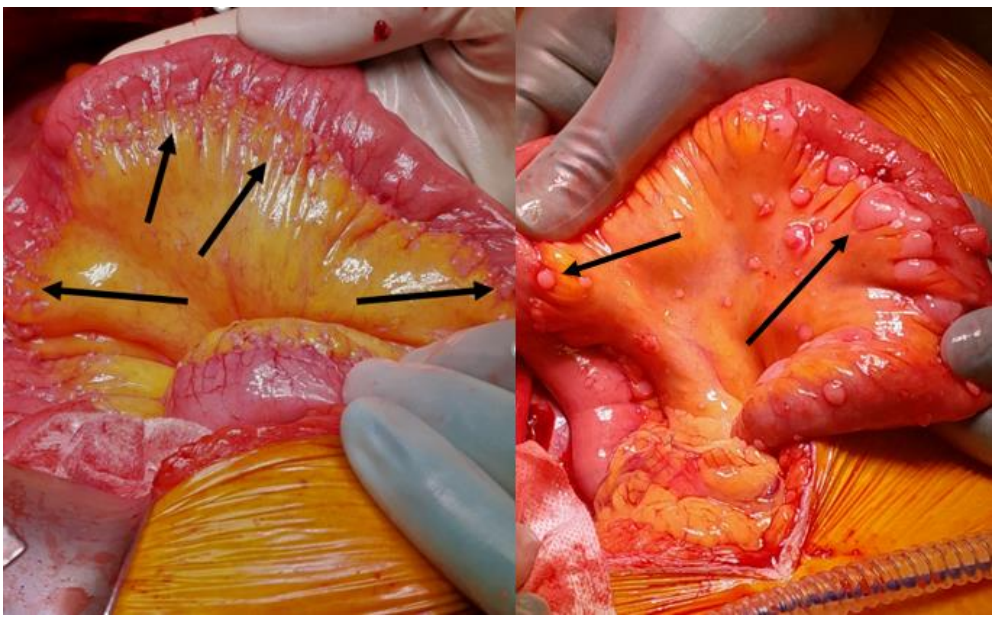

Figure 7. Small bowel carcinomatosis in AOC. ©Mihaela Asp 2022

Computed Tomography-PCI (CT-PCI)

As discussed, S-PCI has demonstrated its utility in assessing the extent of tumors and predicting surgical outcome, but surgery and general anesthesia are necessary in order to calculate it. A preoperative estimation of the extent of the tumor is necessary, which allows surgeons to decide ideal treatment strategies for patients, i.e. primary surgery versus neoadjuvant chemotherapy.

Preoperative radiological assessment of PCI is scarce in ovarian cancer. In terms of gastrointestinal malignancy, Schmidt et al. investigated CT, MRI and PET-CT, and found estimates with S-PCI to be very accurate. MRI had the highest sensitivity and FDG PET/CT had the highest specificity. As CT is the most available, economically accessible, and fastest method, it tends to be used in daily practice (Schmidt et al. 2015). If performed by a dedicated radiologist, CT can be used as a single technique (Mazzei et al. 2013).

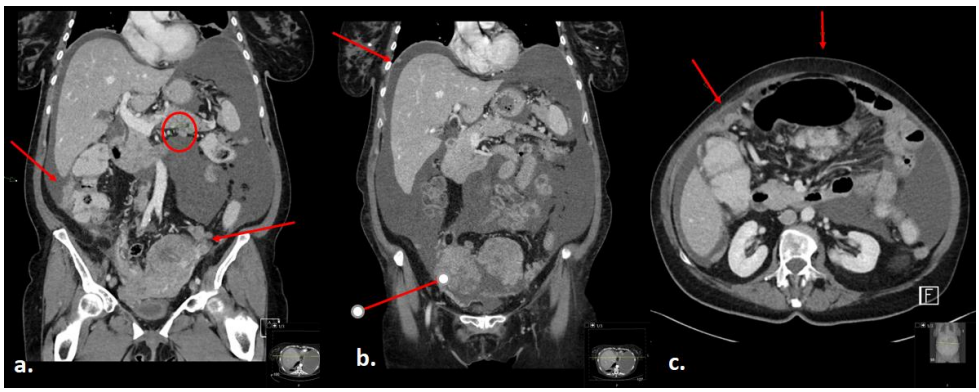

Figure 8. Peritoneal carcinomatosis and ascites in patients with ovarian cancer: a) CT-image (contrast-enhanced CT of the abdomen and pelvis, coronary projection) showing lesser omentum carcinomatosis, left-side pelvic carcinomatosis and peritoneal gutters carcinomatosis, b) CT-image (contrast-enhanced CT of the abdomen and pelvis, coronary projection) showing right diaphragmatic carcinomatosis, right-side pervic carcinomatosis, and pelvic masses, c) CT-image (intravenous and oral-enhanced CT of the abdomen and pelvis, sagitary projection) carcinomatosis in the peritoneal gutters and omentum. © Mihaela Asp 2022

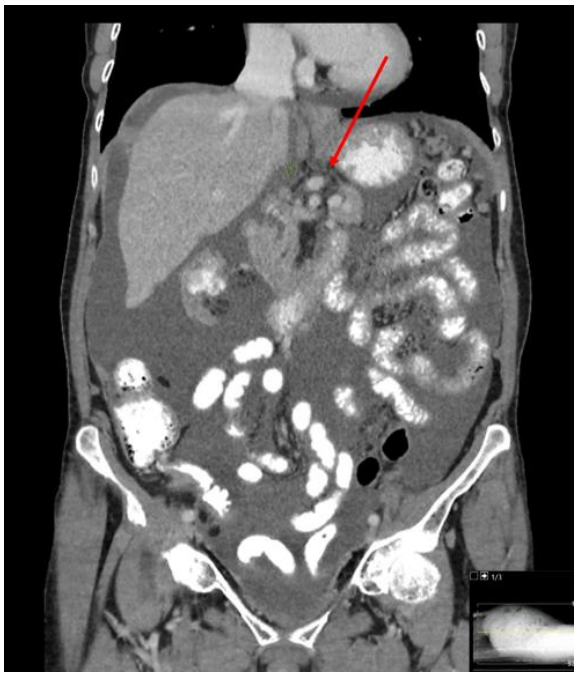

Figure 9. Peritoneal carcinomatosis and ascites in patients with ovarian cancer. CT-image (intravenous and oral-enhanced CT of the abdomen and pelvis, coronary projection) carcinomatosis in truncus coeliacus area. Copyright © 2022, The author(s) (Mihaela Asp 2022)

Multidisciplinary team meeting (MDTM)

MDTMs take place periodically between professionals with different medical expertise. In our institution, the group is composed of gynecological oncologists, a gynecological oncology surgeons, radiologists and pathologists with gynecological expertise, nurses with special expertise in oncology patients, and process coordinators.

MDTMs involving case discussions are an important aspect of the patient treatment plan. Recommendations and different alternatives for treatment are considered, based on relevant patient information and on the best evidence available (Rosell et al. 2019).

In AOC, the preoperative decision-making process involves three main questions: "1. Does the patient's health allow such extensive surgery? 2. Is the disease operable in terms of radical surgery? 3. Is the surgical team able to perform the surgery?"(du Bois et al. 2009).

Detailed documentation is collated to answer the first question, including a patient's age, comorbidity, and patient or family requests. The Gynecology Department at Skåne University Hospital is certified as a European Society of Gynecological Oncology (ESGO) center, which answers the last question. This paper is an attempt to answer the second question, using our clinical data to respond to a much debated and very current clinical problem in daily practice.

Epithelial ovarian cancer treatment

Surgical treatment

Surgery in ovarian cancer is both diagnostic and therapeutic.

Primary surgery in the early stages

In the early stages and in borderline tumors, where there are usually no preoperative histopathological diagnoses, surgery confirms the diagnosis and establishes the stage of the disease. The first step is to remove the tumor, usually by unilateral or bilateral salpingo-ooforectomy, in order to establish its histopathological nature. This can be done intraoperatively by frozen section analysis, or postoperatively on the basis of a final histopathological results. When a diagnosis is known, the patient is surgically staged directly or in a second procedure later. Depending on the histopathological type, staging procedures include hysterectomy, bilateral salpingo-oophorectomy, omentectomy, peritoneal biopsies, appendectomy (mucinous carcinoma), and pelvic and para-aortic lymphadenectomy (which can be omitted in LGSC, MC, low-grade endometrioid and borderline tumors) (Minig et al. 2017; Rosendahl et al. 2017; Colombo et al. 2019)

Fertility-sparing surgery

An important category of patients with ovarian cancer are those within the age of fertility. EOC is less common at this age, but not uncommon, and involves a special strategy in terms of planning therapy. Fertility-preserving surgery is accepted for borderline tumors and for invasive cancer stages IA or IB low-grade EOC (LGSC, endometrioid or mucinous), and after a staging procedure including unilateral salpingo-oophorectomy, peritoneal biopsies, peritoneal washing and omentectomy (du Bois et al. 2013; Colombo et al. 2019). In order to lower the risk of recurrence, radical surgery is recommended after completed child-bearing.

Mini-invasive surgery in ovarian cancer

Laparoscopy can be used in early-stage ovarian cancer for staging purposes, later in some highly selected cases, laparoscopic cytoreduction has been used in advanced

stages. However, since there is a lack of good-quality evidence to support the safety and benefits of laparoscopy versus laparotomy, laparotomy is still the first choice in ovarian cancer surgery (Falcetta et al. 2016; Colombo et al. 2019). Moreover, an upstaging due to formation of port site metastasis is described (Ramirez et al. 2004).

Surgery for advanced ovarian cancer

Treatment for patients with advanced ovarian cancer includes a combination of cytoreductive surgery and platinum-based chemotherapy.

The surgery is a crucial part of the multimodal treatment in AOC. Since the most important prognostic factor in AOC is the extent of residual disease (RD) at the end of surgery, CCS is pursued (du Bois et al. 2009).

Cytoreductive surgery can be primary debulking surgery (PDS) followed by adjuvant chemotherapy or, in selected cases, NACT followed by interval debulking surgery (IDS). In the last few years, a very extensive debate has been taking place about whether PDS or IDS is the best treatment to choose in AOC. Two highly influential randomized trials (EORTC and CHORUS) found no differences in survival rates between PDS and NACT (Vergote et al. 2010; Kehoe et al. 2015). However, in both studies, potential recruitment bias was noted, so that those with more extensive tumors burden were more likely to benefit from NACT, particularly in combination with a low CCS rate. More recent prospective, randomized studies have compared IDS with PDS, with different results. Fagotti et al. performed a superiority trial to assess differences in PFS and postoperative complication between PDS and IDS, with no differences in PFS but a more complex postoperative complication profile for the PDS group (Fagotti et al. 2020). Multiple retrospective studies show improved survival for patients treated with primary complete cytoreductive surgery, while complete cytoreduction at IDS did not have the same results in terms of survival (Bristow and Chi 2006; du Bois et al. 2012; Makar et al. 2016; Lyons et al. 2020). A retrospective review of 326 patients with AOC found a difference in CCS rate between PDS and IDS (41.5% vs 5.1%), but despite a higher CCS rate, 7-year survival was inferior for the IDS group (8.6% vs 41%) (Rosen et al. 2014). However, as there was no randomization for extent of the tumor, the patients with NACT tended to have more extensive disease.

A computational model of cancerous cells in ovarian cancer investigated the dynamic involved in exponential cell growth in HGSC, beginning with a single cancer cell which had all the alterations necessary for proliferation and metastasis but had not developed chemoresistance. The model assumed that during the progression of the tumor, there might be a change in chemoresistance. The model predicted that patients with HGSC already had chemoresistant cells at diagnosis. In upfront cytoreductive surgery, the surgeon reduced both chemosensitive and chemoresistant cells. On the other hand, NACT kill the chemosensitive cells, allowing a proliferation of chemoresistant cells. As the chemosensitive cells were

depleted, the residual tumor, visible to the surgeon, substantially reduced after NACT, making it impossible for interval cytoreductive surgery to remove all chemoresistant cells. The author's conclusion was that PDS was superior to NACT as it could deplete resistant cells more effectively (Gu et al. 2021).

An ongoing international, open, retrospective, randomized, controlled multicenter trial (Trial on Radical Upfront Surgical Therapy: TRUST) conducted by the German Gynecology Oncology Group may be able answer this question, and follow-up results are expected 5 years after the trials, in 2024 (Reuss et al. 2019).

Depending on the surgical outcome, cytoreductive surgery is classified as follows: suboptimal cytoreductive surgery (SCC) with RD exceeding 10mm, optimal cytoreductive surgery with RD below 10mm and CCS with no residual disease (Querleu et al. 2016).

In order to achieve surgical radicality, extensive surgery is needed. This involves pelvic procedures (hysterectomy, salpingo-ooforectomy, pelvic peritonectomy, colorectal resections, partial cystectomy, ureteral resections), medium-abdomen

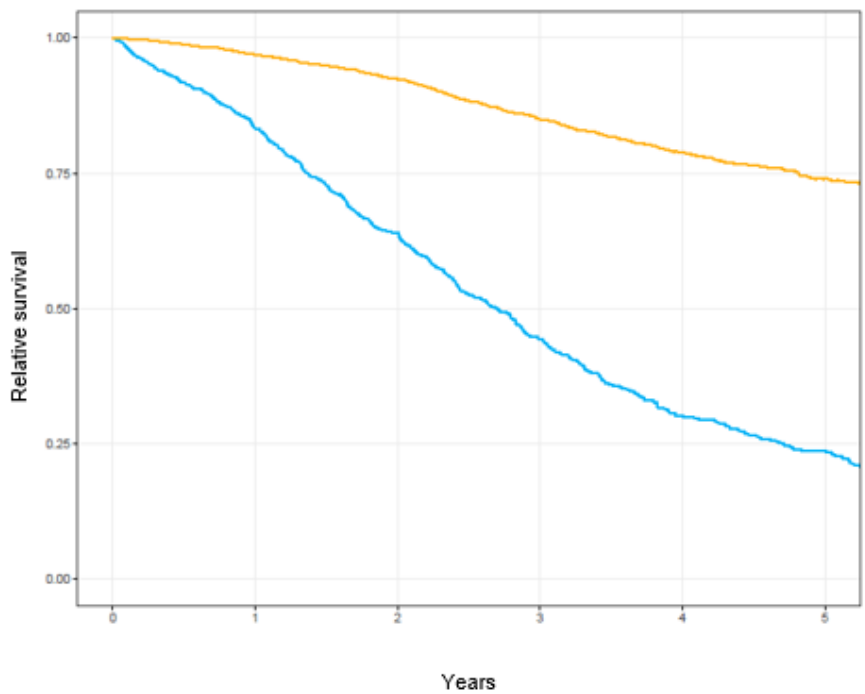

Figure 10. Relative survival for ovarian, fallopian tube and primary peritoneal cancer, comparing patients with complete cytoreductive surgery (CCS) and patients with non-CCS in Sweden, 2019-/2020. Source: Swedish Quality Register for Gynecological Cancer (RCC 2022)

procedures (pelvic nodes, peritonectomy gutters, para-aortic nodes, small bowel resections, large-bowel resections, appendectomy, omentectomy), or upper-abdomen procedures (resection of the lesser omentum, partial gastrectomy, celiac axis nodes, hepatic hilum nodes, diaphragmatic stripping and resections, splenectomy, partial pancreatectomy, liver capsule resection, partial hepatectomy, cholecystectomy, peritonectomy of Morrison pouch). All these procedures are scored using different surgery complexity scores (SCS) such as the Aletti SCS (Aletti et al. 2007).

Table 3. Aletti surgical complexity score (Aletti et al. 2007)

Procedure	**Points**
Hysterectomy and salpingo-ooforectomy	1
Omentectomy	1
Pelvic lymphadenectomy	1
Para-aortic lymphadenectomy	1
Pelvic peritonectomy	1
Abdominal peritonectomy	1
Small bowel resection	1
Large-bowel resection	2
Diaphragmatic stripping/resection	2
Splenectomy	2
Liver resection	2
Recto-sigmoidectomy, reanastomosis	3
Score groups	**Points**
Low Intermediate High	≤3 4-7 ≥8

Primary cytoreductive surgery is not suitable or feasible for all women with AOC. Poor performance status or the extent of peritoneal metastases can be a contraindication for primary surgery. The ESMO-ESGO guidelines describe essential features that may contraindicate CCS (Bristow et al. 2000). The decision on primary or interval surgery is discussed in an MDTM, as noted above.

Table 4. ESGO 2017 recommendations for contraindications for CCS

Diffuse carcinomatosis of the small bowel involving such large parts that resection would lead to a short bowel syndrome (remaining bowel < 1.5 m)
Diffuse involvement/deep infiltration of: stomach/duodenum, head or middle part of the pancreas
Involvement of coeliac trunk, hepatic arteries, left gastric artery
Central or multisegmental parenchymal liver metastases
Multiple parenchymal lung metastases (preferably histologically proven)
Non-resectable lymph nodes (lymph-node enlargement above the renal hilum (larger than 10mm short axis))
Brain metastases

Postoperative complications

Postoperative complications usually refers to complications within 30 days following surgery. The complication rate is affected by a patient's age, comorbidity, preoperative albumin status, the extent of surgery, PDS or IDS (Fotopoulou et al. 2021). In 2011, Wright et al. observed that, in women <50 years old, the complication rate was 17.1% compared to 29.7% at age 70–79, and 31.5% aged ≥80 (Wright et al. 2011).

Fagotti et al. reported a higher complication rate in patients treated with PDS compared with IDS, with 25.9% vs 7.6% major events registered. The same study described a higher SCS and longer operation time in PDS vs IDS, which could clearly contribute to a higher complication rate (Fagotti et al. 2020).

The Clavien-Dindo (CD) classification has been used to classify postoperative complication since 2004 (Dindo et al. 2004).

Table 5. Clavien-Dindo classification of postoperative complication (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 Permitted therapeutic regimens are: drugs such as antiemetics, antipyretics, analgetics, diuretics, electrolytes and physiotherapy. This grade also includes infections in wounds opened at the bedside
II	Requiring pharmacological treatment with drugs other than those 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	Multiorgan dysfunction
V	Death of a patient

The most commonly described complication is pleural effusion, representing up to 51% of all major complications (Fagotti et al. 2020), and where 4.2% of patients operated on for AOC require drainage (Palmqvist et al. 2022). Pleural effusion is more common in patients with diaphragmatic surgery, where more than half develop pleural effusion and up to 15% need postoperative thoracentesis or chest-tube placement (Eisenhauer et al. 2006).

One of the most serious complications is anastomotic leakage after colorectal surgery. With a reported incidence between 1.24% and 9% in ovarian cancer, it is considered a life-threatening complication (Peiretti et al. 2012; Kalogera et al. 2013; Lago et al. 2019).

Different parameters were associated with the risk of complication: age≥80, American Society of Anesthesiologists (ASA) score ≥ 4, bleeding disorders, albumin ≤ 33 g/L, and high PCI score (Cham et al. 2019; Lomnytska et al. 2021).

Oncological treatment

Chemotherapy

Since 1980, the standard oncological treatment for ovarian cancer has been platinum-based chemotherapy. In 1990s, Paclitaxel was added, which significantly improved PFS and OS. (McGuire et al. 1996; Piccart et al. 2000). In the early stages, adjuvant chemotherapy is not necessary for low-grade serous and low-grade endometrioid cancer, while in other histopathological types, depending on whether the patient is correctly staged with pelvic and para-aortic lymphadenectomy, single carboplatin or combination-med paclitaxel should be offered as a treatment option (Colombo et al. 2019). In AOC, intravenous carboplatin (AUC5) and paclitaxel (175mg/m²) are the standard treatment every third week for six cycles. Depending on the timing of the surgery, in the case of IDS the treatment is divided into three cycles preoperatively and three cycles postoperatively (Marchetti et al. 2018).

Angiogenesis inhibitors

Vascular endothelial growth factor (VEGF) is an angiogenesis promoter and an important factor in disease progression in many malignancies (Carmeliet 2005). Bevacizumab, the humanized anti-VEGF monoclonal antibody, was first evaluated as a complement in primary oncological treatment in the RCTs ICON7 and GOG-2018, with four months increased PFS, and no overall benefit in survival (Perren et al. 2011; Burger et al. 2011). The greatest PFS benefit, and a 4.8-month increase in OS was noted for patients with high recurrent risk, such as patients with no primary surgery or with primary non-radical surgery (Oza et al. 2015). In Sweden, bevacizumab has been used in addition to standard chemotherapy since 2014 for patients with non-radical surgery, and for FIGO stage IV epithelial ovarian cancer (RCC 2022).

Poly (ADP) ribose polymerase inhibitors

Breast Cancer Susceptibility Gene (*BRCA*) *1* and *BRCA2* are two tumor suppressor genes that are in the repairing process of DNA double-strand breaks via the homologous recombination (HR) repair pathway. Tumors with HR deficiency (HRD) relay on PARP inhibitors, which are oral small-molecule inhibitors of PARP enzymes 1, 2 and 3, to repair single-strand breaks of DNA via the base excision repair pathway (Jiang et al. 2019).

Substantially increased three-year PFS and five-year OS were observed when the PARP inhibitor (PARPi) Olaparib was added to standard chemotherapy in AOC

with germline *BRCA* mutation (Banerjee et al. 2021). Similar results were noted in several RCTs for other PARPi, such as niraparib (PRIMA), valiparib (VELA) or olaparib combined with Bevacizumab (PAOLA-1), when administered to AOC with HRD mutation (González-Martín et al. 2019; Coleman et al. 2019; Ray-Coquard et al. 2019).

Survival

Survival depends on various factors and can be expressed in different ways.

Progression-free and disease-free survival (DFS)

The progression-free survival measurement has the advantage of not needing a long follow-up, and is often used in survival measurements in clinical research as a surrogate measure of clinical benefit for drug approvals. While PFS measures the time from treatment initiation until disease progression, DFS measures the time after primary treatment to the first relapse, and requires complete remission after primary treatment.

Overall survival

This is defined as the proportion of people still alive at a given period of time after diagnosis, and includes all causes of death (Mariotto et al. 2014).

Median survival

This is the length of time after which 50% of patients have survived and 50% have died.

Mean survival

The length of time patients diagnosed with a specific disease are still alive after the date of diagnosis or the start of treatment.

Five-year survival

This measures survival at five years after a specific diagnosis.

Survival rate

The percentage of patients who are still alive for a certain amount of time after they have been diagnosed with or started treatment for a specific disease.

Relative survival

This is a net survival measure, calculating survival in the absence of other causes of death by dividing the overall survival time after a specific diagnosis by the survival

time observed in a similar population (age and gender) who have not been diagnosed with the disease.

Age-specific survival

This is the mortality rate reported for a specific age-group of patients.

Aims

General aims

The overall aims of this thesis were to evaluate diagnostic tools along the diagnostic pathway, from the preoperative to the intraoperative stage, and to investigate how an accurate diagnosis could predict surgical outcome and ultimate survival in patients with advanced ovarian cancer.

Specific aims

Study I

- To investigate the reliability and safety of preoperative histopathological diagnosis using the tru-cut biopsy procedure. Clinical applicability was a second aim of this study.

Study II

- To investigate the reliability of intraoperative histopathological diagnosis using frozen section. An overview from a multidisciplinary perspective was a second aim of this study.

Study III

- To determine whether the preoperative quantification of tumor spread using the peritoneal cancer index (CT-PCI), the presence of radiologically enlarged CPLN and the quantity of ascites visualized by computed tomography (CT-ascites) could assess the extent of the tumor (S-PCI) and residual disease (RD) in advanced ovarian cancer (AOC) patients treated with upfront surgery.

Study IV

- To examine whether the extent of the tumor and ascites evaluated on the CT scan and at the beginning of surgery affected overall survival (OS) and progression-free survival (PFS) in AOC patients treated with PDS, especially patients with no residual disease at the end of surgery.

Materials and methods

Study I

In Sweden, the management of advanced ovarian cancer is centralized in regional university hospitals, where the majority of patients are treated. For patients who are not candidates for surgery, either because of poor performance status or inoperability, secondary to extensive tumor spread, histological confirmation of tumor type is very important for treatment selection.

The primary data source involved charts from 309 patients who had undergone tru-cut biopsy between 1st of January 2015 and 31st of December 2020 at the tertiary center for oncological gynecological surgery in the Department of Obstetrics and Gynecology, Skåne University Hospital, Lund. Sweden. Patients were identified through the Laboratory Information Management System (LIMS) used by pathologists, by searching for true-cut biopsies required by the gynecological department. The clinical characteristics of the patients were collected from the patient data system, and were as follows: age, BMI, CA–125 and FIGO stage (where applicable), and primary diagnosis (when recurrence was suspected). The pathologists performed the histopathological diagnoses on formalin-fixed and paraffin-embedded material.

Three main indications were identified for the tru-cut biopsies: a) diagnosis of tumors of gynaecological types, b) identifying patients with tumors of non-gynecological origin for further referral and c) recurrences.

The biopsies were performed by different health-care providers: gynecological oncologists, gynecologists or radiologists subspecializing in ultrasound diagnosis, radiologists specializing in performing CT-guided biopsies, and general gynecologists.

Technical information was collected such as biopsy site, approach and number of tissue samples. The biopsy sites consisted of pelvic tumors, peritoneal carcinomatosis, omental cake, lymph nodes and others (including liver and thorax).

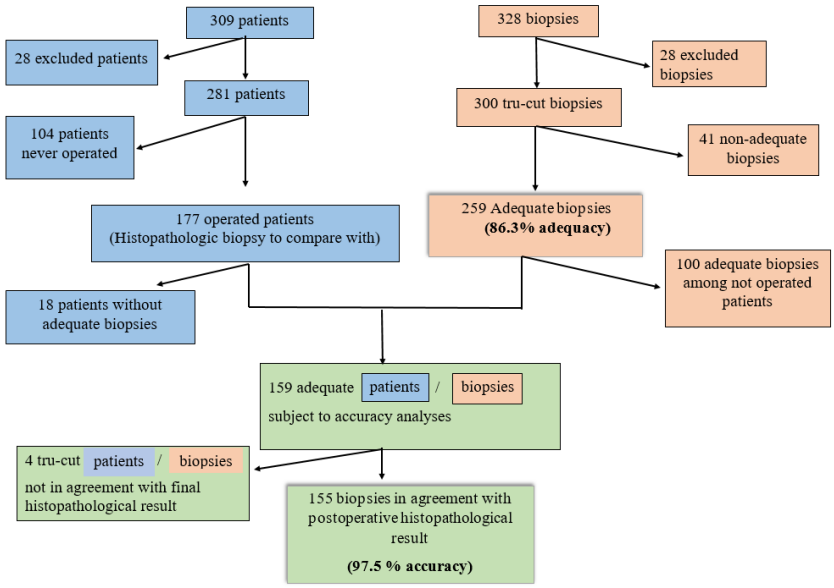

Figure 11 The flowchart of patients (blue) and biopsies (brown). Correspondent biopsy for each patient- flow chart to analyze accuracy (green)

A tru-cut biopsy was considered adequate if the quality and quantity was sufficient to identify the subtype/origin of the tumor, including performance of immunohistochemistry analyses. Different parameters affecting the adequacy, such as BMI, ascites, biopsy approach, site of biopsy and type of operator, were registered and analyzed using logistic regression analyses.

Accuracy was defined as the agreement between the diagnosis of an adequate tru-cut biopsy compared to the postoperative histology.

All complications, which had occurred within 30 days after the performance of the biopsies, were registered, and analyzed in relation to the operator, the site of the biopsy and the biopsy approach.

Study II

In total 358 patients who had undergone surgery for suspected ovarian cancer between 1 July 2018 and the 30 June 2020 were identified using the surgical management IT-system Orbit, with the diagnostic codes for *malignant tumor in the ovary* or *tumor of uncertain nature in the ovary*. The patients were then divided into two groups, depending on the presence or absence of a frozen section diagnostic, into a FS group and a non-FS group.

Patients subjected to restaging surgery, or surgery registered incorrectly as *ovarian tumor operation*, were excluded.

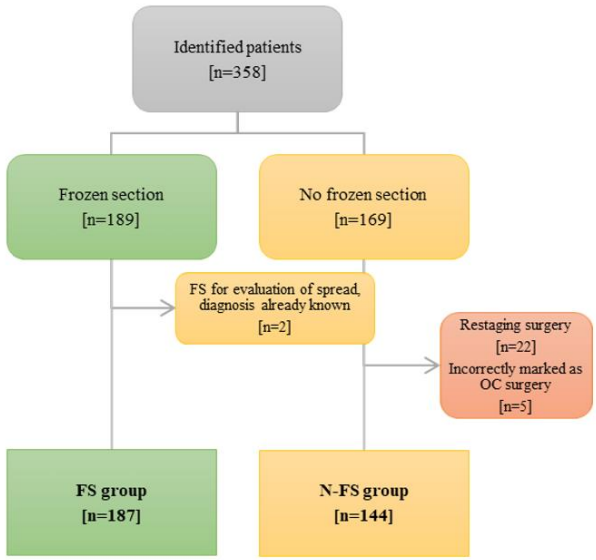

Figure 12. Flow-chart of study population

The final histopathological diagnosis with formalin-fixed and paraffin-embedded material, was considered the diagnostic reference standard (gold standard), while the frozen section diagnosis was considered a diagnostic test.

Prevalence, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated for each outcome: benign, borderline and malignant. Since the statistical analysis required a binary system, the three outcomes were compared as 1:2 (ex: malignant versus borderline and benign tumors). In order to maintain the accuracy of the result, inconclusive diagnoses were also included in these computations.

Studies III-IV

In total, 194 consecutive patients were investigated who had been diagnosed and treated for AOC from January 2016 to December 2018 at the Gynecology Department, Skåne University Hospital. Patient data were collected retrospectively from the patients' medical records. The inclusion criteria were: 1) AOC; 2) upfront cytoreductive surgery; 3) available preoperative CT scan of the thorax and

abdomen; 4) follow-up data until January 2021. Patients were excluded if they had received neoadjuvant chemotherapy with interval debulking surgery or with palliative chemotherapy only. Patients with early stages of ovarian cancer (FIGO I and II) and patients with incomplete data were also excluded. In total, 118 patients who had been selected for upfront extensive surgery were included in the studies.

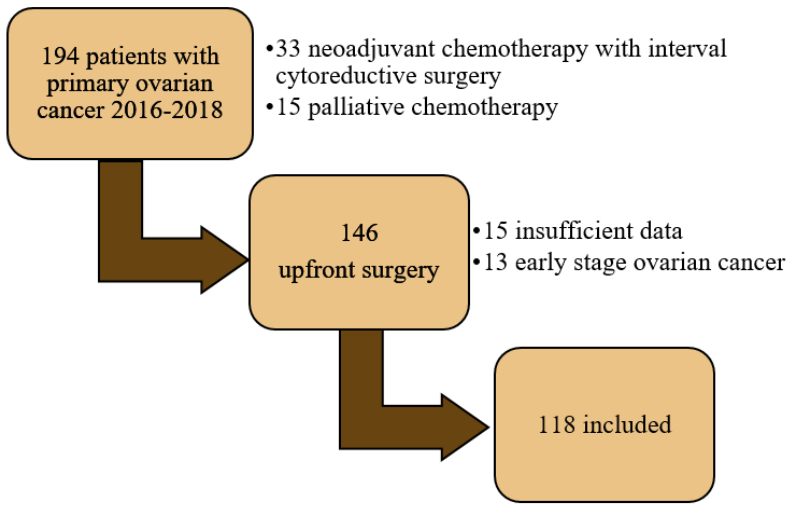

Figure 13. Study population. Flow chart of sampling.

Patient data were collected involving age and ECOG performance status, as well as information on the characteristics of the tumor: histology type, FIGO stage and tumor extent. The extent of the tumor was expressed in terms of preoperative PCI (CT-PCI) and intraoperative PCI (S-PCI). The 13 abdominal regions were assessed for tumor content and scored from 0 to 3 depending on the tumor size: 0 points indicated no visible tumor, and 1, 2 or 3 points indicated lesions with maximum diameters of 0.5, 5.0 or > 5cm respectively, or confluent lesions with a final score between 1 and 39. Data were analyzed as continuous data, and were categorized into three intervals (1-10, 11-20, ≥21). The presence of ascites (CT-ascites and S-ascites) and radiologically enlarged CPLN (short axis ≥5mm) was registered.

Due to the retrospective nature of data collection, to ensure the accuracy of surgical documentation and S-PCI we compared the retrospective calculation of S-PCI from medical records with a prospective evaluation of S-PCI for a series of 25 patients in the cohort. The normal distribution of data meant that the student's t-test was used, and no differences were found between the retrospective and intraoperative S-PCI mean values (17.07 vs 16.23).

Data regarding the extent and outcome of surgery were collected, as well as data on complications. The extent of surgery was estimated using the Aletti surgical complexity score (SCS). The surgery was grouped into complete cytoreductive surgery (CCS) with zero residual disease at the end of the surgery, and patients with residual disease of any size (non-CCS). Complications were scored using the Clavien-Dindo classification system, and all severe complications defined as Clavien-Dindo≥3 were registered. The dates of first relapse and overall survival were collected.

Image analyses

All eligible patients had undergone CT in the supine position with intravenous and oral contrast. As would be usual, all digital CT-images had been reformatted in the coronal and sagittal planes. The radiologists were blinded to the intraoperative evaluation of PCI and surgical outcome.

The standardized cancer pathway in Sweden stipulates that all patients should have initiated treatment within 24 days after diagnosis. The time interval between CT evaluation and surgery was registered in order to evaluate the possible effect on PCI evaluation and surgical outcome. It was categorized into three groups (≤20 days, 21-40 days and >40 days).

Means, medians, standard deviations and percentages were used for descriptive analyses. A Kolmogorov-Smirnov test was used to analyze the normal distribution of data. Linear regression and interclass correlation (ICC) were used to analyze the agreement between the preoperative and intraoperative evaluation of PCI (continuous data). Weighted kappa and percent agreement were calculated. A kappa value of 1 is reflective for perfect agreement, 0.81-1.00 shows a very good agreement, 0.61-0.8 indicate good agreement, and 0 indicate no agreement at all.

To determine the correlation between the CT-PCI, S-PCI and surgical outcome, linear and logistic regression analyses were used. The ROC curve was used to calculate a cut-off value for CCS and OS for both CT-PCI and S-PCI.

Survival was analyzed using univariate and multivariate analyses. The mean and median survival rate was calculated using the Kaplan-Meier method, and Cox regression for different cut-off values for CT-PCI and S-PCI, and CCS and non-CCS. To compare the statistical significance between different Kaplan-Meier curves, The Log-Rank test was used.

Ethical considerations

All patient data were handled according to the Word Medical Association's Declaration of Helsinki and in compliance with the Swedish national law.

Study I and II: The research was conducted as a retrospective population-based reviews after receiving approval from the Swedish Ethical Review Authority (2020-02818).

Studies III and IV: The Swedish Ethical Review Authority with apl.no.2019/00450 approved this study.

Results

Study I

Out of 328 registered biopsies, 300 were identified as tru-cut, performed on 281 patients. In 15 patients, additional biopsies had been needed as follows: 13 patients had required a second biopsy, one patient had undergone a third biopsy and one patient had undergone five biopsies due to low quantity and/or quality of the samples.

The median age of the patient group was 71 (24-96), BMI 25 (15-47) and CA-125 99 (6-32832).

Ovarian cancer diagnosis was the most common, with 149 biopsies, nearly half of the patients included in the study. The biopsy indication was primary tumor in 196 cases (65.3%), metastatic tumor in 12 (4%) and suspicion of recurrence in 92 (30.7%). In 123 (41%) of the cases, the tru-cut biopsy procedure was performed by a gynecologist with competence in ultrasound diagnosis, and in 120 cases (40%) by a gynecological oncologist. During the whole study period, the procedure was consistently performed by gynecological oncologists and radiologists, while the gynecologist with competence in ultrasound diagnosis undertook the procedure in four out of six of the years (Figure 14).

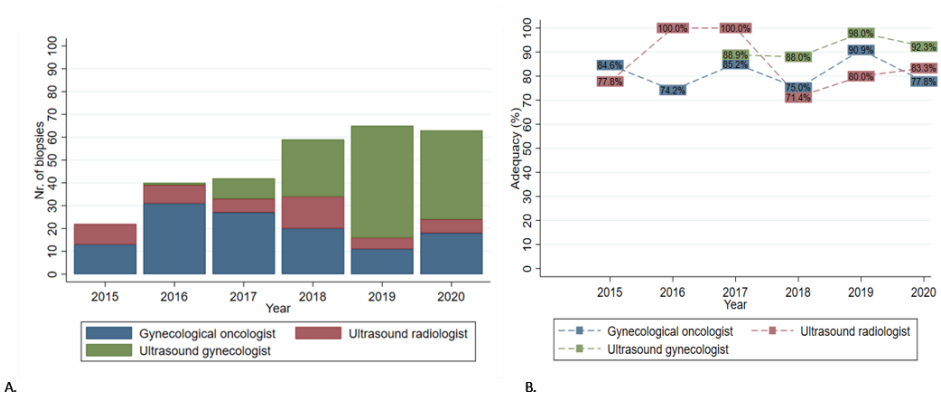

Figure 14. Clinical development showing the number of biopsies (A) and adequacy (B) by operator during the study period.

Overall adequacy was 86.3%. An adequate tumor sample was obtained in 259 out of 300 biopsies. In 41 of the tru-cut biopsies (34 patients), the result was not representative in terms of determination of the tumor type or origin. For 15 of these patients, one or several biopsies were repeated. Of the remaining ones, 19 patients required other diagnostic methods or never received a histopathological diagnosis. One (1) patient underwent an open biopsy (superficial, subcutaneous metastasis), seven (7) patients underwent laparoscopy or laparotomy, and in two (2) patients a fine-needle biopsy was performed. For one (1) patient with actinomycosis the diagnosis was settled by microbiology culture, and in two (2) patients by cytology. In six (6) patients no final diagnosis was registered: two with poor performance status and advanced disease died before the diagnosis was completed, in three a follow-up was planned, and one moved abroad and was lost to follow-up.

The adequacy of the tru-cut biopsy was not influenced by the age of the patient, the quantity of ascites, the CA-125 level or the technical approach.

The biopsy site negatively influenced adequacy, with a 66% higher risk of failed biopsy from pelvic tumors. The odds of an adequate biopsy were 3.3 times higher if the procedure was performed by a gynecologist with a subspecialty in ultrasound diagnostics. This result was sustained even after the data were adjusted for biopsy site, approach and indication (OR 2.9; 95CI: 1.249–6.722, p=0.013).

Out of 281 patients, 177 underwent surgery at some point and had a postoperative histopathological biopsy. In 18 out of these 177 patients, the tru-cut biopsies were not adequate and were thus excluded from the analyses on accuracy. The remaining 159 patients with both an adequate tru-cut biopsy and a postoperative histopathological diagnosis, were included in the analysis of accuracy.

In four out of 159 patients, the tru-cut biopsy was not in agreement with the postoperative histopathological result, resulting in an accuracy of 97.5%.

In four (4/300) cases, minor complications occurred (1.3%). All complications were infection related. No patient required surgery.

Study II

In total, 358 patients subjected to surgery were identified. After excluding restaging surgery and incorrectly documented surgery, 331 patients were included in the study population. In total, 187 patients were included in the FS group and 144 patients in the N-FS group.

A preoperative histopathological diagnosis was present in 19 out of 187 patients in the FS group, and in 52 out of 144 patients in the N-FS group.

For various reasons, the FS diagnosis was necessary despite the preoperative histopathological diagnosis in order to distinguish between a borderline and a malignant tumor, to establish an unclear preoperative diagnosis where there was suspicion of an another, coinciding tumor, or because of incomplete communication between the surgeon and the pathologist.

For benign and borderline tumors, the surgeon almost exclusively sampled parts of the uterine adnexa, 98.4% and 100%, respectively, while in cases of malignancy 33.6% of sampled material was of extra-adnexal origin.

An FS analysis was required by the surgeon in 62 (49.2%) out of 126 benign cases, 24 (68.6%) out of 35 borderline cases, and 101 (59.4%) out of 170 malignant cases.

In total, 168 out of 187 patients were correctly diagnosed by the FS technique, resulting in overall accuracy of 89.8%. Two patients with an inconclusive FS diagnosis were later diagnosed with malignant tumors, one with gastrointestinal stromal tumor and one with adult granulosa cell tumor.

Table 6. Concordance of frozen section diagnosis with final histopathological diagnosis.

	Final histopathological diagnosis		
Frozen section	Benign	Borderline	Malignant
Benign	61	5	3
Borderline	1	18	7
Malignant		1	89
No definitive diagnosis			2

The sensitivity for benign and malignant diagnosis was 98.4% and 88.1% respectively. The corresponding specificity was 93.6% and 98.8%. For the borderline tumors, the sensitivity and specificity were 75.0% and 95.1% respectively.

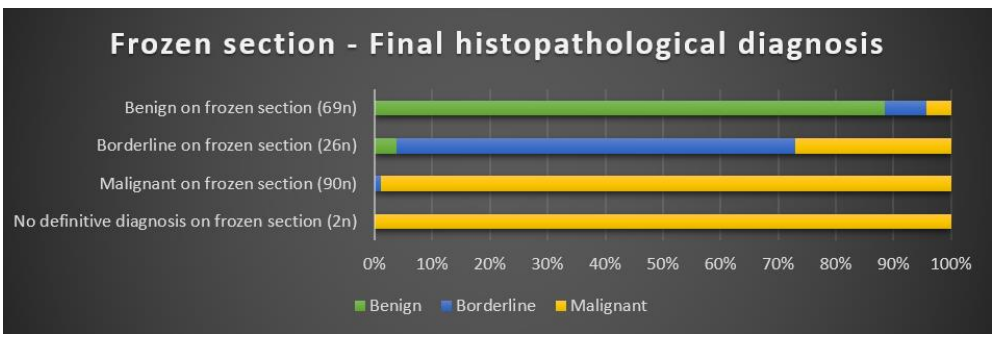

Figure 15. Frozen section diagnosis and corresponding final histophatological diagnosis in percentages, illustrating the positive predictive value (PPV) for the three diagnoses: 88.4, 69.2 and 98.9% for benign, borderline and malignant tumors respectively.

Fifteen out of 19 patients subjected to reclassification were underdiagnosed, two patients were over-diagnosed, and an inconclusive diagnosis was corrected for two patients. In six out of 19 patients the treatment was changed due to initial misclassification on frozen section.

Studies III-IV

In total, 118 patients were identified as suitable for Study III and again for Study IV. All patients were candidates for upfront cytoreductive surgery at the Skåne University Hospital, Lund, from January 2016–December 2018 (Figure 13).

Preoperative evaluation of the tumor extent

A positive correlation was found between CT-PCI and S-PCI in both crude and adjusted data. When data were adjusted for age, CA-125 ascites and time between CT scan and surgery, we found that a one-unit increase in CT-PCI corresponded to a 0.4-unit increase in S-PCI (0.397(95% CI 0.252-0.541) p<0.001).

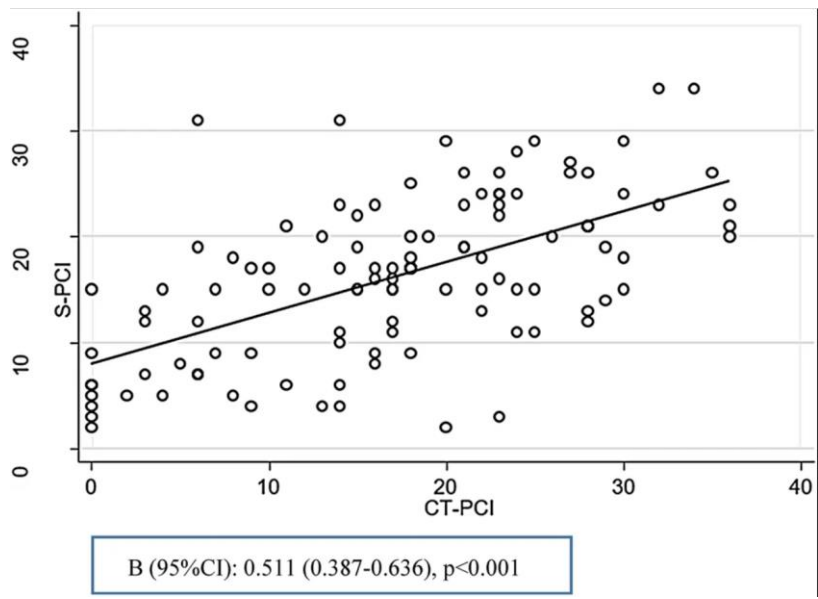

Figure 16. Linear regression analysis (crude data) showing a positive correlation between increasing CT-PCI and S-PCI (Asp et al. 2022b)

The preoperative evaluation of ascites correlated well with intraoperative ascites volume, with a kappa value of 0.68, and 86% agreement between these two measurements of ascites. The quantity of ascites was also positively correlated with tumor extent. For ascites volume above 1000ml estimated by CT scan, the risk of high tumor burden increased by 4.4 times (4.390 (1.027-7.753)).
The extent of the tumor increased with the time between CT scan and surgery, as shown in Table 7.

Table 7. CT-PCI, CA-125, ascites and time interval between CT scan and surgery, as predictive of the extent of a tumor (S-PCI)

Variables	β (95%)	p-value
CT-PCI	0.397 (0.252–0.541)	<0.001
Log2 (CA-125)	-0.040 (-0.840 to 0.760)	0.921
Days from CT to surgery		0.021
<20 days	Ref.	
20-39 days	3.163 (0.230–6.097)	
≥40 days	4.678 (1.260–8.097)	
Ascites		0.038
<500ml	Ref.	
500-1000ml	2.542 (-2.147 to 7.231)	
≥1000ml	4.390 (1.027–7.753)	

Preoperative evaluation of the risk of residual disease at the end of surgery

The results from logistic regression models showed a statistically significant association between CT-PCI (1.069 (1.009–1.132), p<0.023) and CT-ascites > 1000ml (3.5 (1.298–9.491), p<0.013) and residual disease of any magnitude at the end of surgery.

The ROC analyses calculated a cut-off value of 21 for CT-PCI predicting non-CCS, with an AUC of 0.715 (0.609–0.822), p=0.000.

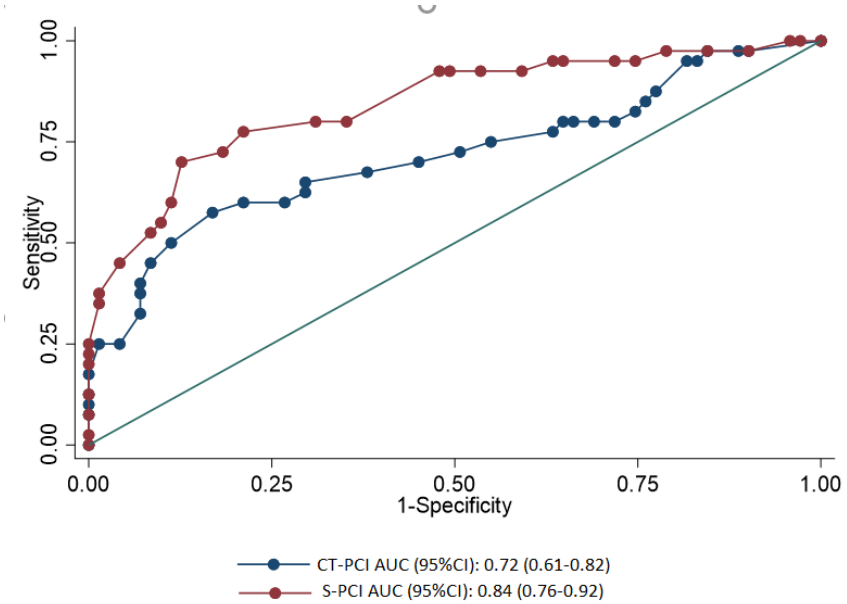

Figure 17. ROC curve for the reported CT-PCI and S-PCI to residual disease.

In terms of patients with suboptimal cytoreductive surgery (residual disease ≥ 10mm), we undertook a separate analysis of the reasons for unresectability. In 12 out of 19 patients, the site of the residual disease was small intestine carcinomatosis. In 9 (75%) of these cases, intestinal carcinomatosis, referred to as abdominal regions 9 to 12 (i.e., the small intestine), was described on CT scans.

Other preoperative markers, such as the presence of radiologically enlarged CPLN and CA-125 level, did not correlate with residual disease.

Analysis of survival in the cohort

CT-PCI, S-PCI, ascites≥1000ml and surgical outcome were found to be associated with impaired PFS. OS was affected by age, ECOG, PCI and surgical outcome.

Impact of PCI on PFS and OS

Both CT-PCI and S-PCI seemed to correlate with PFS, as shown in Table 8.

Table 8. Multivariate Cox regression analyses to predict progression-free survival (PFS):

	A		B	
	HR (95%)	**p-Value**	**HR (95%)**	**p-Value**
CCS	1.852 (1.144–2.997)	0.012	1.745 (1.056–2.882)	0.030
CT-PCI	1.069 (1.037–1.101)	0.001	1.065 (1.030–1.102)	0.001
S-PCI	1.059 (1.025–1,095)	0.001	1.053 (1.012–1.092)	0.011

CCS: Complete cytoreductive surgery; PCI: Peritoneal cancer index; S-PCI: Surgical PCI; CT-PCI: Computed tomography-PCI. Unadjusted analyses evaluating one variable at a time; B: adjusted for age and ECOG, PCI-variables also adjusted for surgical outcome.

Overall survival was affected by the tumor extent at the preoperative CT evaluation (CT-PCI) and at the beginning of surgery (S-PCI), and the residual disease at the end of surgery (CCS vs non-CCS).

A cut-off value of 24.5 was found for CT-PCI predicting impaired OS (AUC=0.617 (0.511-0.719), p<0.031). When a Kaplan-Meier test was designed to compare patients exhibiting a CT-PCI below or above the cut-off value of 24.5, significant differences in OS were found (28 vs 44.4 months, p<0.019). A doubled risk of dying of the disease was found in univariate Cox regression analyses (2.06 (1.112–3.830), p<0.022), but this result was not sustained by multivariate Cox regression analyses (0.517 (0.759–3.035), p<0.239).

When the same analyses were performed in order to appreciate the effect of S-PCI on OS, a cut-off value of 18.5 was found for S-PCI predicting survival (AUC=0.634 (0.596–0.791), p<0.000). The median survival time was 28.9 months for patients exhibiting S-PCI above 18.5. For patients with S-PCI<18.5, the mean survival time was 46.3 months (28.9 for patients with PCI≥18.5), the median survival time was not reached, meaning that by the end of our follow-up, more that 50% of the patients (66.7%) in this particular group were still alive.

Cox regression analyses showed a 3-times higher risk of dying for patients with S-PCI above 18.5. After adjusting for age, ECOG status and even for completeness of surgery, OS was still impaired for patients with S-PCI above 18.5 (2.177 (1.235–3.838), p<0.007).

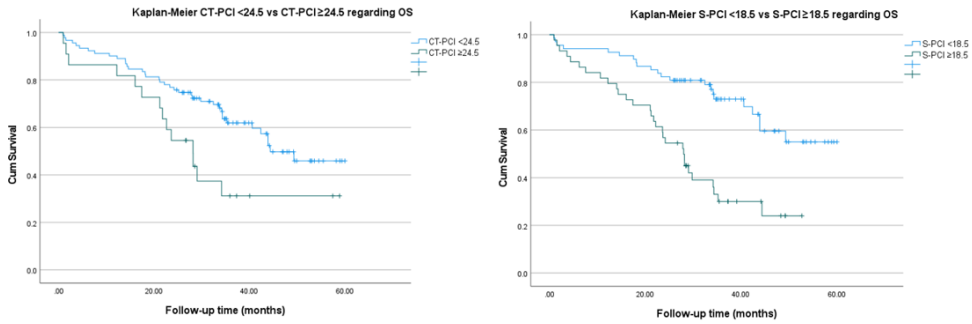

Figure 18. Kaplan-Meier curve for patients with CT-PCI below (green) and above (blue) the cut-off value in terms of OS

In the primary (published data), we calculated the survival analyses with a follow-up date of January 2021. When I began to write up the paper for the dissertation, I recalculated overall survival with a new follow-up date of over a year later. I largely wished to evaluate the median survival for S-PCI, which was not possible at the time of the first follow-up, as more than half the patients with PCI above 18.5 were still alive. In our newly analyzed data, overall survival time was the same (43.9 months). No changes were found in OS for patients with CT-PCI≥24.5, and slightly increased survival times were found for patients with CT-PCI<24.5 (49.05 vs 44.3). In terms of S-PCI, the median survival time for patients with S-PCI ≥18.5 decreased slightly (27.8 vs 28.02). The median survival time for patients with S-PCI < 18.5 was 56.28, still significantly better survival than for patients with S-PCI above the cut-off value ($p<0.001$).

The completeness of cytoreductive surgery had a significant effect on survival, and patients with residual disease of any magnitude at the end of surgery were estimated to have a doubled risk of dying of the disease, compared to patients with zero residual disease (2.177 (1.235–3.383), p=0.007). Kaplan-Meier analyses showed median survival of 28.02 months for patients with residual disease. The median survival was not reached in patients with zero residual disease, meaning that at the end of our follow-up, more that 50% of patients (65.3%) with zero residual disease were still alive.

Following the same logic, we recalculated the OS with a follow-up date of March 2022. Median survival time was the same for the whole group, with small differences for patients with residual disease, meaning a slight decrease in survival time in the new analyses (27.86 vs 28.03 months). The median survival for patients with zero residual disease was 51.6, still significantly higher than in patients with residual disease of any magnitude ($p<0.01$).

Impact of the extent of surgery and complications on survival

For patients with high PCI, the surgical effort was lower. The mean SCS for patients with S-PCI above 18.5 was 6.8, and 7.5 for patients with S-PCI below 18.5. No relationship was found between the complexity of surgery and survival. Together with a higher complexity score for patients with S-PCI below 18.5, a longer operation time (345 vs 317 minutes, $p<0.0019$) and greater blood loss (862 vs 770ml) were registered. No correlation was found between these two parameters and survival.

Diaphragmatic and small bowel carcinomatosis was more likely to be found in patients with high PCI scores. 93.3% of patients with S-PCI above 18.5 exhibited diaphragmatic carcinomatosis, and 66.7% small bowel carcinomatosis. The presence of carcinomatosis on the diaphragm did not affect survival (0.974 (0.909–1,043), $p<0.446$), while small bowel carcinomatosis was related to OS in the crude data (1.86 (1.07–3.21), $p<0.026$). When data were adjusted for age, ECOG and completeness of surgery, no statistically significant correlation was found.

In total, 34 (28.8%) developed major postoperative complications. No differences in complication profile were registered between patients with high and low S-PCI scores. The reported median survival time for patients with major complications was 35 months, while for patients without major complications, median survival was 42 months ($p<0.107$).

Discussion

In ovarian cancer and other cancer diagnoses, the outcomes depend on timely diagnosis, as well as access to appropriate surgery and systemic therapy. These parameters can be considered indicators of the effectiveness of a country's health-care system (Lheureux et al. 2019). A global assessment by world region and Human Development Index showed that inadequate public-health systems with fewer facilities for diagnosis could have an impact on ascertaining cases and could also negatively contribute to lower survival. In contrast, many high-income countries either had centralized diagnostics and treatment for ovarian cancer, or they were in the process of centralization, which had previously been linked to improved survival (Dahm-Kähler et al. 2016; Edwards et al. 2016; Cabasag et al. 2022b).

Correct characterization of the tumor and its spread before initial intervention can help to select effective therapeutic approaches for each patient. Histotype-specific and/or stage-dependent treatment options are needed, in combination with a patient's characteristics such as age, comorbidity, and personal or family wishes.

Study I

Many studies have described and evaluate the efficacy and safety of preoperative histological and cytological investigation. A number of studies have shown that the tru-cut technique is both adequate and accurate when performed under ideal circumstances in clinical practice, including access to highly specialized healthcare, which is not a daily reality in all cancer centers. Zikan et al. describe strong adequacy of 91.3% when the biopsy is performed by ultrasound specialists, compared to 93.5% in our study when comparing the same specialist category (Zikan et al. 2010). However, overall adequacy in our study was 86.3%, with differences depending on indication, site of biopsy and operator. This is also comparable to another Swedish study describing adequacy of 88% (Epstein et al. 2016). Our study is new in that it investigated the method from the point of view of daily clinical reality, where access to a highly specialized ultrasonography department might be limited.

A gynecological oncologist performing tru-cut biopsies has the advantage of being able to perform a biopsy during the patient's appointment, with no delay in diagnosis

or initiating treatment, which could otherwise have a negative influence on survival (Liu et al. 2017). However, although a tru-cut performed by a gynecological oncologist is 80.8% adequate, the risk of an inadequate sample is 53% higher, which could contribute to a delay in the diagnostic process if a second biopsy is required.

Some patients are referred to the radiology department for both CT and ultrasound-guided biopsies. Differences in approach and targeted tumor were registered, with a greater use of the transabdominal approach in the radiology department. Tumors outside the pelvis were more often targeted, and specific localizations such as liver biopsy were performed exclusively in the radiology department. This was partly a result of the diagnostic arrangement, and emphasizes the importance of multidisciplinary collaboration in cancer-patient care.

Sampling of pelvic tumors negatively influenced the adequacy of the sample. This could be explained by necrosis, cystic components and mobility of pelvic tumors (Roberts et al. 2018). The adequacy was influenced by indication of tru-cut biopsy. Primary diagnosis of a gynecological tumor was more likely to involve an adequate sample, compared to suspicion of metastasis from a non-gynecological cancer or recurrent disease. This could be explained by the fact that most of the patients with a primary diagnosis had FIGO stages III and IV (high tumor burden), whereas recurrences could be smaller in size, impairing the ability to collect representative material. Another explanation might be that the presence of necrosis, which is often described in colorectal and gastric-cancer metastasis, negatively affecting the quality of the samples (Zikan et al. 2012).

With just four cases where the tru-cut biopsy was not in total agreement with the postoperative/final histopathology diagnosis, the accuracy was high (97.5%), which is comparable to other studies describing accuracy between 80 and 98.3% (Fischerova et al. 2008; Zikan et al. 2010; Mascilini et al. 2020) . In two cases the primary tumor involved breast and lung cancer with unusual dissemination to the peritoneal cavity (Hanane et al. 2016; Beniey 2019). In both cases the malignant diagnosis was identified but, for the purposes of subtyping, required further investigation through a stereotactic breast biopsy and a thoracoscopic biopsy respectively. The other two cases were a mucinous and low-grade type tumor. A difficulty in diagnosing this entity involves tumor origin, since mucinous tumors in different organs can be very similar (Kurman and Shih Ie 2010). In the fourth case, a benign tru-cut biopsy was followed by a LGSC in the final postoperative histopathological specimen. We considered the biopsy to be adequate due to the quality and quantity of the ovarian tissue in the sample, but this could be questioned, since the final postoperative histopathological result for the same ovary showed mixed benign tissue with a non-invasive and invasive low-grade serous tumor.

About 20% of ovarian/fallopian tube cancer patients carry germline mutations in the *BRCA* genes, and about 0.4% have mutations in DNA mismatch repair genes(Alsop et al. 2012; Norquist et al. 2016). In recurrent and inoperable cancer,

histopathological confirmation including *BRCA* analyses is extremely important in individualizing treatment. Poly (ADP-ribose) polymerase (PARP) treatment has demonstrated its efficiency in treating both primary and recurrent ovarian cancer (González-Martín et al. 2019; Coleman et al. 2019; Banerjee et al. 2021). In our study, the *BRCA* status was required from tru-cut biopsy samples in 21 cases, and all cases were adequate samples for analysis. Since *BRCA* screening was not clinical routine at that time, and was only performed for a subset of these patients. Since our study was not designed to consider this particular aspect of the tru-cut procedure, why further studies are needed to investigate this capability.

Unpublished data

Another aim of the study was to investigate whether differences in adequacy between different operators had an impact on time of initiation of treatment, which might affect survival. We therefore registered the different time spans between the various steps involved in the procedure. However, there were local variations in clinical routines, why we chose not to publish these data, though we consider them relevant for local clinical practice.

We analyzed the number of days between the decision on the requirement for a tru-cut biopsy (A) to the day of tru-cut biopsy procedure itself (B), between the procedure and the histopathological result (C), and finally the time span between the decision to conduct a tru-cut biopsy, and from the tru-cut procedure to the initiation of treatment (D) (Figure 19). Differences in time interval (days) are presented in Table 9, expressed as a mean between different operators and indication for biopsy.

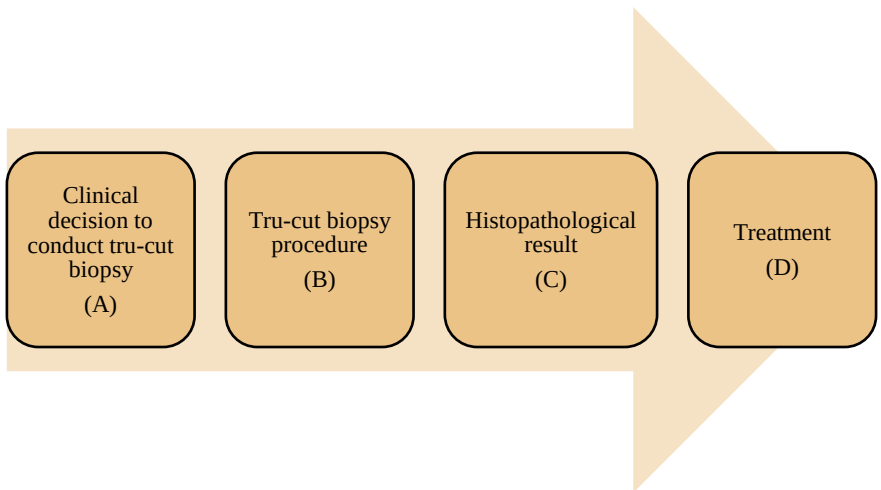

Figure 19. Flow-chart of tru-cut biopsy from clinical decision to treatment

Table 9. Mean time intervals between different moments of the diagnostic process, and their variation between different parameters.

	A to B Mean (days) (SD)	***p***	**B to C Median (days) (SD)**	***p***	**B to D Mean (days) (SD)**	***p***	**A to D Mean (days) (SD)**	***p***
	6.7(10.7)		**8.7(6.9)**		**41.1 (39.1)**		**48 (43.6)**	
Primary diagnosis	6.3(10.4)	0.31	8.2(6.6)	0.08	32.9(25.2)	**0.001**	38.6(26.8)	**0.001**
Relapse diagnosis	7.7(11.2)		9.72(7.58)		58.5(54.8)		68.9(61.9)	
Gynecological oncologist	5.9(12.7)		8.51(6.39)		46.8(45.1)		52.3(48.4)	
Gynecological ultrasonographist	6.4(9.9)	0.09	8.06(6.08)	0.16	31.0(22.5)	**0.008**	37.2(24.4)	**0.004**
CT-lead	14.9(13.1)		8.14(8.27)		31.1(24.5)		48.4(20.8)	
Radiological ultrasonographist	6.8(10.7)		10.7 (9.7)		53.5(51.4)		67.8(62.7)	

A to B: time from clinical decision to tru-cut procedure; B to C: time from tru-cut procedure to histopathological result; B to D: time from tru-cut procedure to initiation of treatment; A to D: time from clinical decision to initiation of treatment

One Way ANOVA test (Games-Howell) analyses showed significant mean-differences between the number of days from the date of the tru-cut biopsy and when treatment was initiated. This difference was statistically significant when comparing the procedure carried out by a gynecological oncologist and a gynecologist with competence in ultrasound diagnostics (mean difference 15.66 days, $p<0.018$). When the whole time period was analyzed between the decision to conduct a tru-cut biopsy and the initiation of treatment, a statistically significant difference was found in whether the procedure was carried out by a gynecological oncologist or a gynecologist with competence in ultrasound diagnostics (mean difference 15.03 days, $p<0.043$), and in whether it was performed by a radiologist or gynecologist with competence in ultrasound diagnostics (mean difference 30.50 days, $p<0.048$). No differences in time were found between the decision to conduct a biopsy and the tru-cut biopsy procedure itself, or between the procedure and the histopathological diagnosis.

Significant differences were found between primary and relapse diagnoses, which may be an effect of relapses not being included in the standardized cancer pathway. It may also be due to lower adequacy scores for diagnosis on tru-cut material in recurrent tumors, as demonstrated in our study. In order to investigate whether a relapse diagnosis was the reason for prolonged time to treatment when the procedure was conducted by a gynecological oncologist or radiologist with competence in ultrasound diagnostic, we also analyzed the differences between primary and relapse diagnosis for these operators. Ultrasound-guided tru-cut biopsy was used by all operators for preponderant targeted primary tumors, while CT-led tru-cut biopsy was used more often for diagnosing recurrence.

The high adequacy score for tru-cut biopsy when performed by a gynecologist with competence in ultrasound diagnostics is reflected further in the number of days to initiation of treatment. As noted above, the advantage of a gynecological oncologist performing a tru-cut biopsy relatively adequately (80.8%) is that it can be performed during the patient's appointment, with no delay in diagnosis or initiation of treatment. On the other hand, the risk of an inadequate tissue sample is 53% higher, involving a 53% higher risk of requiring a new biopsy and consequently a secondary delay in initiating treatment. We found a mean difference of 15 days in delays to treatment when the tru-cut was performed by a gynecological oncologist, and a mean difference of 30 days when it was performed by a radiologist with competence in ultrasound diagnostics.

Prolonged time to initiation of treatment could have a negative influence on overall survival, which is not analyzed in our study but is described in the literature(Liu et al. 2017; Seagle et al. 2017).

Another practical aspect of the tru-cut biopsy is its cost. Between 2015 and 2020, 200 biopsies were externalized to the radiology department, totaling 653 150 sek. In 145 out of 200 cases (457 036 sek) the extra costs could have been avoided if the tru-cut had been performed internally. The remaining 55 cases were biopsies from liver, breast and lung, or difficult lymph-node biopsies which required other levels of specialization. However, these calculations should be interpreted with caution, as more extensive costs, such the costs of competence, were not taken into consideration.

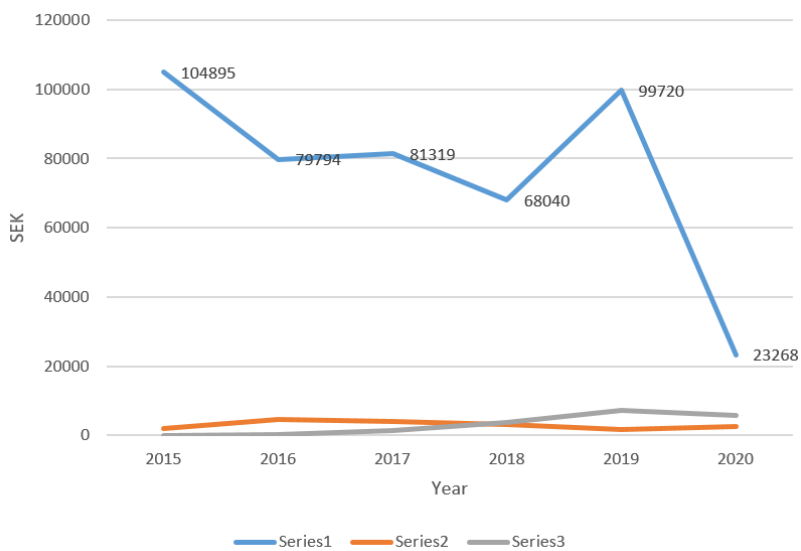

Figure 20. Tru-cut biopsy costs during the study period. Series 1 : Radiology department; Series 2: Gynecological oncology department; Series 3: Gynecological ultrasound department

These results underline the importance of centralizing cancer care, for effective prioritization of economic and competency resources to ensure patients are offered the best cancer care available.

Study II

As discussed above, treatment plans for ovarian cancer depend on the type and spread of the tumor. Patients with primary ovarian cancer need comprehensive staging or cytoreductive surgery. On the other hand, benign, borderline and some malignant tumors can be treated with limited and fertility-sparing surgery. An intraoperative frozen section is performed in order to adapt the surgery, or to avoid unnecessary surgery and prolonged anesthesia with possible peri/postoperative complications.

The reliability of FS is well documented, but variations in clinical routines, histopathological terminology and diagnostic criteria, as well as issues in the handling of specimens, particularly in borderline tumors, lead to a need to update the data in a current clinical setting (Seidman et al. 2004; Hauptmann et al. 2017; Seidman et al. 2020). This study included a short period from start to finish, in order to minimize the influence of variations in terminology.

In a Cochrane review, Ratnavelu et al. found sensitivity and specificity for correctly distinguishing invasive malignant tumors on frozen section to be 90% and 99.5% respectively, compared to 88.1% and 98.8% establish in this study (Ratnavelu et al. 2016). The results are similar to our study despite the differences in prevalence of malignancy (29% in the Cochrane review and 54% in our study). These differences in malignancy rate could be explained by the differences in study population. The Cochrane review included exclusively early-stage ovarian cancer treated in both secondary and tertiary centers, while our study included both early and advanced stages, treated in a tertiary center only. Since sensitivity was lower than specificity in both studies, frozen section diagnosis could be criticized as under-diagnosing, resulting in a probable need for secondary surgery. However, it could rarely be criticized for surgical over-treatment.

The borderline tumor diagnoses had a lower reliability (75.0% sensitivity, 95.1% specificity and 66.6% accuracy), which was in agreement with previous research (Song et al. 2011; Heatley 2012). Borderline-type tumors were more likely to be reclassified, and 27% of them were ultimately identified with invasive components. The histopathological heterogeneity in borderline-related tumors, resulting in variations in morphology within the same tumor, implicates the importance for the sampling of the tumor, and can explain the differences between FS and the final histopathological result. However, in our study, almost all borderline-related cases was delivered including the whole adnexa of the uterus to be analyzed by FS,

disabling the possibility of a deficient sampling by the surgeon. On the other hand, the surgeon's knowledge of clinical data and macroscopic per-operative tumor characteristics is extremely important in the decision-making process, in choosing which cases are candidates for FS and which tissue area that are the most representative for FS diagnostics. This is important both for the quality of FS and to keep the workload in the pathology department reasonable. During our analyses we observed that the surgeon mainly asked for an FS in borderline tumors, which could indicate that borderline tumors are a diagnostic challenge for both surgeons and pathologists (68.6% vs 49.2% and 59.4% respectively for benign and malign tumors).

Also, clear cell and mucinous carcinoma are other challenges during FS diagnostics, with a discordance rate of 40.5% noted for mucinous carcinoma (Yoshida et al. 2021).

In six out of 19 patients subject to reclassification, the therapy plan was adjusted after the final histopathological result. One patient needed secondary surgery and five required adjuvant chemotherapy. During the surgery, the surgeon and pathologist communicated any concerns about a borderline diagnosis, which resulted in correct surgical staging, and no delays in the start of adjuvant chemotherapy.

In advanced ovarian cancer, the timing of postoperative chemotherapy it showed to be important for patients' survival (Singh et al. 2016; Seagle et al. 2017). This makes rapid histopathological confirmation of the tumor type extremely important (Wright et al. 2008). Our study found that FS diagnostics were very reliable in diagnosing malignant disease, why postoperative chemotherapy can be initiated on the basis of FS results, avoiding unnecessary delays.

Studies III and IV

Epithelial ovarian cancer has the highest mortality rate of all gynecological malignancies. The most important factor affecting survival is the completeness of cytoreductive surgery (Bristow et al. 2002; du Bois et al. 2009). Intraperitoneal spread can be numerically indexed by PCI, as noted above. Many studies have analyzed the role of PCI in predicting the surgical outcome and identifying the patients who would benefit from cytoreductive surgery in terms of complete macroscopic clearance. Most of the studies focused on intraoperative PCI (S-PCI), but the intraoperative nature of S-PCI observation means that the patient could be subject to unnecessary surgery involving anesthesia, and also possible complications. This makes it easier to argue for preoperative assessment of PCI in clinical terms.

Different cut-off values for S-PCI have been described. Chéreau et al. found a mean PCI score of 16 and a 92% complete resection for PCI<10 (Chéreau et al. 2010). Llueca et al. established a predictive model for unresectability using CT, laparoscopy and laparotomy. Radiologic-laparoscopic criteria for unresectability (RLCU) were used in order to calculate the risk of suboptimal cytoreductive surgery (≥ 10mm). RLCU involved lung metastasis, hepatic metastasis in three or more hepatic segments, severe involvement and progression of hepatic pedicle after NACT on CT scan, and diffuse serous small bowel disease on laparoscopy. The study calculated a cut-off value of PCI> 20, predicting suboptimal cytoreductive surgery for the three diagnostic tools, with 91% specificity and 27% sensitivity for CT scans (Llueca et al. 2018a; Llueca et al. 2019). These results were sustained by Muallem et al. in a retrospective analysis on 70 patients, exploring the correlation between serum CA125 and the peritoneal cancer index, and their predictive value for residual tumor at the end of surgery. A three-times higher risk for residual tumor was found for CA-125 > 600 U/ml and a 9-times higher risk for PCI >20. In a more recent study by Jónsdóttir et al., a cut-off value of 24 was found for S-PCI, above which neoadjuvant chemotherapy was recommended as a justifiable treatment option (Jónsdóttir et al. 2020). In our study, a mean S-PCI value of 16 was found for the whole cohort, with differences between the CCS and non-CCS group, and a cut-off value of 18 for CCS.

In order to avoid unnecessary surgery with its consequent risks, different diagnostic methods have been analyzed in terms of preoperative evaluation of the extent of the tumor and predictive factors for postoperative residual disease.

Fagotti et al. developed a laparoscopy-based model in 2006, updated in 2015, based on the intraoperative presence/absence of some specific cancer feature (Fagotti et al. 2006) (Petrillo et al. 2015). Diagnostic laparoscopy is not accepted as routine in many cancer centers, as existing non-invasive, accessible diagnostic methods such as CT scan, ultrasound and DW-MRI are considered good alternatives. Other reasons diagnostic laparoscopy is not used routinely involve economic and organizational challenges in relation to limited operating-theater capacity (Lof et al. 2022). Beyond these logistical challenges, the method has limitations in evaluating the small intestine, stomach infiltration and the hepatoduodenal ligament, which are more predictive of residual disease and survival (Rosendahl et al. 2018). A comparison between the laparoscopic and laparotomic peritoneal cancer index using a two-step surgical protocol showed that laparoscopic assessment underestimates the final PCI score by two points. Furthermore, the delay between surgeries increased the differences, and an optimal time interval of 10 days was recommended between surgeries (Angeles et al. 2021). Another important clinical inconvenience involves the risk of upstaging due to port site metastasis, described in 47% of cases. This has no impact on overall survival but involves significantly more wound-healing disorders and greater postoperative morbidity (Ataseven et al. 2016).

A meta-analysis showed that MRI had sensitivity of 91% and specificity of 85% for diagnosing ovarian cancer. Nodularity, necrosis, a septal or wall thickness of >3mm and papillary projections of >4cm are linked to ovarian cancer (Dai et al. 2019). Important information can be delivered by MRI, such as the involvement of pelvic organs or sidewall, peritoneal disease, ascites and lymphadenopathy (Tsili et al. 2008). Dynamic contrast-enhanced MRI and diffusion-weighted MRI can be used to differentiate between benign, borderline and malign tumors, as a second-line tool after ultrasonography (Timmerman et al. 2021a). In terms of the role of MRI in diagnosing peritoneal carcinomatosis and in predicting the completeness of cytoreductive surgery, some studies have found promising results (Garcia Prado et al. 2019). Two ongoing multicenter studies aim to define the role of MRI in women with AOC (Clinical Impact of Dedicated MR Staging of Ovarian Cancer (MRStagingOC) ; The impact of multiparametric MRI on the staging and management of patients with suspected or confirmed ovarian cancer.2015 20/11/2018).

Ultrasound has an established role in differentiating between benign, borderline and malign tumors, and between the different types of ovarian malignancy (Valentin et al. 2006). In an ISAAC study, a prospective, single-center analysis compared ultrasound, CT and whole-body DWI/MRI (with a CCS rate of 68%). Ultrasound was found not to be inferior to CT in an assessment of overall peritoneal carcinomatosis. Compared to WB-DWI/MRI and CT, transvaginal ultrasound was more accurate and more sensitive in detecting carcinomatosis in the pelvis. Evaluation of deep rectosigmoid wall infiltration was better predicted by ultrasound, supporting the potential role of ultrasound in planning rectosigmoid resection. In contrast, ultrasound had the lowest detection rate for intestinal serosa and mesenterial carcinomatosis. The authors concluded that, in experienced hands, ultrasound could be an alternative to WB-DWI/MRI and CT in assessing the extent of a tumor and predicting resectability (Fischerova et al. 2022).

Another diagnostic tool which has been investigated is PET-CT. Limitations due to differences in fluorodeoxyglucose uptake in histological subtypes such as clear cell and mucinous invasive subtypes have a negative impact on its diagnostic performance (Tanizaki et al. 2014). PET-CT is especially useful in detecting lymph-node metastases, especially outside the abdominal cavity, but is limited in evaluating bowel serosa and mesenterial carcinomatosis, especially in low-volume disease (Michielsen et al. 2014). The ESGO/ISUOG/IOTA/ESGE Consensus Statement on preoperative diagnosis of ovarian tumors does not recommend PET-CT be used in clinical decision-making in ovarian cancer (Timmerman et al. 2021b).

New techniques are being developed such as PET/MRI, a combination of MRI and PET in a single scanner. A recent paper by Jónsdóttir et al. shows that PET/MRI and DW/MRI correlate well with surgical PCI, PET/MRI being an even more accurate diagnostic, especially in primary tumors and inoperable patients with a high tumor burden. Furthermore, PET/MRI seems to demonstrate greater specificity

in diagnosing bowel carcinomatosis, compared to DWI alone (Jónsdóttir et al. 2021).

Computed tomography is the most common diagnostic tool in estimating the extent of a tumor and planning treatment for patients with AOC. CT is non-invasive and has the advantage of being highly accessible in routine clinical practice.

Many studies have investigated the correlation between CT-PCI and S-PCI, with different results. CT seems to have high specificity and low sensitivity in describing the extent of carcinomatosis, meaning that when a CT scan does not describe carcinomatosis, the surgeon can assume that it is absent (Nasser et al. 2016). However, the most challenging aspect for the surgeon is to identify patients who will not benefit from cytoreductive surgery. Our study found a good correlation between the total PCI estimated preoperatively and the intraoperative extent of carcinomatosis. CT scans may both underestimate and overestimate the S-PCI, with a tendency to underestimate when the S-PCI is low, and overestimate when the S-PCI is high. Open-close surgery could increase as a result of the risk of underestimation. However, we consider that there is only a low risk of unnecessary surgery, as overestimation often occurs at a PCI below 20, when surgery is the first choice. On the other hand, overestimation can result in an increased number of patients being referred to NACT and interval surgery, where the effect on survival is still being debated (Reuss et al. 2019; Fagotti et al. 2020).

As noted above, coeliac trunk, hepatic arteries, the left gastric artery, bowel serosa, mesentery and lymph nodes above the renal hilum are associated with suboptimal cytoreductive surgery, strongly supporting the supposition that specific regions are more predictive of completeness of surgery. PCI regions corresponding to the hepatoduodenal ligament and small intestine were found to be more predictive of complete resection and even survival than the whole PCI (Rosendahl et al. 2018). Our study demonstrated the same trend. Twelve out of 19 patients who had received suboptimal cytoreductive surgery exhibited intestinal carcinomatosis, and their overall survival was impaired.

The CT scan was predictive of surgical outcome, in terms both of estimating peritoneal carcinomatosis and assessing ascites volume. The odds ratio for CT-PCI was low, which needs to be interpreted with caution. On the other hand, residual disease is often expressed by diffusely disseminated carcinomatosis, which is difficult to assess by CT scan, but also by other diagnostic imaging tools. CT-ascites estimated above 1000ml were strongly correlated with both high S-PCI and an unsatisfactory surgical result, which could be explained by the higher risk of miliary disease (Eng et al. 2017). Our conclusion is that CT, combining CT-PCI and CT-ascites (as an indirect diagnostic for miliary carcinomatosis), in association with the overall clinical context, is a reliable diagnostic tool in terms of choosing candidates for PDS. This is in concordance with another study by Mazzei et al., which

concludes that CT can be used as a single technique in selecting candidates for PDS if it is performed and read by an expert radiologist (Mazzei et al. 2013).

The prognostic role of PCI has previously been investigated. Tentes et al. reported for patients with PCI<10, a 65% 5 year survival rate, and a mean survival of 80±12 months. Patients with PCI≥10 had a 29% five-year survival rate and a mean survival of 38±7 months (Tentes et al. 2003). Gasimli et al. investigated the prognostic role of PCI on survival in patients who had undergone upfront surgery. No impact was found on survival after complete cytoreductive surgery and adjuvant chemotherapy. Age and lymph nodes involvement were the only independent factors affecting survival (Gasimli et al. 2015).

In our study, the PCI was prognostic for survival, even after adjusting the data for age, ECOG status and completeness of surgery. A cut-off value of 18.5 was found, above which a twofold risk of dying of the disease was observed, regardless of the completeness of cytoreductive surgery. The most established prognostic factor for OS in AOC is residual disease at the end of surgery, and this was confirmed by our study. No differences were found in major complication rate between patients with PCI above or below 18.5, and no relationship between complication and survival. This disables the supposition that a higher PCI implies extensive surgery and secondary high complication rate, affecting survival.

Lomnytska et al. found a relationship between a high PCI and complications but failed to demonstrate the effect of complications on survival (Lomnytska et al. 2021). Falconer et al. described a negative relationship between surgical complexity score and survival, where patients with high complexity scores were subject to almost twice the risk of dying, although it is not clear whether the data were adjusted for complete resection (Falconer et al. 2020). No relationship was found in our study between high complexity scores and survival.

There is little research on the prognostic role of CT-PCI. Diaz-Gil et al. identified CT-PCI along with ECOG performance status as a predictor for survival of 5 years in patients with AOC. For patients with ECOG status 0 and CT-PCI below 10, there is a six to nine times higher probability of 5 years of survival compared to patients with CT-PCI> 10 and poor performance status (ECOG > 1). The results were not affected by eventually NACT (Diaz-Gil et al. 2016). A previous study by our research group found that the CT-PCI was prognostic for survival, even after adjusting for histological-subtype and clinical stage. A disadvantage of this study was the lack of information about surgical method, surgical outcome and ultimate NACT (Sartor et al. 2020).

Table 10. Studies on the peritoneal cancer index (S-PCI) in advanced ovarian cancer (AOC) (Tentes et al. 2003; Chéreau et al. 2010; Gasimli et al. 2015; Elzarkaa et al. 2018; Llueca et al. 2018b; Muallem et al. 2020; Avesani et al. 2020; Jónsdóttir et al. 2020; Asp et al. 2022a)

Author Year	Total number of patients	FIGO stage	PDS / IDS	S-PCI median/mean/%	S-PCI cut-off for CCS	CT-PCI mean
Tentes 2003	62	III and IV	PDS+IDS	10	10	no
Cherau 2010	61	I to IV	PDS+IDS	16 (median)	10	no
Gasimli 2015	80	III and IV	PDS	12	no	no
Rosendahl 2018	507	III and IV	PDS	14 (median)	14	no
Elzarkaa 2018	96	III and IV	PDS	12 (mean)	13	no
Llueca 2018	80	III and IV	PDS	12 (median)	20	no
Muallem 2020	70	III and IV	PDS	≤20 (61.4%) >20 (38.6%)	20	no
Avesani 2020	297 (including FIGO I and II)	I to IV	PDS+IDS	no	no	9
Jónsdóttir 2021	167	III and IV	PDS+IDS	22 (median)	24	no
Asp 2022	118	III and IV	PDS	16	18	17

More recent analyses by Avesani found a correlation between CT-PCI and surgery outcome, as well as with DFS and OS. However, the study population, which included both early stages and NACT, makes it difficult to compare the data with our study (Avesani et al. 2020). The latter found a correlation between CT-PCI and PFS.

CT-PCI cut-off for CCS	CCS rate (%)	Survival analyses	Conclusion
no	52	yes	PCI can assess peritoneal spread in AOC, and can predict CCS and survival. Significant differences were found in five-year survival rates (65 vs 29%) between patients with PCI ≤10 and PCI >10.
no	80	yes	The PCI score is well suited for assessing ovarian cancer, as it is associated with CCS rate and postoperative complications.
no	67	yes	PCI affected PFS but not OS in patients who had undergone CCS for primary ovarian cancer.
no	51	yes	Regions 9-12 and 2, corresponding to the small intestine and hepatoduodenal ligament, are more predictive of CCS than the entire PCI. PCI≥14 was a predictor for OS.
no	64.6	yes	PCI is reliable in assessing the extent of disease and may predict CCS, but it does not predict survival.
20	64	yes	PCI of >20 predicts the risk of SCS. Impaired OS and PFS were related to PCI≥15.
no	61.4	no	A combination of PCI<20, CA-125 and intraoperative tumor mapping predicts CCS in 90% of cases.
16	77	yes	CT-PCI predicts CCS and is prognostic for both OS and PFS.
no	82	no	PCI>24 is predictive of incomplete CCS with an increased complication rate.
21	63.6	yes	CT-PCI predicts the extent of a tumor and CCS. S-PCI≥18.5 is prognostic for survival. CT-PCI is prognostic for PFS.

A relationship with OS was found in univariate analyses, as well as a cut-off value of 24.5, where patients doubled the risk of dying if they had a CT-PCI above 24.5, compared to patients with a lower CT-PCI (median survival 29.2 months vs 49 months). However, these results were not sustained by multivariate analyses. After adjusting for age, ECOG performance status and completeness of cytoreductive surgery, a 50% higher risk of dying was observed, though this was not statistically significant.

Conclusion

- Tru-cut biopsy in gynecological cancer is a safe procedure with good adequacy and accuracy. The adequacy of tru-cut biopsy depends on the site of the tissue sample, indications for the biopsy and the experience of the operator.
- Tru-cut biopsy is a safe method to use in an outpatient setting, avoiding additional costs due to unnecessary admissions for post-biopsy observation.
- Frozen section is a reliable method for correctly diagnosing invasive malignancies, and for ruling out benign pathology. Frozen section was observed to underestimate malignancy, but overestimation was rare.
- Detailed history, optimal tissue sampling and a correlation to the preoperative findings are crucial for correct FS diagnoses.
- A FS diagnosis is less accurate for borderline and rare tumors, and this tumor types are challenging for both surgeons and pathologists.
- CT is a reliable diagnostic tool in preoperative assessment of peritoneal carcinomatosis and ascites, and can also predict surgical outcome. CT is highly accessible and can be used by an experienced radiologist as a single technique in selecting patients as candidates for PDS.
- High volumes of ascites are an indicator of both a high tumor burden and impaired chances of reducing the tumor to zero at the end of surgery.
- The extent of a tumor at the beginning of surgery seems to affect survival in patients with advanced ovarian cancer, regardless of the completeness of cytoreductive surgery or postoperative complications. CT-PCI is an independent prognostic for PFS, but a correlation with OS is still to be investigated.
- Multidisciplinary collaboration is very important in the diagnostic process, along with choosing the right moment for referring patients. Good collaboration facilitate a rapid and safe track for diagnosing gynecological malignancies and initiating treatment.

Future aspects

- Preoperative diagnostic tools should be further investigated to improve the process of selecting patients. A prospective study is ongoing to investigate the complementary role of CT scans and ultrasound in assessing the extent of a tumor, and their role in predicting completeness of surgery in advanced ovarian cancer. We hope to be able to complete this in the near future. An interesting aspect for further investigation involves the fact that different histology types have different characteristics in terms of imaging, with regard to both the primary tumor and the pattern of spread (Prat et al. 2018; Moro et al. 2021).
- A pilot project would be useful on using machine learning in the preoperative diagnostic process and in prognostic prediction of operability. Identifying variables and patient characteristics before primary therapeutic intervention could help choose the best approaches. Machine learning is a branch of artificial intelligence technology that allows computers to "learn" and recognize potential patterns from past examples (Kourou et al. 2015; Xu et al. 2022). A model combining clinical and survival data could predict surgical outcome and survival with 77% and 93% accuracy respectively (Enshaei et al. 2015).
- Another ongoing study is investigating postoperative complications with a focus on intestinal surgery. Our observations indicate that the risk factor profile in gynecological malignancy is different to that of colorectal malignancy (Golda et al. 2020; Valenti et al. 2022). A preoperative risk assessment has gradually been introduced in clinical practice, and has decreased stoma formation and even the incidence of anastomose leakage in our clinic subjectively. We intend to chart these risk factors in order to improve planning for pre-habilitation and surgery in patients with advanced gynecological malignancies.

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