

Role of the Surgery in Advanced Ovarian Cancer

*Papel de la cirugía en el cáncer de
ovario avanzado*

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ROLE OF THE SURGERY IN ADVANCED OVARIAN CANCER

PAPEL DE LA CIRUGÍA EN EL CÁNCER DE OVARIO AVANZADO

Thesis submitted by

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Por la presente declaramos que **Martina Aida Angelès Fité** ha realizado, bajo nuestra supervisión, los estudios presentados en la tesis doctoral titulada **PAPEL DE LA CIRUGÍA EN EL CÁNCER DE OVARIO AVANZADO**. Esta tesis ha sido estructurada siguiendo la normativa de presentación como compendio de publicaciones con nuestra autorización y la de la Comisión Académica para obtener el título de **Doctor en Medicina con Mención Internacional** y los artículos mencionados están listos para ser presentados al Tribunal.

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PRESENTACIÓN

PRESENTACIÓN

La presente tesis ha sido estructurada, siguiendo la normativa de Tesis Doctoral, como compendio de artículos para obtener el título de **Doctor en Medicina con Mención Internacional**. Ha sido aprobada por la Comisión Académica del programa de doctorado el XX de mayo de 2023. Los proyectos de investigación incluidos en esta tesis pertenecen a una misma línea de investigación, lo que permitió la publicación de cinco artículos en revistas internacionales. Los artículos que se incluyen en el apartado *published studies* se encuentran tal y como aparecen en la literatura científica.

Artículo 1

Angeles MA, Rychlik A, Cabarrou B, Spagnolo E, Guyon F, Pérez-Benavente A, Gil-Moreno A, Siegrist J, Querleu D, Mery E, Gladieff L, Hernández A, Ferron G, Martinez A.

A multivariate analysis of the prognostic impact of tumor burden, surgical timing and complexity after complete cytoreduction for advanced ovarian cancer.

Gynecol Oncol. 2020 Sep;158(3):614-621. DOI: 10.1016/j.ygyno.2020.06.495. Epub 2020 Jul 22. PMID: 32709536.

Estado: Publicado. Factor de impacto de la revista (2019): 4,623; 1^{er} cuartil.

Artículo 2

Angeles MA, Cabarrou B, Gil-Moreno A, Pérez-Benavente A, Spagnolo E, Rychlik A, Martínez-Gómez C, Guyon F, Zapardiel I, Querleu D, Illac C, Migliorelli F, Bétrian S, Ferron G, Hernández A, Martinez A.

Effect of tumor burden and radical surgery on survival difference between upfront, early interval or delayed cytoreductive surgery in ovarian cancer.

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Estado: Publicado. Factor de impacto de la revista (2020): 4,401; 1^{er} cuartil.

Artículo 3

Angeles MA, Hernández A, Pérez-Benavente A, Cabarro B, Spagnolo E, Rychlik A, Daboussi A, Migliorelli F, Bétrian S, Ferron G, Gil-Moreno A, Guyon F, Martinez A.

The effect of major postoperative complications on recurrence and long-term survival after cytoreductive surgery for ovarian cancer.

Gynecol Oncol. 2022 Jul;166(1):8-17. DOI: 10.1016/j.ygyno.2022.05.002. Epub 2022 May 12. PMID: 35568582.

Estado: Publicado. Factor de impacto de la revista (2021): 5,304; 1^{er} cuartil.

July 2022 Issue's Editor's choice, accompanied by a commissioned Editorial by J.H. Tseng and R.E. Bristow, entitled "Complications associated with cytoreductive surgery for advanced ovarian cancer: Surgical timing and surmounting obstacles".

Podcast recorded in July 2022, entitled "Complications after cytoreductive surgery and its impact on survival: where do we go from here?"

Artículo 4

Bétrian S, **Angeles MA**, Gil-Moreno A, Cabarro B, Deslandres M, Ferron G, Mery E, Floquet A, Guyon F, Pérez-Benavente A, Spagnolo E, Rychlik A, Gladieff L, Hernández Gutiérrez A, Martinez A.

Survival impact of histological response to neoadjuvant chemotherapy according to number of cycles in patients with advanced ovarian cancer.

Int J Gynecol Cancer. DOI: 10.1136/ijgc-2021-003313. Epub 2022 Jul 20. Online ahead of print. PMID: 35858711.

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Podcast released on August the 1st, 2022, entitled "Chemotherapy Response Score in Ovarian Cancer with Alejandra Martinez" and Journal Club conducted on August the 31st.

Artículo 5

Angeles MA, Spagnolo E, Cabarrou B, Pérez-Benavente A, Gil-Moreno A, Guyon F, Rychlik A, Migliorelli F, Bataillon G, Navarro AS, Bétrian S, Ferron G, Hernández A, Martinez A.

Impact of pattern of recurrence on post-relapse survival according to surgical timing in patients with advanced ovarian cancer.

Int J Gynecol Cancer. 2023 Jan 3;33(1):50-56. DOI: 10.1136/ijgc-2022-003985. Epub 2022 Nov 29. PMID: 36446410.

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ABSTRACT

ABSTRACT

The best timing to schedule cytoreductive surgery to obtain the maximal survival benefit for patients with advanced ovarian cancer presenting with carcinomatosis is a topic that remains today controversial. The decision to perform upfront cytoreductive surgery or neoadjuvant chemotherapy (NACT) is always made individualizing each case and pondering all the medical factors of each patient, but there is a lack of standardization of what factors should be considered. The aim of this thesis is to increase the current knowledge on this subject and to clarify some important aspects that could guide the decision of the best timing for cytoreductive surgery.

We performed a retrospective study including patients with IIIC-IV FIGO stage ovarian cancer who underwent cytoreductive surgery at four high-volume institutions between January 2008 and December 2015. Several univariable and multivariable analyses were conducted. Disease-free survival (DFS) and overall survival (OS) were estimated for primary debulking surgery -*PDS group*-, early interval debulking surgery after 3-4 cycles of NACT -*early IDS group*- or delayed debulking surgery after 6 cycles of NACT -*DDS group*- with no residual (CC-0) or minimal residual (CC-1) disease. Survivals were also estimated according to peritoneal cancer index (PCI) and Aletti score, according to the occurrence of major postoperative complications, and according to the histological response to chemotherapy defined by the validated chemotherapy response score. Survival analyses were conducted using the Logrank test and the Cox model. Cumulative incidences of the different patterns of recurrence were estimated using a competing risk methodology.

We included 549 patients, 175 (31.9%) underwent PDS, 224 (40.8%) had early IDS after 3-4 cycles of NACT, and 150 (27.3%) underwent DDS after 6 cycles of NACT. Median DFS in PDS, IDS at 3-4 cycles and DDS at 6 cycles were 23.0 months (95% CI = [20.0–29.3]), 18.0 months (95% CI = [15.9–20.0]) and 17.1 months (95% CI = [15.0–20.9]), respectively; $p < 0.001$. Median OS were 84.0 months (95% CI = [68.3–111.0]), 50.7 months (95% CI = [44.6–59.5]) and 47.5 months (95% CI = [39.3–52.9]), respectively; $p < 0.001$. In multivariable analysis, high PCI score (>10) and NACT were negatively associated to DFS and OS. High surgical complexity (Aletti score ≥ 8) and CC-1 were negatively associated to DFS. Regardless of Aletti score, median OS after PDS was

significantly higher than after early IDS or DDS, but the survival difference was higher in women with an Aletti score <8. Among patients with PCI ≤ 10 , median OS after PDS was significantly higher than after early IDS or DDS. In women with PCI >10, there were no differences between PDS and early IDS, but DDS was associated with decreased OS. The overall rate of major surgical complications was 22.4%. Patients who underwent PDS had a higher rate of major complications (28.6%) than patients who underwent either early IDS (23.2%) or DDS (14.0%). Multivariable analysis revealed that extensive peritonectomy and surgical timing were associated with the occurrence of major complications. Median DFS and OS were 16.9 months (95% CI = [13.7-18.4]) and 48.0 months (95% CI = [37.2-73.1]) for the group of patients with major complications, and 20.1 months (95% CI = [18.6-22.4]) and 56.7 months (95% CI = [51.2-70.4]) for the group without major complications. Multivariable analysis revealed that major surgical complications were significantly associated with DFS, but not with OS. For the analysis of chemotherapy response score, only the 365 patients who received NACT were included: 219 (60.0%) received 3-4 cycles of NACT and 146 (40.0%) had 6 cycles of NACT before cytoreductive surgery. There were no significant differences in early relapses, DFS and OS according to the number of NACT cycles. However, regardless of the number of NACT cycles, persistent extensive histological disease (chemotherapy response score of 1-2) was significantly associated with a higher PCI, minimal residual disease (CC-1) and early relapses. Median DFS in patients with complete or near-complete response (chemotherapy response score of 3) was 28.3 months (95% CI = [21.6-36.8]), whereas it was 16.3 months in patients with chemotherapy response score of 1-2 (95% CI = [14.7-18.0]), ($p < 0.001$). Regarding recurrences, the cumulative incidence of peritoneal recurrences at two years was higher with increasing NACT cycles (24.4%, 30.9% and 39.2%; $p = 0.019$). For pleural or pulmonary recurrences, it was higher after early interval surgery (9.9%, 13.0% and 4.1%; $p = 0.022$). Median post-relapse OS was 33.5 months (95% CI = [24.3-44.2]), 26.8 months (95% CI = [22.8-32.6]), and 24.5 months (95% CI = [18.6-29.4]) for PDS, early IDS, and DDS groups, respectively ($p = 0.025$). The pattern of recurrence within a lymph node (HR 0.42, 95% CI = [0.27-0.64]), DDS (HR 1.53, 95% CI = [1.11-2.13]) and time to first recurrence (HR 0.95, 95% CI = [0.93-0.96]) were associated with post-relapse OS. For PDS and early IDS, lymph node recurrences were associated with significantly longer post-relapse OS.

In conclusion, PDS offered a survival gain of almost three years compared to early IDS and DDS in patients with minimal or no residual disease after surgery. The benefit of PDS compared with NACT was maximal in patients with a low surgical complexity. In patients with low tumor burden, there was a survival benefit of PDS over early IDS or DDS. In women with high tumor load, DDS impaired the oncological outcome. Patients who experienced major

surgical complications had reduced DFS, compared with patients without major morbidity. Extensive peritonectomy and surgical timing were predictive factors of postoperative morbidity. Complete or near-complete histological response to NACT improved oncological outcome regardless of the number of NACT cycles. The pattern of first recurrence was associated with surgical timing, with peritoneal recurrences being more frequent with the increasing number of cycles of NACT and pleural or pulmonary recurrences being more frequent after early interval surgery. Lymph node recurrences were associated with better prognosis, having higher post-relapse OS. This improved prognosis of lymphatic recurrences was not observed in patients who underwent delayed surgery. PDS should remain the standard of care for advanced ovarian cancer when complete cytoreduction can be achieved, particularly in patients with low tumor burden and requiring less complex surgeries.

RESUMEN

RESUMEN

El mejor momento para realizar una cirugía citorreductora en pacientes con cáncer de ovario avanzado con carcinomatosis para obtener el máximo beneficio de supervivencia es un tema que sigue siendo controvertido hoy en día. La decisión de realizar una cirugía citorreductora primaria o quimioterapia neoadyuvante (QTNA) siempre se toma individualizando cada caso y teniendo en cuenta todos los factores médicos de cada paciente. Aun así, existe una falta de estandarización de los factores que deben considerarse para dicha decisión. El objetivo de esta tesis es aumentar el conocimiento actual sobre este tema y aclarar algunos aspectos clave que podrían guiar la decisión del mejor momento para la cirugía citorreductora.

Se realizó un estudio retrospectivo que incluyendo pacientes con cáncer de ovario en estadio IIIC-IV de la FIGO que se sometieron a cirugía citorreductora en cuatro instituciones de alto volumen entre enero de 2008 y diciembre de 2015. Se realizaron varios análisis univariantes y multivariantes. Se estimó la supervivencia libre de enfermedad (SLE) y la supervivencia global (SG) para el grupo de cirugía de citorreducción primaria - grupo CCP -, la cirugía de citorreducción de intervalo temprana después de 3-4 ciclos de QTNA - grupo CCI temprana - y la cirugía de citorreducción tardía después de 6 ciclos de QTNA - grupo CCT - sin enfermedad residual (CC-0) o con mínima enfermedad residual (CC-1). También se estimó la supervivencia según el índice de cáncer peritoneal (PCI) y el score de Aletti, en función de la aparición de complicaciones postoperatorias mayores y de la respuesta histológica a la QTNA evaluada mediante el score validado de respuesta a la quimioterapia. Los análisis de supervivencia se realizaron utilizando la prueba de Logrank y el modelo de Cox. Las incidencias acumuladas de los diferentes patrones de recurrencia se estimaron utilizando una metodología de riesgo competitivo.

Incluimos 549 pacientes, 175 (31,9%) se sometieron a CCP, 224 (40,8%) a CCI temprana después de 3-4 ciclos de QTNA, y 150 (27,3%) a CCT después de 6 ciclos de QTNA. La mediana de SLE en CCP, CCI temprana a los 3-4 ciclos y CCT a los 6 ciclos fueron 23,0 meses (IC del 95% = [20,0–29,3]), 18,0 meses (IC del 95% = [15,9–20,0]) y 17,1 meses (IC del 95% = [15,0–20,9]), respectivamente; $p < 0,001$. La mediana de SG fue de 84,0 meses (IC del 95% = [68,3–111,0]),

50,7 meses (IC del 95% = [44,6–59,5]) y 47,5 meses (IC del 95% = [39,3–52,9]), respectivamente; $p < 0,001$. En el análisis multivariable, un puntaje alto del PCI y la QTNA se asociaron negativamente con la SLE y la SG. La complejidad quirúrgica (score de Aletti ≥ 8) y CC-1 se asociaron negativamente con la SLE. Independientemente del puntaje de Aletti, la mediana de SG después de CCP fue significativamente mayor que después de CCI temprana o CCT, pero la diferencia de supervivencia fue mayor en mujeres con un puntaje de Aletti < 8 . Entre los pacientes con PCI ≤ 10 , la mediana de SG después de CCP fue significativamente mayor que después de CCI temprana o CCT. En mujeres con PCI > 10 , no hubo diferencias entre CCP y CCI temprana, pero CCT se asoció con una disminución de la SG. La tasa general de complicaciones quirúrgicas mayores fue del 22,4%. Los pacientes que se sometieron a CCP tuvieron una tasa más alta de complicaciones mayores (28,6%) que los pacientes que se sometieron a CCI temprana (23,2%) o CCT (14,0%). El análisis multivariable reveló que una peritonectomía extensa y el momento quirúrgico se asociaron con la aparición de complicaciones mayores. La mediana de SLE y SG fue de 16,9 meses (IC del 95% = [13,7-18,4]) y 48,0 meses (IC del 95% = [37,2-73,1]) para el grupo de pacientes con complicaciones mayores, y 20,1 meses (IC del 95% = [18,6-22,4]) y 56,7 meses (IC del 95% = [51,2-70,4]) para el grupo sin complicaciones mayores. El análisis multivariable reveló que las complicaciones quirúrgicas mayores estaban significativamente asociadas con la SLE, pero no con la SG. Con relación al análisis del score validado de respuesta a la quimioterapia, solo se incluyeron los 365 pacientes que recibieron QTNA: 219 (60,0%) recibieron 3-4 ciclos y 146 (40,0%) recibieron 6 ciclos antes de la cirugía citorreductora. No hubo diferencias significativas en las recaídas tempranas, la SLE y la SG según el número de ciclos de QTNA. Sin embargo, independientemente del número de ciclos de QTNA, la enfermedad histológica extensa persistente (puntuación del score validado de respuesta a la quimioterapia de 1-2) se asoció significativamente con un PCI más alto, una enfermedad residual mínima (CC-1) y recaídas tempranas. La mediana de la SLE en pacientes con respuesta completa o casi completa (puntuación del score validado de respuesta a la quimioterapia de 3) fue de 28,3 meses (IC del 95% = [21,6-36,8]), mientras que fue de 16,3 meses en pacientes con una puntuación del score validado de respuesta a la quimioterapia de 1-2 (IC del 95% = [14,7-18,0]) ($p < 0,001$). En cuanto a las recurrencias, la incidencia acumulada de recurrencias peritoneales a los dos años fue mayor con el aumento de los ciclos de QTNA (24,4%, 30,9% y 39,2%; $p = 0,019$). Para las recurrencias pleurales o pulmonares, fue mayor después de la CCI temprana (9,9%, 13,0% y 4,1%; $p = 0,022$). La mediana de la supervivencia después de la recaída fue de 33,5 meses (IC del 95% = [24,3-44,2]), 26,8 meses (IC del 95% = [22,8-32,6]) y 24,5 meses (IC del 95% = [18,6-29,4]) para los grupos CCP, CCI temprana y CCT, respectivamente ($p = 0,025$). El patrón de recurrencia dentro de un ganglio linfático (HR 0,42, IC del 95% = [0,27-0,64]), la CCT (HR 1,53,

IC del 95% = [1,11-2,13]) y el tiempo hasta la primera recurrencia (HR 0,95, IC del 95% = [0,93-0,96]) se asociaron con la supervivencia después de la recaída. Para CCP y CCI temprana, las recurrencias en los ganglios linfáticos se asociaron con una supervivencia después de la recaída significativamente más larga.

En conclusión, la CCP ofreció una ganancia de supervivencia de casi tres años en comparación con la CCI temprana y la CCT en pacientes con enfermedad residual mínima o nula después de la cirugía. El beneficio de la CCP con citorreducción completa en comparación con la QTNA fue máximo en pacientes con baja complejidad quirúrgica. En pacientes con baja carga tumoral, hubo un beneficio de supervivencia de la CCP sobre la CCI temprana o la CCT. En las mujeres con una alta carga tumoral, la CCT afectó negativamente el resultado oncológico. Las pacientes que experimentaron complicaciones quirúrgicas mayores tuvieron una SLE reducida en comparación con los pacientes sin complicaciones mayores. La peritonectomía extensa y el momento quirúrgico fueron factores predictivos de la morbilidad postoperatoria. Una respuesta histológica completa o casi completa a la QTNA mejoró el resultado oncológico independientemente del número de ciclos de QTNA. El patrón de la primera recurrencia se asoció con el momento quirúrgico, siendo las recurrencias peritoneales más frecuentes con el aumento del número de ciclos de QTNA. Las recurrencias en los ganglios linfáticos se asociaron con un mejor pronóstico, con una mayor supervivencia después de la recurrencia. Este mejor pronóstico de las recurrencias linfáticas no se observó en los pacientes que se sometieron a una cirugía tardía. La CCP debería seguir siendo el tratamiento estándar para las pacientes con cáncer de ovario avanzado cuando se pueda lograr una citorreducción completa.

INTRODUCTION

INTRODUCTION

1. EPIDEMIOLOGY

Ovarian cancer is the third most common gynecological malignancy worldwide after cervical and uterine cancer, and the second most common in high-income countries after uterine malignancy¹. It is the second cause of death from gynecological malignancies worldwide after cervical cancer, and the first in high-income countries¹. In 2020, 313,959 women were diagnosed with ovarian cancer worldwide and 207,252 died from this disease¹.

Epithelial ovarian, fallopian tube, and peritoneal malignancies are considered a single clinical entity because they have the same clinical behavior and therapeutic management. Furthermore, there is accumulating evidence suggesting a shared pathogenesis among these carcinomas. Fallopian tube and peritoneal carcinomas have been thought to be very infrequent. However, their incidence is now supposed to be higher as when they are diagnosed in an advanced stage, they are indistinguishable from advanced ovarian cancer^{2,3}.

In Table 1, we expose the FIGO 2014 staging classification system for ovarian, fallopian tube and peritoneal cancer⁴. From here to the end of the manuscript, when mentioning ovarian cancer, we will implicitly refer to the entity including ovarian, fallopian tube, and peritoneal cancer.

Most patients with ovarian cancer are diagnosed with an advanced stage of the disease with peritoneal carcinomatosis. This is due to the lack of symptoms at early stages and due to the nonexistence of effective screening strategies⁵. These issues will be further discussed in the following sections.

Table 1. FIGO staging classification for cancer of the ovary, fallopian tube, and peritoneum⁴

FIGO 2014	Description	TNM
Stage I	Tumor confined to ovaries or fallopian tubes	T1-N0-M0
IA	Tumor limited to 1 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 washings	T1b-N0-M0
IC	Tumor limited to 1 or both ovaries or fallopian tubes, with any of the following:	T1c-N0-M0
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 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 peritoneal cancer, with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes	T1-3/N0-1/M0
IIIA1	Positive retroperitoneal lymph nodes only (cytologically or histologically proven):	T1/T2-N1-M0
IIIA1(i)	Metastasis up to 10 mm in greatest dimension	
IIIA1(ii)	Metastasis more than 10 mm in greatest dimension	
IIIA2	Microscopic extrapelvic (above the pelvic brim) peritoneal involvement with or without positive retroperitoneal lymph nodes	T3a2-N0/N1-M0

IIIB	Macroscopic peritoneal metastasis beyond the pelvis up to 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes	T3b-N0/N1-M0
IIIC	Macroscopic peritoneal metastasis beyond the pelvis more than 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes (includes extension of tumor to capsule of liver and spleen without parenchymal involvement of either organ)	T3c-N0/N1-M0
Stage IV	Distant metastasis excluding peritoneal metastases	Any T, any N, M1
IVA	Pleural effusion with positive cytology	
IVB	Parenchymal metastases and metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)	

FIGO: International Federation of Gynecology and Obstetrics.

While the staging classification system used for these three anatomic sites is the same, the histologic subtypes of this malignancy include a heterogeneous group of diseases with different pathogenesis, genetic risk factors, clinical behavior, response to systemic treatment, and prognosis. Epithelial carcinoma accounts for 90-95% of all ovarian malignancies and, in this manuscript, we will focus on this histologic type^{6,7}. The remaining ovarian malignancies arise from other ovarian cell types (germ cell tumors and sex cord-stromal tumors). In Figure 1, we display the different cell origin of ovarian tumors.

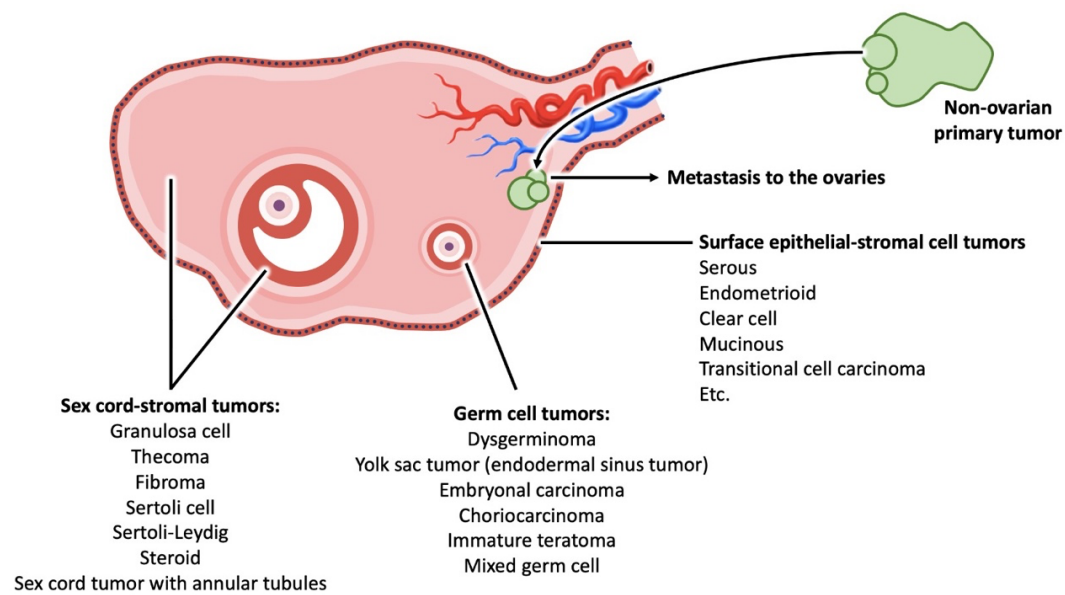


Figure 1. Different origins of ovarian tumors

In Table 2, we present the five main epithelial subtypes of this malignancy.

Table 2. Histologic subtypes of epithelial ovarian⁸ cancer and relative proportions⁹

High-grade serous carcinoma	70-80%
Endometrioid carcinoma	10%
Clear cell carcinoma	10%
Mucinous carcinoma	3%
Low-grade serous carcinoma	<5%
Other rare epithelial subtypes: transitional cell carcinoma, carcinosarcoma, undifferentiated or dedifferentiated carcinoma	

High-grade and low-grade serous carcinomas are considered two different diseases with different pathogenesis. Even if it is thought that both are originated in the fallopian tube, it is

suggested that serous tubal intraepithelial carcinoma is the precursor of high-grade serous carcinoma and endosalpingiosis is the precursor of low-grade serous carcinoma⁹.

Some factors have been recognized as risk factors or protective factors for ovarian cancer development¹⁰. The following **risk factors** have been associated with ovarian cancer occurrence: older age, early menarche, late menopause, genetic factors such as breast cancer (BRCA) mutations or Lynch syndrome, nulliparity, endometriosis, among others. As well, bilateral salpingo-oophorectomy, tubal ligation, oral contraception, intrauterine device, breastfeeding, parity, among other factors have been established as **protective factors** for ovarian cancer occurrence.

Regarding the **screening of ovarian cancer**, none of the evaluated strategies (cancer antigen [CA] 125 dosage, transvaginal ultrasound, or a combined or sequential approaches) has been shown to reduce the mortality related to this disease in asymptomatic women without a genetic predisposition or family history of ovarian cancer¹¹. Screening strategies are associated with a high rate of false-positive tests and risk of harm from invasive testing in these patients.

2. DIAGNOSIS

The **clinical manifestation** of ovarian cancer is most commonly subacute with unspecific symptoms such as pelvic and abdominal pain, abdominal distension and bloating, nausea, anorexia, early satiety, urinary urgency or frequency, among others. These nonspecific symptoms which may also be caused by other medical conditions explain the delay in diagnosis and, as previously mentioned, lead to diagnose most patients in advanced stages¹².

Although less frequent, clinical presentation of ovarian cancer can also be acute, usually associated with advanced stages. Acute symptoms and signs can include ascites, pleural effusion, bowel obstruction, and venous thromboembolism, among others¹².

More rarely, the diagnosis of ovarian cancer can be done incidentally, and in these cases, the disease can be diagnosed in an earlier stage. An adnexal mass can be found during routine pelvic examination, during surgery for another indication, or in an imaging study¹².

The **diagnostic evaluation** of these patients includes a physical exam, an imaging study, a blood test with serum biomarkers, and histological assessment. Abdominal and pelvic **physical examination** is usually the first step of the evaluation and can help to find the adnexal mass. Typically, the initial **imaging** preferred and performed by the gynecologists is the **pelvic ultrasound**, which can assess the degree of suspicion when done by experienced sonographers. Subsequent imaging can be an **abdomino-pelvic magnetic resonance imaging** (MRI) which can help to characterize the adnexal mass because its excellent soft tissue contrast resolution. However, a **thoraco-abdomino-pelvic computed tomography** (CT) is more often performed, being less expensive and more comfortable for patients, and helps to assess the disease spread (retroperitoneal, inguinal, mediastinal or supraclavicular lymph node involvement, ascites, peritoneal carcinomatosis, pleural effusion, pleural involvement, etc.)¹². In case of suspicion of extra-abdominal disease spread, a positron emission tomography (**PET**)/CT can be performed as some studies suggest the increase of detection of metastatic disease with this imaging study. PET/CT has a high sensitivity to detect extra-abdominal disease in ovarian cancer, such as supra-diaphragmatic lymph node metastases or pleural invasion, up-staging the disease to FIGO stage IV, which can modify the therapeutic management^{13–16}.

Regarding **serum biomarkers**, CA 125 may be elevated in up to 80% of patients with epithelial ovarian cancer¹⁷. CA 125 testing may also be useful to assess the response to systemic treatment and to diagnose a disease recurrence. Human epididymis protein 4 (HE4), carcinoembryonic antigen (CEA), and cancer antigen 19-9 (CA 19-9) are other serum biomarkers that may be increased in some epithelial ovarian cancer patients¹⁸.

Performing a **paracentesis** or a **thoracentesis** may help to relieve the symptoms of patients with advanced disease, but it also allows to obtain a peritoneal or pleural cytology which can confirm the diagnosis of malignancy. However, a cytology cannot replace a biopsy to establish the diagnosis of ovarian cancer, and a biopsy is mandatory before starting systemic treatment.

Surgical exploration with a **diagnostic laparoscopy** may be part of the diagnostic evaluation. In case of advanced disease with carcinomatosis, peritoneal and/or omental biopsies will be performed to establish a histological diagnosis. In case of absence of carcinomatosis, removing the adnexal mass is part of the diagnostic evaluation. This can be done by laparoscopy or by laparotomy if there is a high risk of rupture.

Ultrasound- or CT-guided biopsy of the carcinomatosis can be considered in frail patients to avoid performing a laparoscopic procedure¹⁹. However, the biopsies are usually smaller than those obtained by laparoscopy. Performing a biopsy of the adnexal mass should be avoided to prevent tumor spillage and upstaging the disease.

Testing for a hereditary syndrome:

Approximately one-quarter of all ovarian cancers are caused by a heritable genetic condition²⁰. Of these, mutations in BRCA1 and BRCA2 genes are the most common, accounting for almost 40% of ovarian cancers in women with a family history of the disease²¹. Other many genes are those associated with the Fanconi anemia pathway or otherwise involved with homologous recombination²⁰. Germline mutations in BRCA1 and BRCA2 have been identified in 13%-15% of women diagnosed with ovarian cancer, and somatic mutations are found in an additional 5-7% of cases²²⁻²⁷.

Irrespective of their family cancer history, all women with epithelial ovarian cancer should be offered at diagnosis a germline genetic testing for BRCA1, BRCA2, and other ovarian cancer susceptibility genes, as it may have clinical implications²⁸. These patients may present a higher response rate to platinum-based chemotherapy and to poly (ADP-ribose) polymerase inhibitors (PARPi)²⁹. Somatic tumor testing (less sensitive than germline testing) for BRCA1 and BRCA2 should be performed in women who do not carry a germline pathogenic or likely pathogenic BRCA1/2 variant, as an additional 5-7% of cases will be detected.

Regarding the different histologic subtypes, high-grade serous ovarian cancer has the highest mutation frequency of BRCA mutations, but other histologic subtypes such as endometrioid, clear cell, low-grade serous, or carcinosarcoma subtypes have appreciable rates of mutations, and genetic testing should not be restricted to high-grade serous subtype^{26,30}. Conversely, women with a diagnosis of mucinous ovarian cancer are the least likely to have germline hereditary mutations in BRCA³¹. Parallely, mutations conferring dMMR are found more frequently in non-serous subtypes, specifically, in endometrioid (19.2%), mucinous (16.9%), and clear cell (11.5%)³²⁻³⁴. Women diagnosed with these lastly mentioned subtypes should be offered somatic tumor testing for mismatch repair deficiency (dMMR)²⁸.

3. PROGNOSIS

The patients diagnosed with early-stage disease have a favorable prognosis, with approximately 80% of them without evidence of disease five years after diagnosis. Conversely, most of the patients who are diagnosed with advanced disease will experience the first recurrence during the following years after diagnosis. Relapse of the disease is typically considered incurable. The natural history of advanced ovarian cancer includes a variable number of subsequent recurrences which will be treated with multiple additional lines of systemic treatment and will ultimately lead to a fatal outcome in most patients. Table 3 displays the five-year survival rates by stage⁵.

Table 3. Five-year disease-specific survival (%) for epithelial ovarian cancer⁵

Stage*	Five-year disease-specific survival				
	All epithelial subtypes	Serous	Endometrioid	Mucinous	Clear cell
All stages	47	43	82	71	66
Stage I	89	86	95	92	85
Stage II	71	71	84	69	71
Stage III	41	42	59	30	35
Stage IV	20	26	29	13	16

*American Joint Committee on Cancer (AJCC) Cancer Staging Manual, 6th edition.

The prognostic factors associated with an impaired prognosis in patients with ovarian cancer have been evaluated in several studies³⁵. In the following lines, we will discuss the main prognostic factors of this disease:

- **Age** is an independent prognostic factor in ovarian cancer patients. Multiple studies have demonstrated that younger age is associated with a favorable prognosis^{35–37}. Moreover, younger patients have a better baseline performance status and are more likely to be completely cytoreduced^{36,38,39}. Less aggressive histologic subtypes such as low-grade serous are more frequent in these patients and younger women are usually diagnosed at earlier stages^{36,39}.

- **Performance status** is an independent predictor of recurrence and survival^{35,40–43}. Moreover, patients with a poorer performance status will be less likely to undergo cytoreductive surgery and to tolerate chemotherapy, and overall to receive adequate and optimal treatment.

- **BRCA gene mutations**, particularly BRCA2, appear to have a better prognosis than noncarriers²⁹.

- Different histologic subtypes have been associated with different prognoses^{40,44}. **Serous** subtypes have been associated with an improved prognosis, particularly low-grade disease. Mucinous and clear-cell subtypes are thought to have a poorer prognosis, particularly in advanced stages³⁵. This could be partially due to their increased chemoresistance. Some studies describe that mucinous histology has an increased risk of death compared with clear cell subtype³⁵.

- **FIGO stage** has been shown to be an independent prognostic factor, earlier stages having an improved prognosis compared to advanced stages. Even in case of absence of residual disease at the end of cytoreductive surgery, FIGO stage seems to impact on patients' survival^{45,46}.

- **Residual disease** after cytoreductive surgery has been consistently established as the main prognostic factor of advanced ovarian cancer in several reports⁴⁷⁻⁴⁹. Absence of residual disease is defined as no visible macroscopic residual tumor at the end of cytoreductive surgery. Moreover, the volume of residual disease is the only major prognostic factor that the surgeon can address, as the resectability of the disease is partially influenced by the judgment, surgical skills, and surgical effort of the surgeon⁵⁰.

- **Decrease of CA 125** during neoadjuvant chemotherapy has been associated with patients' survival. The modeled CA 125 ELIMination rate constant K (KELIM) is calculated based on the longitudinal kinetics during the first three cycles (100 days) of platinum-based chemotherapy. This tool seems to be an indicator of tumor chemosensitivity, it is associated with the likelihood of achieving complete cytoreduction at interval debulking surgery, as well as with subsequent platinum-free interval, progression-free survival, overall survival, and with the efficacy of maintenance therapy⁵¹.

4. TREATMENT

Generalities:

The treatment of epithelial ovarian cancer varies according to the stage in which the disease is diagnosed, combining both surgery and systemic treatment. Early stages include patients diagnosed with stage IA to IIA and advanced stages comprise those with stage IIB to IVB. In early stages, the surgical goal is to remove the adnexal mass and to perform a peritoneal and lymph node staging. Women with early-stage disease are treated with an initial surgery including the following procedures:

- Bilateral salpingo-oophorectomy
- Total extrafascial hysterectomy
- Infracolic omentectomy
- Peritoneal biopsies (suspicious lesions or random if there are not suspicious lesions)
- Bilateral pelvic and paraaortic lymphadenectomy (from the circumflex vein and obturator nerve *-caudal limit-* to the left renal vein *-cranial limit-*)
- Appendectomy (in case of visible lesions or mucinous histology)
- Peritoneal cytology (ascites or peritoneal washing if there is not ascites)

It is very important to perform a thorough exploration of the abdominal cavity to detect any peritoneal lesion which would upstage the disease and, in some cases, modify adjuvant treatment. The surgical procedure can be done either by minimally invasive (laparoscopic or robotic) or laparotomic approach, this should be decided according to the feasibility of the procedure without rupturing the adnexal mass (to avoid tumor spillage) and being sure to achieve an optimal exploration of the abdominal cavity. A fertility-sparing management can be offered to young patients with an active childbearing wish, and it includes the preservation of the contralateral ovary and the uterus.

Patients presenting with advanced-stage disease, in whom we will focus on the manuscript of this thesis, are managed with a combined surgical and medical approach, which are the cornerstones of first-line treatment⁵²⁻⁵⁴. The standard management of advanced ovarian cancer with carcinomatosis includes a **cytoreductive surgery** (also known as debulking surgery), which can be primary *-performed before chemotherapy-* or interval *-performed after neoadjuvant chemotherapy-*, and **systemic chemotherapy** followed by **maintenance therapy**. The standard systemic treatment delivered to these patients is a platinum and taxane-based chemotherapy, usually a regimen with carboplatin with area under the curve (AUC) 5-6 and paclitaxel 175 mg/m², every three weeks until completing a total of six cycles. Since the results of SOLO1²⁹, PRIMA⁵⁵ and PAOLA⁵⁶ trials, PARPi are the new standard of care in the first-line maintenance treatment of advanced epithelial ovarian cancer and the vast majority of patients will receive a PARPi (olaparib^{29,56}, rucaparib⁵⁷ or niraparib⁵⁵), alone or in combination with the anti-angiogenic bevacizumab⁵⁸. We will not extent on the description and indications of these treatments as it is out of the scope of this thesis. Moreover, the study period of our work was previous to PARPi era and, therefore, the patients included in the study did not receive maintenance therapy with PARPi.

Surgical goal:

Regarding cytoreductive surgery, the **goal** of this procedure is to remove all the macroscopic disease, as it has been shown that absence of residual tumor after cytoreductive surgery -*complete cytoreduction*- is the main prognostic factor in these patients^{47,48}. The goal of the surgery has evolved over the years, as two decades ago the objective of debulking surgery was to achieve residual tumor ≤ 1 cm -*optimal cytoreduction*-.⁵⁹ The reason for this change of paradigm was due to an improved survival of patients with complete cytoreduction compared to those with optimal cytoreduction⁴⁹.

Surgical procedures:

Cytoreductive surgery should be performed by skilled gynecological oncologists in referral high-volume centers as it has been shown to improve patient's survival⁶⁰⁻⁶². As the tumor burden is mainly located in the pelvis, the omentum and the right diaphragmatic peritoneum, the **common surgical procedures** performed during debulking surgery are (1) en-bloc pelvic peritonectomy with total extrafascial hysterectomy and bilateral adnexectomy by a retroperitoneal access, with or without rectosigmoid resection, (2) radical infragastric omentectomy with or without gastroepiploic arcade preservation depending on tumor involvement, (3) right diaphragmatic peritonectomy with previous liver mobilization. Other common procedures are bilateral paracolic gutter peritonectomy, appendectomy, and pelvic and paraaortic lymphadenectomy. Since the publication of LION's trial, this latter procedure is no longer routinely performed as it is associated with increased morbidity without survival benefit⁶³. Currently, selective resection of bulky lymph nodes is indicated to obtain a complete resection of the disease.

In recent decades, there has also been an **evolution in the radicality** of cytoreductive surgery to achieve complete cytoreduction. Surgical effort has gradually been expanded by incorporating extensive surgical procedures in the upper abdomen^{64,65}. The incorporation of these procedures has increased the rate of complete and optimal cytoreduction and it has improved the survival of women with advanced ovarian cancer^{64,66-68}. Upper abdomen procedures which may be required during debulking surgery are splenectomy, bowel resection, partial hepatectomy, transfixing diaphragm resection, porta hepatis or celiac lymph node resection, transdiaphragmatic cardiophrenic lymph node resection, among others. All these procedures should only be performed if complete cytoreduction is achievable. In this purpose, it is recommended to start the cytoreductive surgery by the most technically challenging procedures and by those which may preclude complete cytoreduction, in order to abort the

surgery before adding more morbidity in case of non-resectability. Cytoreductive procedures need to be performed in surgical teams including gynecological oncologist trained to perform these procedures or with multidisciplinary collaboration with digestive surgeons.

Prediction of resectability:

As cytoreductive surgery is a major abdominal surgery with potential associated morbidity and without a survival benefit in the case of suboptimal cytoreduction, it is essential to be sure of the feasibility of a complete cytoreduction before starting the procedure. Preoperative imaging may be useful in assessing the resectability of the disease, particularly in case of massive tumor involvement. However, conventional imaging such as CT and MRI are not able to detect ovarian peritoneal carcinomatosis when lesions measure less than 1 cm^{69,70}. Other imaging tools such as PET/CT have been evaluated, showing a high rate of false negative results in lesions of ovarian carcinomatosis below 5 mm⁷¹.

Staging laparoscopy may add valuable information before primary treatment, avoiding unnecessary and futile exploratory laparotomies and decreasing the delay to neoadjuvant chemotherapy⁷²⁻⁷⁶. Objective assessment during staging laparoscopy to standardize the term of resectable disease is needed. For this reason, some scores such as peritoneal cancer index (PCI) have been developed⁷⁷. PCI describes the extent and anatomic distribution of peritoneal carcinomatosis, and it objectively quantifies the tumor burden⁷⁷. Tentes et al. showed that peritoneal spread in advanced ovarian cancer could be assessed in detail using PCI, and that this score was a significant prognostic factor of survival⁷⁸. Several studies have evaluated PCI accuracy to predict complete cytoreduction⁷⁹⁻⁸¹. Fagotti et al. developed a different laparoscopic scoring algorithm, referred to as the predictive index value (PIV)⁸². It includes seven parameters: omental cake, peritoneal carcinomatosis, diaphragmatic carcinomatosis, mesenteric retraction, bowel and/or stomach infiltration, and liver metastasis. Each parameter is scored with a value of two points. Several studies have shown a good accuracy of PIV to predict resectability⁸²⁻⁸⁵. Other groups propose an early intraoperative examination of the small bowel and the hepatoduodenal ligament regions by a periumbilical laparotomy before performing a xiphopubic laparotomy⁸⁶. However, this approach is associated with increased morbidity and postoperative pain^{73,74}.

Surgical timing:

Classically, in patients with completely resectable disease and good performance status, **primary debulking surgery** followed by adjuvant chemotherapy is the mainstay of therapeutic

strategy⁵²⁻⁵⁴, as it has been consistently associated with improved survival outcomes in retrospective studies^{53,54,87}. In case of non-operable patients -who are not fit to tolerate surgery owing to older age, poor performance status, poor preoperative nutritional status, or medical comorbidities-, low likelihood of achieving complete cytoreduction, or high surgical complexity expected, neoadjuvant chemotherapy is preferred with non-inferior survival benefit⁸⁸⁻⁹⁰. Despite the classical indications of neoadjuvant chemotherapy, the best timing to perform cytoreductive surgery is still controversial. Two randomized controlled trials comparing primary debulking surgery followed by adjuvant chemotherapy and neoadjuvant chemotherapy followed by interval debulking surgery suggested that the second strategy has a non-inferior survival outcome^{91,92}. Nevertheless, these trials have been extensively criticized due to their low rate of complete cytoreduction in patients with primary debulking surgery, being as low as 20%^{91,92}. More recently, SCORPION randomized trial including patients with high tumor load showed that primary debulking surgery and neoadjuvant chemotherapy had superimposable survival outcomes⁹³. Few meta-analyses have been conducted reporting controversial results. While some of them report superior survival rates in patients undergoing primary debulking surgery^{54,94,95}, others have stated no survival differences between primary and interval surgeries^{96,97}. A recent review including 24 publications compared the impact of complete cytoreduction after primary and interval debulking surgery. The authors found an improved median survival of almost two years in patients who underwent upfront procedures⁵³.

Regarding the **timing of interval debulking surgery**, delivering three cycles of neoadjuvant chemotherapy is the standard of care according to EORTC 55971 and CHORUS trials^{91,92}. Three cycles of adjuvant chemotherapy are delivered after the surgery to complete a total of 6 cycles of chemotherapy. Reports evaluating the role of interval debulking surgery after more than four cycles of neoadjuvant chemotherapy are controversial⁹⁸⁻¹⁰⁵. While some have shown that survival is similar to that of patients undergoing interval surgery after three cycles of neoadjuvant chemotherapy⁹⁹⁻¹⁰², other studies have described an impaired prognosis of delayed interval debulking surgery^{103,104}. It is then an option to deliver three additional cycles of chemotherapy and perform delayed IDS in patients who are still non-resectable after the first three cycles of NACT⁹⁹⁻¹⁰². To date, there has been no randomized controlled trial to determine the best timing for interval debulking surgery, but there is an ongoing randomized controlled trial (CHRONO; NCT03579394), which will answer this question.

Neoadjuvant chemotherapy has been associated with lower morbidity and postoperative mortality, higher rates of complete cytoreduction, and less extensive surgical

procedures^{88,106}. Neoadjuvant chemotherapy allows *in vivo* tumor chemosensitivity assessment according to histopathological response. Complete histopathological response, defined as the absence of surgical residual disease, is achieved in fewer than 10% of patients receiving neoadjuvant chemotherapy, and is associated with significantly longer survival^{107,108}. A chemotherapy response score has been developed to describe the response to neoadjuvant chemotherapy in high-grade serous carcinomas^{109–112}. This score is obtained on interval debulking specimens, it has been associated to platinum-sensitivity and has shown a prognostic role^{109–112}. The counterpart of neoadjuvant chemotherapy is that it has been associated with chemoresistance. It has been hypothesized that chemoresistant clonal cells can be selected with neoadjuvant chemotherapy⁵⁴, meaning that surgery after neoadjuvant treatment would be less effective than upfront surgery, leading to a higher rate of recurrences. Therefore, still today the timing of cytoreductive surgery in advanced ovarian cancer remains a controversial topic.

5. JUSTIFICATION OF THE PROJECT

As previously mentioned, the best timing to schedule cytoreductive surgery to obtain the maximal survival benefit has been a topic largely debated and remains nowadays controversial. In some patients, the therapeutic strategy is clear and will be homogeneous along different surgical teams. Patients with good performance status and low tumor burden (e.g., confined to the pelvis, involving few peritoneal surfaces, or not requiring bowel or visceral resections) are good candidates for primary debulking surgery. As well, in young patients with less chemosensitive histological subtypes (i.e. low-grade serous ovarian carcinoma) upfront surgery is preferred over neoadjuvant chemotherapy, even if complete resection cannot be achieved^{113,114}. Patients with poor performance status, important comorbidities, or those with non-resectable disease (e.g., deep infiltration of the mesenteric root, diffuse carcinomatosis involving large parts of the small bowel, stomach, porta hepatis or celiac trunk, infiltration of the duodenum or the pancreas not limited to the pancreatic tail, or parenchymal liver involvement) should undergo neoadjuvant chemotherapy. While in these previous groups of patients the management is well established, there is a range of patients in whom the best strategy is unclear, and the management will vary according to the surgical team based on their surgical skills and philosophy. To date, there is no established PCI cutoff to decide whether to perform primary debulking surgery or neoadjuvant chemotherapy because other factors such as age, performance status, medical comorbidities, histological type, and chemosensitivity

should be considered in this decision. Patients with good performance status and high intraabdominal tumor load requiring multivisceral resection, multiple bowel resections, or radical upper-abdomen procedures to achieve complete cytoreduction, or those with stage IVB resectable disease may undergo primary debulking surgery or neoadjuvant chemotherapy depending on the decision of the surgical treating team. Of course, the decision is always made individualizing each case and considering all the medical factors of each patient, but there is a lack of standardization of what factors should be taken into account when deciding the timing of cytoreductive surgery.

With the aim to increase the current knowledge on this subject, we conducted this work which will attempt to further clarify some important aspects that could guide the decision of the best timing for cytoreductive surgery.

5.1. CLINICAL ISSUE 1: SURGICAL TIMING

As previously stated, it is unclear if there is a survival benefit of primary debulking surgery over either early interval debulking surgery (after 3-4 cycles of neoadjuvant chemotherapy) or delayed debulking surgery (after 6 cycles of chemotherapy) in the setting of patients who undergo cytoreductive surgery with minimal or no residual disease.

As well, defining in these patients -with complete cytoreduction or with minimal residual disease- which are the factors influencing their long-term survival may help to guide the decision on the ideal surgical timing.

5.2. CLINICAL ISSUE 2: IMPACT OF PROGNOSTIC FACTORS ON SURVIVAL BENEFIT

Besides the absence of residual disease after cytoreductive surgery, which is the main prognostic factor in patients with advanced ovarian cancer, some other factors have been associated with impaired prognosis. Tumor burden and surgical complexity seem to negatively impact patients' survival. It is currently unknown if these negative prognostic factors may modify the benefit conferred by primary debulking surgery. This information could be of precious value

as it could help to guide the decision on when to perform cytoreductive surgery according to tumor burden and surgical complexity.

5.3. CLINICAL ISSUE 3: IMPACT OF POSTOPERATIVE MORBIDITY ON SURVIVAL

As mentioned before, the paradigm of cytoreductive surgery has evolved over the last two decades, including increasingly complex upper abdomen procedures. Primary debulking surgery has been associated with increased postoperative morbidity due to more extensive and complex surgical procedures performed in this setting. In other abdominal malignancies such as colon cancer, major postoperative complications have been associated with an impaired oncological outcome. In ovarian cancer, there is a lack of evidence regarding the impact on survival of major postoperative complications, and which factors are associated with the occurrence of these complications. This is an important aspect to consider when evaluating the ideal timing to perform a cytoreductive surgery: more extensive surgery in a primary setting vs. less extensive procedure in interval surgery.

5.4. CLINICAL ISSUE 4: IMPACT OF RESPONSE TO CHEMOTHERAPY

Neoadjuvant chemotherapy has the aim of decreasing tumoral load to increase the possibility of achieving complete cytoreduction at the end of debulking surgery, but it also allows to decrease the associated surgical morbidity due to less extensive surgical procedures. The response to neoadjuvant chemotherapy is a recognized prognostic factor associated with survival. However, the impact on survival of this response according to the number of cycles of neoadjuvant chemotherapy is currently unknown. Understanding if the response to neoadjuvant chemotherapy (measured by chemotherapy response score) has a different value depending on the number of cycles of chemotherapy delivered could guide the decision on surgical timing.

5.5. CLINICAL ISSUE 5: IMPACT OF SURGICAL TIMING ON RECURRENCE PATTERN

Despite the maximal surgical effort and improved survival with the addition of maintenance treatment strategies, most patients with advanced ovarian cancer will experience a recurrence of their disease. However, there is a lack of robust data in the literature assessing the influence of surgical timing on the natural history of recurrent ovarian cancer. Knowing if the pattern of the first recurrence may vary according to the timing of cytoreductive surgery could provide valuable information to tailor the decision on surgical timing. As well, it is essential to understand if the pattern of recurrence has an impact on patients' survival after recurrence diagnosis.

6. HYPOTHESIS

According to the previously exposed ideas, the following hypotheses were generated:

1. Survival is associated with surgical timing in patients undergoing cytoreductive surgery with complete cytoreduction (CC-0) or cytoreduction to minimal residual disease (CC-1) for advanced ovarian cancer (IIIC-IVB), and both tumor burden and surgical complexity may have an impact on their survival.
2. The impact on survival of surgical timing can vary according to tumor burden and surgical complexity in these patients.
3. Major postoperative complications are associated with survival of patients who underwent a cytoreductive surgery with CC-0 or CC-1 for advanced ovarian cancer, and there are some predictive factors of the occurrence of these complications.
4. The impact on survival of chemotherapy response score can vary according to the number of cycles of NACT in patients with advanced ovarian cancer non-eligible for primary surgery.
5. There is an association between the timing of cytoreductive surgery and the pattern of presentation of the first recurrence in patients who underwent a cytoreductive surgery with CC-0 or CC-1 for advanced ovarian cancer. The impact on post-relapse overall survival of the pattern of recurrence can vary according to surgical timing in these patients.

7. OBJECTIVES

FIRST STUDY

1. To assess the **survival benefit** of **primary debulking surgery** compared to **early interval debulking surgery** at 3-4 cycles or **delayed debulking surgery** at 6 cycles of neoadjuvant chemotherapy after **complete cytoreduction** (CC-0) or **cytoreduction to minimal residual disease** (CC-1) in patients with advanced ovarian cancer (IIIC-IVB).
2. To evaluate the **prognostic impact** of **tumor burden** (PCI score) and **surgical complexity** (Aletti score) on patients' survival.

SECOND STUDY

3. To evaluate the **impact on survival** of the **surgical timing according to tumor burden** (PCI score) and **surgical complexity** (Aletti score) in patients with advanced ovarian cancer (IIIC-IVB) treated with CC-0 or CC-1 at cytoreductive surgery.

THIRD STUDY

4. To assess the **impact on survival** of **major postoperative complications** in patients who underwent a cytoreductive surgery with CC-0 or CC-1 for advanced ovarian cancer (IIIC-IVB).
5. To identify the **factors associated** with **major postoperative complications** in patients who underwent a cytoreductive surgery with CC-0 or CC-1 for advanced ovarian cancer (IIIC-IVB).

FOURTH STUDY

6. To evaluate the **impact on survival** of **chemotherapy response score according to the number of cycles of neoadjuvant chemotherapy** in patients with advanced ovarian cancer (IIIC-IVB) non-eligible for primary debulking surgery who underwent either early interval debulking surgery (after 3-4 cycles) or delayed debulking surgery (after 6 cycles).

FIFTH STUDY

7. To evaluate the **association** between the **timing of cytoreductive surgery** and the **pattern of presentation of the first recurrence** in patients who underwent a cytoreductive surgery with CC-0 or CC-1 for advanced ovarian cancer (IIIC-IVB).
8. To assess the **impact on post-relapse overall survival** of the **pattern of recurrence according to surgical timing** in patients who underwent a cytoreductive surgery with CC-0 or CC-1 for advanced ovarian cancer (IIIC-IVB).

PUBLISHED STUDIES

PUBLISHED STUDIES

Article 1

**A multivariate analysis of the prognostic impact of tumor burden,
surgical timing and complexity after complete cytoreduction for
advanced ovarian cancer**

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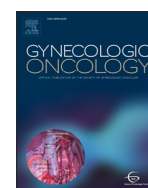
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A multivariate analysis of the prognostic impact of tumor burden, surgical timing and complexity after complete cytoreduction for advanced ovarian cancer

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HIGHLIGHTS

- After complete cytoreduction, primary surgery offers a survival gain of almost three years compared to interval surgery
- High tumor burden and neoadjuvant chemotherapy were associated with decreased overall survival
- Surgical complexity and minimal residual disease were negatively associated to disease-free survival
- Upfront complete cytoreduction should remain the standard of care for advanced ovarian cancer
- Patients with high tumor load may also benefit from debulking surgery if complete cytoreduction is achieved

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ABSTRACT

Objective. To assess the survival benefit of primary debulking surgery (PDS) compared to interval debulking surgery (IDS) after complete cytoreduction (CC-0) or cytoreduction to minimal residual disease (CC-1) in advanced ovarian cancer. Secondary objective was to evaluate the effect of tumor load and surgical complexity on patients' survival.

Methods. A retrospective multicentric study was designed, including patients with IIIC-IV FIGO stage ovarian cancer who underwent PDS or IDS with CC-0 or CC-1 from January 2008 to December 2015 in four high-volume institutions. Patients were classified in three groups: PDS, IDS after 3–4 cycles of neoadjuvant chemotherapy (NACT), and IDS after 6 cycles. Disease-free survival (DFS) and overall survival (OS) were estimated. Univariable and multivariable analyses were conducted.

Results. We included 549 patients, 175 (31.9%) underwent PDS, 224 (40.8%) had IDS after 3–4 cycles of NACT, and 150 (27.3%) underwent IDS after 6 cycles. Median DFS in PDS, IDS at 3–4 cycles and IDS at 6 cycles were 23.0 months (95%CI = [20.0–29.3]), 18.0 months (95%CI = [15.9–20.0]) and 17.1 months (95%CI = [15.0–20.9]), respectively; $p < .001$. Median OS were 84.0 months (95%CI = [68.3–111.0]), 50.7 months (95%CI = [44.6–59.5]) and 47.5 months (95%CI = [39.3–52.9]), respectively; $p < .001$. In multivariable analysis, high peritoneal cancer index score and NACT were negatively associated to DFS and OS. Surgical complexity and CC-1 were negatively associated to DFS.

Conclusion. PDS offered a survival gain of almost three years compared to IDS in patients with minimal or no residual disease after surgery. PDS should remain the standard of care for advanced ovarian cancer.

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1. Introduction

Complete cytoreduction leaving no residual macroscopic tumor is the most important prognostic factor in advanced ovarian cancer [1,2]. Cytoreductive surgery (CRS) followed by platinum and taxane-based chemotherapy is the mainstay of therapeutic strategy [3–5]. In case of non-operable patients or in case of low likelihood of achieving complete cytoreduction, neoadjuvant chemotherapy (NACT) is preferred, as it is associated with lower morbidity and postoperative mortality [6,7].

The best timing to schedule CRS in order to obtain the maximal survival benefit has been largely debated. Two randomized controlled trials (RCTs) comparing primary debulking surgery (PDS) followed by adjuvant chemotherapy and NACT followed by interval debulking surgery (IDS) have suggested that NACT has a non-inferior survival outcome [8,9]. Nevertheless, these trials have been extensively criticized due to their low rate of complete cytoreduction in patients with PDS, being as low as 20% [8,9]. Few meta-analyses have been conducted reporting controversial results. While some of them report superior survival rates in patients undergoing PDS [5,10,11], others have stated no survival differences between PDS and IDS [12,13]. A recent review including 24 publications compared the impact of complete cytoreduction after PDS and IDS. Authors found an improved median survival of almost two years in patients who underwent upfront procedures [4]. Up to our knowledge, there are no large series in the literature assessing the impact of surgical timing, disease burden assessed by peritoneal cancer index (PCI), and surgical radicality assessed by different scores in patients undergoing CRS with minimal or no residual disease.

The aim of the present study was to evaluate survival impact of complete cytoreduction or cytoreduction to minimal residual disease depending on the timing of CRS in high-volume institutions. Secondary objective was to evaluate the prognostic impact of disease burden and surgical radicality on patients' survival.

2. Methods

2.1. Patients and study design

A computer-generated search of the institutional patient database was carried out to retrospectively identify all patients who underwent PDS or IDS with complete cytoreduction (CC-0) or cytoreduction to minimal residual disease (CC-1) for stage IIIC-IV epithelial ovarian, fallopian, or primary peritoneal cancer between January 2008 and December 2015 in four institutions meeting the requirements of ESGO quality indicators in France and Spain. The study was approved by the National and Institutional Review Boards (SLN/MFI/AR193997 and HULP code PI-3432).

2.2. Preoperative assessment, surgical principles and chemotherapy treatment

All patients underwent a preoperative imaging study including a computed tomography (CT) of the chest, abdomen and pelvis. In selected cases of extra-abdominal disease suspicion, a positron emission tomography/computed tomography (PET/CT) was performed. An exploratory laparoscopy was routinely performed at diagnosis to assess resectability and to obtain an histological exam.

All cytoreductive procedures were performed or supervised by experienced oncological surgeons. The surgical technique of CRS was performed following Sgarbaker principles of peritonectomy [14]. The extent and distribution of the disease throughout the 13 abdominopelvic regions were evaluated with PCI. The main goal of surgery was to obtain a complete cytoreduction, evaluated using the Completeness of Cytoreduction score (CC-0: no residual tumor; CC-1: residual disease less than 2.5 mm in diameter; CC-2: residual nodules between 2.5 mm and 2.5 cm; and CC-3 residual nodules greater than 2.5 cm or a confluence of unresectable disease) [15]. We used the Aletti

Score to quantify surgical complexity [16]. Surgical procedures were considered ultraradical when at least two of the following techniques were performed: small or large bowel resection, splenectomy, atypical hepatic resection, cholecystectomy, partial gastrectomy, distal pancreatectomy and celiac lymph node resection [17]. Postoperative complications were recorded according to Clavien-Dindo classification [18].

Patients with deep infiltration of the small bowel mesentery, diffuse carcinomatosis involving large parts of the small bowel, stomach, infiltration of the duodenum or pancreas (not limited to the pancreatic tail) were considered non-resectable and were selected for primary chemotherapy. NACT was also indicated in unfit patients to withstand multivisceral resection due to medical co-morbidities or poor performance status, or when too extensive surgery was needed to achieve complete cytoreduction. After three cycles of platinum and taxane-based chemotherapy, a clinical, biological and imaging evaluation by thoraco-abdomino-pelvic CT or PET/CT were performed. In case of poor response or bad performance status, three additional cycles of chemotherapy were administered before IDS. In selected patients with stable disease on CT after NACT, an exploratory laparoscopy was performed before IDS to assess resectability. Adjuvant chemotherapy was delivered, when feasible, within two months after CRS with carboplatin and paclitaxel until completing a total of six cycles. In case of poor response to NACT or in case of high tumor burden or CC-1 after PDS, two to three cycles of chemotherapy and antiangiogenic maintenance treatment with bevacizumab were added after discussion at the tumor board.

Patients with residual disease ≥ 2.5 mm (\geq CC-2), and patients with non-epithelial histology or borderline tumors were excluded from the study.

2.3. Study data

Medical databases were examined to collect all relevant information. Patient demographic data, WHO (World Health Organization) performance status, cancer antigen-125 (CA-125) dosage, presence of ascites, NACT, PCI scores recorded during laparotomy, surgical procedures performed during CRS, histologic data, adjuvant treatment and follow-up data were retrieved from medical records.

2.4. Statistical analysis

Data were summarized by frequency and percentage for categorical variables and by median and range for continuous variables. Comparisons between groups were performed using the Chi-squared or Fisher's exact test for categorical variables. Disease-free survival (DFS) was defined as the time from the date of diagnosis until relapse or death, patients alive and disease-free were censored at last follow-up news. Overall survival (OS) was defined as the time from the date of diagnosis until death, patients alive were censored at last follow-up news. Survival data were summarized using the Kaplan-Meier method. Univariable and multivariable analyses were performed using the logrank test and the Cox proportional hazards model; hazard ratios (HR) were estimated with their 95% confidence intervals (95% CI). All tests were two-sided and p -values $< .05$ were considered statistically significant. Statistical analyses were conducted using STATA 13 (StataCorp, Texas, USA) software.

3. Results

During the study period, 2018 patients were treated for ovarian cancer at our four institutions. A total of 549 patients met the inclusion criteria and were considered for the analysis. Median age was 61 years and median BMI was 24.2 kg/m². At diagnosis, 95.7% of patients had a WHO performance status of 0 or 1. FIGO stage was IIIC for 81.8% of women, IVA for 7.8% and IVB for 10.4%. The baseline characteristics are shown in Table 1. Among the 549 included patients, 175 (31.9%)

underwent PDS, 224 (40.8%) had IDS after 3 to 4 cycles of NACT, and 150 (27.3%) underwent IDS after 6 cycles of NACT. Median PCI was 10 (range 0–39). All data from surgical procedures are shown in Table 2. In 481 patients (87.6%) a complete cytoreduction (CC-0) was performed, and in 68 (12.4%) a cytoreduction to minimal residual (CC-1) disease was performed. According to our previous definition, 159 patients (29%) underwent an ultraradical surgery, 61 after PDS and 98 after IDS. According to Aletti surgical complexity score, 23 patients (4.2%) had a low score, 277 patients (50.5%) had an intermediate score, and 249 patients (45.3%) had a high score. Intraperitoneal chemotherapy was used after PDS in 19 patients (3.5%) and hyperthermic intraperitoneal chemotherapy (HIPEC) was done in 10 patients (1.8%), one patient after PDS and 9 after IDS. Maintenance treatment with bevacizumab was administered in 107 patients (19.5%), 32 (18.3%) after PDS and 75 (20.1%) after IDS.

The overall rate of major surgical complications (grade III–V) according to Clavien–Dindo classification was 22.4% (123/549), 28.6% (50/175) after PDS and 19.5% (73/374) after IDS. Among women undergoing an ultraradical surgery, the major surgical complication rate was 35.2% (56/159)–39.3% (24/61) after PDS and 32.7% (32/98) after IDS, while it was of 17.2% (67/390) in non-ultraradical procedures, ($p < .001$). Regarding the type of complication \geq grade III, 51 patients (9.3%) presented a digestive complication, 49 (8.9%) an infectious complication, 28 (5.1%) a respiratory complication, 24 (4.4%) an abdominal wall complication, 19 (3.5%) a lymphatic complication, 18 (3.3%) an hemorrhagic complication, 13 (2.4%) a urinary or renal complication, 10 (1.8%) a cardiac event, and 2 (0.4%) a neurologic event. Ten patients (1.8%) died due to postoperative complications, 2 (1.1%) in the PDS group, 5 (2.2%) after IDS at 3–4 cycles and 3 (2%) in the IDS at 6 cycles group.

Median overall follow-up was 65.1 months (95% CI = [62.1–70.6]). During the study period, 435/549 patients (79.2%) relapsed, 127/175 (72.6%) in the PDS group, 186/224 (83%) in the IDS after 3–4 cycles of NACT group, and 122/150 (81.3%) in the IDS after 6 cycles of NACT group. Median DFS for all patients was 19.4 months (95% CI = [18.1–20.6]). Median DFS in the group of patients with PDS, IDS at

Table 1
Baseline characteristics of overall patients ($n = 549$).

Age (years), median (range)	61 (21–88)
BMI (kg/m^2), median (range)	24.2 (15.6–52.0)
Missing	20 (–)
WHO performance status classification, n (%)	
0	355 (66.1)
1	159 (29.6)
≥ 2	23 (4.3)
Missing	12 (–)
Preoperative CA-125 (UI/ml), median (range)	740 (5–86,000)
Missing	52 (–)
FIGO stage, n (%)	
IIIC	449 (81.8)
IVA	43 (7.8)
IVB (pleural and/or lymphatic involvement)	57 (10.4)
Histological subtype, n (%)	
Serous carcinoma	489 (89.5)
High-grade	408 (74.7)
Low-grade	30 (5.5)
Grade N/A	51 (9.3)
Mucinous carcinoma	2 (0.4)
Endometrioid carcinoma	18 (3.3)
Clear cell carcinoma	18 (3.3)
Malignant Brenner tumor	1 (0.2)
Undifferentiated carcinoma	2 (0.4)
Mixed epithelial	6 (1.1)
Carcinosarcoma	10 (1.8)
Missing	3 (–)
Ascites (liter), median (range)	1 (0–10)
Missing	68 (–)

BMI: body mass index; WHO: World Health Organization; CA-125: cancer antigen 125; FIGO: International Federation of Gynecology and Obstetrics.

Table 2
Surgical data of overall patients ($n = 549$).

PCI, median (range)	10 (0–39)
Missing	6 (–)
PCI, n (%)	
≤ 10	287 (52.9)
> 10	256 (47.1)
Missing	6 (–)
Surgical timing, n (%)	
PDS	175 (31.9)
IDS 3–4 cycles	224 (40.8)
IDS 6 cycles	150 (27.3)
Surgical procedures, n (%)	
Hysterectomy	491 (89.4)
Unilateral or bilateral salpingoophorectomy	502 (91.4)
Pelvic lymphadenectomy	495 (90.2)
Aortic lymphadenectomy	488 (88.9)
Infragastric omentectomy	540 (98.4)
Small bowel resection	44 (8.0)
Large bowel resection	225 (41.0)
If large bowel resection, rectosigmoid resection [$n = 225$]	204 (90.7)
Multiple bowel resection	48 (8.7)
Appendectomy	278 (50.6)
Right diaphragm stripping	327 (59.6)
Left diaphragm stripping	163 (29.7)
If diaphragm stripping, diaphragm resection [$n = 330$]	72 (21.8)
Atypical hepatic resection	15 (2.7)
Cholecystectomy	45 (8.2)
Celiac lymph node resection	65 (11.8)
Splenectomy	127 (23.1)
Distal pancreatectomy	31 (5.6)
Partial gastrectomy	11 (2.0)
Extended peritonectomy	256 (46.6)
Glissonectomy	46 (8.8)
Mesentery or bowel vaporization	125 (22.8)
Partial abdominal wall resection	100 (18.2)
Inguinal lymph node resection	13 (2.4)
Partial cystectomy or ureteral resection	8 (1.5)
Axillary lymph node resection	2 (0.4)
Partial colectomy	1 (0.2)
CC-score	
CC-0	481 (87.6)
CC-1	68 (12.4)
Ultraradical surgery	
No	390 (71.0)
Yes	159 (29.0)
Aletti Score, n (%)	
≤ 3	23 (4.2)
4–7	277 (50.5)
≥ 8	249 (45.4)

PCI: peritoneal cancer index.

PDS: primary debulking surgery.

IDS: interval debulking surgery.

PH: porta hepatis.

Extended peritonectomy: peritonectomy of more than three abdominal regions.

Partial abdominal wall resection: partial resection of anterior abdominal wall sheath, omphalectomy or port site resection.

CC-score: completeness of cytoreduction score.

3–4 cycles and IDS at 6 cycles were 23.0 months (95% CI = [20.0–29.3]), 18.0 months (95% CI = [15.9–20.0]) and 17.1 months (95% CI = [15.0–20.9]), respectively; $p < .001$. There were no significant differences in DFS between patients undergoing IDS at 3–4 cycles or 6 cycles of NACT ($p = .656$).

Among the 549 women included in the study, 287 (52.3%) died, 71/175 (40.6%) in the PDS group, 122/224 (54.5%) in the IDS after 3–4 cycles of NACT group, and 94/150 (62.7%) in the IDS after 6 cycles of NACT group. Median OS for all patients was 56.3 months (95% CI = [50.2–67.4]). Median OS in the group of patients with PDS, IDS at 3–4 cycles and IDS at 6 cycles were 84.0 months (95% CI = [68.3–111.0]), 50.7 months (95% CI = [44.6–59.5]) and 47.5 months (95% CI = [39.3–52.9]), respectively; $p < .001$. There were no significant differences in OS between patients undergoing IDS at 3–4 cycles or 6 cycles of NACT ($p = .525$).

There were not significant differences in DFS and OS between the four centers. Median OS for patients with CC-0 and CC-1 were 59.5 months (95% CI = [51.8–74.2]) and 43.7 months (95% CI = [35.4–52.9]), respectively ($p = .013$). Median OS for patients with PCI ≤ 10 was 65.8 months (95% CI = [52.5–91.9]), and 48.3 months (95% CI = [40.4–58.5]) for patients with PCI > 10 , ($p = .002$). Among patients with PCI > 10 , median OS was 67.4 months (95% CI = [44.7–86.1]) after PDS and 43.9 months (95% CI = [37.6–52.1]) after NACT ($p = .041$).

Univariable analysis of DFS and OS in overall patients is shown in Table 3. In multivariable analysis (Table 4), both PCI score and NACT were significantly associated with DFS and OS. Aletti score and CC-score were significantly associated with DFS. Age at diagnosis, FIGO stage and ultraradical surgery were not significantly associated with survival.

Fig. 1 displays DFS and OS curves according to the surgical timing (A. and B., respectively), according to PCI (C. and D., respectively), according to Aletti score (E. and F., respectively), and according to CC-score (G. and H., respectively).

4. Discussion

4.1. Optimal timing for cytoreductive surgery

Absence of residual tumor after CRS has been described as the single most important prognostic factor in advanced ovarian cancer patients [1,2,19]. Our series also showed that patients with CC-1 after CRS yielded an inferior median survival of 16 months when compared to patients with CC-0. Median OS in our series was 56 months, 84 months for patients who underwent PDS and around 50 months for patients who underwent IDS. Survival rates in our series are in line with previous

Table 3
Univariable disease-free and overall survival analysis in overall patients.

	Disease-free survival			Overall survival		
	HR	95% CI	p-value	HR	95% CI	p-value
Age at diagnosis (years)	1.00	[1.00–1.01]	0.293	1.01	[1.00–1.02]	0.041
Cycles of NACT						
0	1.00	Ref.		1.00	Ref.	<0.001
3–4	1.51	[1.21–1.89]		1.60	[1.19–2.14]	
6	1.43	[1.12–1.83]	<0.001	1.73	[1.27–2.35]	
FIGO stage						0.953
IIIC	1.00	Ref.		1.00	Ref.	
IV	1.27	[1.01–1.60]	0.044	1.01	[0.75–1.37]	
Histological type						0.400
Serous	1.00	Ref.		1.00	Ref.	
Other	1.02	[0.75–1.39]	0.907	1.17	[0.81–1.71]	
PCI						0.002
≤ 10	1.00	Ref.		1.00	Ref.	
> 10	1.52	[1.26–1.83]	<0.001	1.43	[1.13–1.80]	
Aletti score						0.017
< 8	1.00	Ref.		1.00	Ref.	
≥ 8	1.35	[1.12–1.62]	0.002	1.33	[1.05–1.67]	
Ultraradical surgery						0.052
No	1.00	Ref.		1.00	Ref.	
Yes	1.26	[1.03–1.55]	0.023	1.28	[1.00–1.65]	
CC-score						0.013
CC-0	1.00	Ref.		1.00	Ref.	
CC-1	1.56	[1.19–2.04]	0.001	1.49	[1.08–2.04]	
Bevacizumab						0.615
No	1.00	Ref.	0.282	1.00	Ref.	
Yes	0.88	[0.70–1.11]		0.93	[0.68–1.25]	

HR: hazard ratio.

95% CI: 95% confidence interval.

NACT: neoadjuvant chemotherapy.

FIGO: International Federation of Gynecology and Obstetrics.

PCI: peritoneal cancer index.

CC-score: completeness cytoreduction score.

Table 4
Multivariable disease-free and overall survival analysis in overall patients.

	Disease-free survival			Overall survival		
	HR	95% CI	p-value	HR	95% CI	p-value
Age at diagnosis	1.00	[1.00–1.01]	0.300	1.01	[1.00–1.02]	0.089
Cycles of NACT						
0	1.00	Ref.		1.00	Ref.	
3–4	1.49	[1.18–1.87]	<0.001	1.60	[1.19–2.16]	0.002
6	1.54	[1.19–2.00]	0.001	1.90	[1.37–2.62]	<0.001
FIGO stage			0.082			0.950
IIIC	1.00	Ref.		1.00	Ref.	
IV	1.24	[0.97–1.57]		0.99	[0.73–1.35]	
PCI			0.002			0.032
≤ 10	1.00	Ref.		1.00	Ref.	
> 10	1.43	[1.14–1.80]		1.36	[1.03–1.81]	
Aletti score			0.039			0.112
< 8	1.00	Ref.		1.00	Ref.	
≥ 8	1.30	[1.01–1.67]		1.29	[0.94–1.75]	
Ultraradical surgery			0.632			0.990
No	1.00	Ref.		1.00	Ref.	
Yes	0.94	[0.73–1.22]		1.00	[0.72–1.38]	
CC-score			0.007			0.100
CC-0	1.00	Ref.		1.00	Ref.	
CC-1	1.46	[1.11–1.91]		1.32	[0.95–1.82]	

HR: hazard ratio.

95% CI: 95% confidence interval.

NACT: neoadjuvant chemotherapy.

FIGO: International Federation of Gynecology and Obstetrics.

PCI: peritoneal cancer index.

CC-score: completeness cytoreduction score.

reports. Most series describe median survival rates below 80 months for patients undergoing PDS, ranging from 45 months to 86 months [4]. Regarding IDS, the majority of studies report median survival rates below 50 months, ranging from 28 months to 78 months [4].

Since the publication of the two RCTs of Vergote et al. and Kehoe et al., which reported a non-inferior survival benefit of NACT [8,9], the decrease of postoperative morbi-mortality and the increase of the rate of complete or optimal cytoreduction after NACT have prompted an increase of its use in current clinical practice [7–9,12,13,20]. Nevertheless, these RCTs have been extensively criticized due to their excessively low rate of complete cytoreduction after PDS, of 20.4% and 17% in EORTC trial and CHORUS trial, respectively [8,9]. For this reason, there are two ongoing RCTs in high-volume hospitals with expert surgical teams which will define the optimal timing of CRS for maximal survival benefit in patients with advanced ovarian cancer. SCORPION trial (Surgical Complications Related to Primary or Interval debulking in Ovarian Neoplasm, NCT01461850) is a single-institution trial randomizing FIGO stage IIIC patients with high tumoral load to PDS followed by adjuvant chemotherapy or to 3–4 cycles of NACT followed by IDS and adjuvant chemotherapy until 6 cycles. Progression free-survival and surgical complications are the primary endpoints [21]. TRUST trial (Trial of Radical Upfront Surgical Therapy in advanced ovarian cancer (ENGOT ov33/AGO-OVAR OP7, NCT02828618)) is a multicentric international trial which randomizes FIGO stage IIIB–IVB ovarian cancer patients to PDS followed by adjuvant chemotherapy or to 3 cycles of NACT followed by IDS and 3 cycles of adjuvant chemotherapy; OS is the primary endpoint. Moreover, only centers fulfilling a preestablished requirement regarding the rate of PDS and CC-0 are allowed to participate [22].

There is strong evidence in the literature supporting a survival benefit of PDS. Bristow et al. conducted a meta-analysis reporting that NACT was associated with an inferior OS compared to PDS. In a more recent meta-analysis, Qin et al. reported from multiple observational studies that PDS yielded better OS than IDS, and that this benefit remained even in patients with low residual disease [10]. Similar findings were described by Xiao et al., with a significant improved OS in patients undergoing PDS [11].

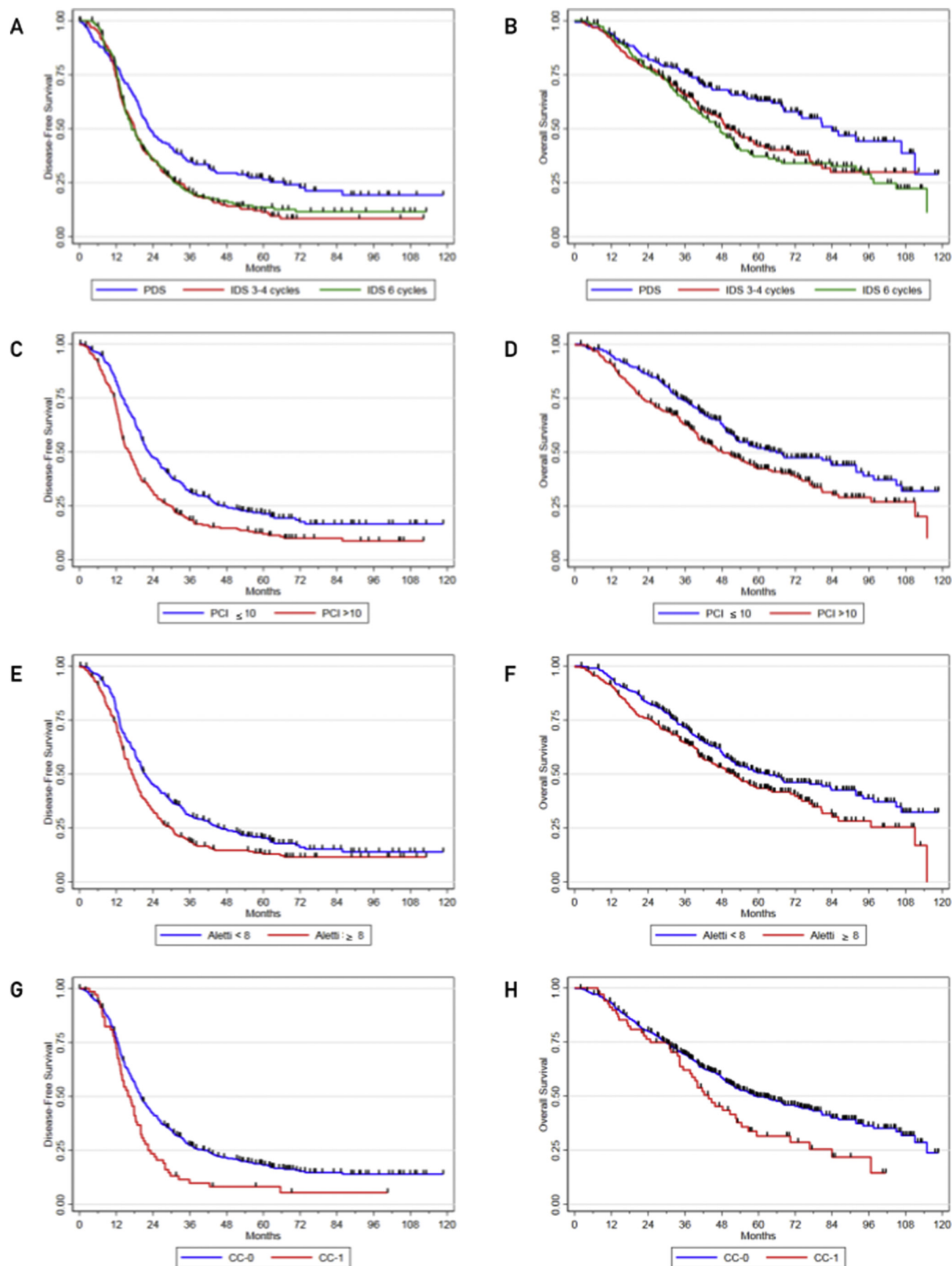


Fig. 1. Disease-free survival (DFS) and overall survival (OS) according to different factors. A. DFS according to the timing of cytoreductive surgery. B. OS according to the timing of cytoreductive surgery. C. DFS according to PCI score. D. OS according to PCI score. E. DFS according to Aletti score. F. OS according to Aletti score. G. DFS according to CC-score. H. OS according to CC-score.

Biologic rationale of starting the treatment by PDS is based on removal of bulky disease before starting chemotherapy, which would allow a better perfusion of microscopic residual tumor and, therefore, an improved effect of chemotherapy. As well, removal of bulky tumor would allow an improvement of host immunocompetence [23]. NACT may also select chemoresistant tumoral clones. The outgrowth of these chemoresistant cells would explain the platinum resistance [24].

The effect of delay on surgical timing after NACT was traduced by loss of median survival of almost three years in patients undergoing CC-0 or CC-1 cytoreduction, evidencing that the absence of residual tumor after IDS does not overcome the deleterious effect of delaying the surgery. Our results are in keeping with a recent review published by Chiva et al., which selected multiple studies including data of patients with complete cytoreduction after PDS and IDS. They showed that complete cytoreduction after IDS had a reduced survival benefit of almost two years compared with complete cytoreduction after PDS [4].

Regarding the impact of the timing of CRS after NACT, we did not find significant differences in survival between patients undergoing IDS after 3–4 cycles or 6 cycles of chemotherapy. This might be biologically plausible, as once the chemoresistant clones have been selected, delivering different number of cycles of NACT would not modify survival outcomes. Yoneoka et al. compared patients undergoing IDS after 3 cycles of NACT with patients receiving 3 additional cycles of NACT before surgery without postoperative chemotherapy. They found that 6 cycles of NACT followed by CRS exhibited equivalent effects on survival than IDS after 3 cycles followed by 3 cycles of postoperative chemotherapy [25]. Similarly, Akladios et al. found that number cycles did not seem to play a role in the OS of patients with advanced ovarian cancer [26]. Phillips et al. reported an equivalent survival in patients undergoing ≤ 4 cycles and ≥ 5 cycles of NACT [27]. Stoeckle et al. stated that late IDS yielded higher complete resection rates than early IDS with similar survival outcomes [28]. Contrarily, Bristow et al. found that the number of preoperative chemotherapy cycles was negatively correlated with survival. They hypothesized a progressive emergence of chemoresistant disease with the increasing number of NACT cycles [5]. Other studies have also reported poorer prognosis in patients undergoing more than 4 cycles of NACT, even in case of complete cytoreduction [29,30].

4.2. Prognostic impact of tumor load

The effect of disease burden on survival after complete CRS is still debated in literature [31–34]. Some authors hypothesize that bulky and diffuse spread of the disease may reflect a high biological aggressiveness of the tumor or an existence of the disease for a longer period of time, allowing for advanced growth and implantation [32]. It is unknown if complete removal of all macroscopic disease can completely overcome the negative effect of tumor load and if it can “reset the clock”. In our series, together with the number of cycles of NACT, PCI was the main prognostic factor for decreased OS, meaning that even in patients with no residual or minimal residual disease, disease burden remains a prognostic factor. This is in line with a previous study published by our group in which tumor extension measured by PCI was the only significant prognostic factor associated with decreased DFS in patients who underwent complete cytoreduction after PDS [17]. In a large series of patients with complete or optimal cytoreduction, patients with more extensive disease -defined as upper abdominal disease- had a worse survival outcome [31]. High initial disease burden had a persistent negative effect even when complete surgery was achieved [31,33]. Zivanovic et al. demonstrated that even if there was a survival benefit of optimal cytoreduction in patients with high initial tumor burden, it was less marked in patients with large-volume disease [32]. However, Eisenkop et al. showed that complete surgical cytoreduction had more significant independent influence on survival than total extent of intra-abdominal tumor burden. They stated that the surgical effort during CRS has not to be abbreviated on the presumption of extensive intra-abdominal disease [34]. In our series, the median OS of patients with high tumor

burden was 48 months, which is similar to other series [31]. Patients with high tumor burden (PCI > 10) undergoing PDS have a survival benefit of almost 24 months compared to patients undergoing IDS. Therefore, even if high disease burden is a negative prognostic factor, complete PDS should remain the mainstay of surgical treatment.

In our study, there were not survival differences between patients with a FIGO stage IIIC and IVA or IVB, suggesting that surgical maximal effort should also be done in these patients if complete cytoreduction can be achieved.

4.3. Prognostic impact of surgical radicality and its related morbidity

Complex surgical procedures are performed in approximately 40–50% of CRS [35,36]. In our series, 29% of patients underwent an ultraradical surgery, and 45% underwent a high complexity surgery according to Aletti score. Rate of major complications was 22%, and 35% in patients who underwent ultraradical surgery, which is higher than previous studies reporting complication rates below 15% in patients undergoing radical procedures [35–38].

Extensive and radical procedures have increased the rate of complete cytoreduction and improved patients' survival [35–37]. Nonetheless, ultraradical procedures have also been associated with longer operative time, increased blood loss, higher morbidity and postoperative mortality [36,39,40]. In our study, higher Aletti score values were associated with decreased DFS. Some authors suggest that disease requiring ultraradical surgery in order to obtain complete cytoreduction would reflect a more aggressive infiltrative behavior of the disease and, therefore, the surgical effort would not be enough to compensate tumor biology [32]. In a previous study of our workgroup, we found that patients who needed complex surgical procedures involving two or more visceral resections in order to achieve complete cytoreduction had worse survival outcome than patients with less extensive procedures. This negative impact of surgical complexity was not significant in patients who underwent upfront procedures. On the contrary, Horowitz et al. found that patients with low and moderate disease distribution had an improved survival when surgery was complete, even if complex procedures were required. Therefore, it was not complex surgery which affected patients' survival when accounting for other confounding factors [31]. According to our definition of ultraradical surgery -which includes at least two digestive or visceral procedures-, we did not find that ultraradical procedures were associated to decreased survival. However, our definition and Aletti score do not use the same criteria to assess surgical complexity. The decision to perform a complex cytoreduction procedure should be based on a balance between the extension of the surgery needed to achieve CC-0, histologic type, associated morbidity, patient performance status, and comorbidities. Even if patients with high tumor burden undergoing ultraradical procedures have decreased survival, median survival in this group was 48 months. Therefore, they may also benefit from debulking surgery if complete cytoreduction is achieved.

This is the largest series performed in high-volume ovarian cancer institutions to evaluate prognostic impact of complete cytoreduction depending on surgical timing, tumor burden measured by intraoperative PCI and surgical complexity. Another strength of this study is the long follow-up. However, this study has some limitations such as its retrospective nature and the inherent risk of selection bias due to a better performance status and operability of patients undergoing PDS. As well, BRCA status was not collected and we did not retrieve from records all patients in whom the CRS was not possible or with CC-2 after CRS, therefore, we could not assess our rates of CC-0. Another weakness of our study may be the low number of patients in the PDS group (32%). This could be explained by the fact that most patients with an initial external evaluation had already initiated NACT, and that a non-negligible number of these patients would have been presumable candidates for PDS. Moreover, adjuvant treatment with intraperitoneal chemotherapy or HIPEC was heterogenous among the three groups and the improved

survival in PDS could be partially explained by intraperitoneal chemotherapy. However, due to the low number of patients receiving these types of treatment in our cohort, statistical analyses regarding this issue were not conducted.

5. Conclusion

Complete cytoreduction after PDS increased median OS in almost three years compared to patients treated with IDS. Until the results of TRUST and SCORPION trials, upfront complete cytoreduction should remain the standard of care. Survival benefit decreased with increasing extensive peritoneal disease and high Aletti scores. Even though, patients with high tumor load may also benefit from PDS if CC-0 is achieved.

Declaration of Competing Interest

None.

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Article 2

Effect of tumor burden and radical surgery on survival difference between upfront, early interval or delayed cytoreductive surgery in ovarian cancer

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Effect of tumor burden and radical surgery on survival difference between upfront, early interval or delayed cytoreductive surgery in ovarian cancer

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ABSTRACT

Objective: We sought to evaluate the impact on survival of tumor burden and surgical complexity in relation to the number of cycles of neoadjuvant chemotherapy (NACT) in patients with advanced ovarian cancer (OC) with minimal (CC-1) or no residual disease (CC-0).

Methods: This retrospective study included patients with International Federation of Gynaecology and Obstetrics IIIC–IV stage OC who underwent debulking surgery at 4 high-volume institutions between January 2008 and December 2015. We assessed the overall survival (OS) of primary debulking surgery (PDS group), early interval debulking surgery after 3–4 cycles of NACT (early IDS group) and delayed debulking surgery after 6 cycles (DDS group) with CC-0 or CC-1 according to peritoneal cancer index (PCI) and Aletti score.

Results: Five hundred forty-nine women were included: 175 (31.9%) had PDS, 224 (40.8%) early IDS and 150 (27.3%) DDS. Regardless of Aletti score, median OS after PDS was significantly higher than after early IDS or DDS, but the survival difference was higher in women with an Aletti score <8. Among patients with PCI ≤10, median OS after PDS was significantly higher than after early IDS or DDS. In women with PCI >10, there were no

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Author Contributions

Conceptualization: A.M.A., C.B., G.A., P.A., S.E., R.A., M.C., G.F., Z.I., Q.D., I.C., M.F., B.S., F.G., H.A., M.A.; Data curation: A.M.A., C.B., S.E., R.A., M.C.; Formal analysis: C.B.; Investigation: A.M.A., C.B., G.A., P.A., S.E., R.A., M.C., G.F., Z.I., Q.D., I.C., M.F., B.S., F.G., H.A., M.A.; Methodology: A.M.A., C.B., G.A., P.A., S.E., R.A., M.C., G.F., Z.I., Q.D., I.C., M.F., B.S., F.G., H.A., M.A.; Project administration: A.M.A., C.B., G.A., P.A., S.E., R.A., M.C., G.F., Z.I., Q.D., I.C., M.F., B.S., F.G., H.A., M.A.; Resources: A.M.A., C.B., G.A., P.A., S.E., R.A., M.C., G.F., Z.I., Q.D., I.C., M.F., B.S., F.G., H.A., M.A.; Software: C.B.; Supervision: H.A., M.A.; Validation: A.M.A., C.B., G.A., P.A., S.E., R.A., M.C., G.F., Z.I., Q.D., I.C., M.F., B.S., F.G., H.A., M.A.; Visualization: A.M.A., C.B., G.A., P.A., S.E., R.A., M.C., G.F., Z.I., Q.D., I.C., M.F., B.S., F.G., H.A., M.A.; Writing - original draft: A.M.A.; Writing - review & editing: C.B., G.A., P.A., S.E., R.A., M.C., G.F., Z.I., Q.D., I.C., M.F., B.S., F.G., H.A., M.A.

differences between PDS and early IDS, but DDS was associated with decreased OS.

Conclusion: The benefit of complete PDS compared with NACT was maximal in patients with a low complexity score. In patients with low tumor burden, there was a survival benefit of PDS over early IDS or DDS. In women with high tumor load, DDS impaired the oncological outcome.

Keywords: Ovarian Neoplasms; Fallopian Tube Neoplasms; Peritoneal Neoplasms; Cytoreduction Surgical Procedures; Neoadjuvant Therapy; Tumor Burden

INTRODUCTION

Complete cytoreduction with no residual disease is the main prognostic factor in advanced epithelial ovarian cancer (OC) [1,2]. The gold standard treatment in these patients is the combination of complete cytoreductive surgery (CRS) with platinum and taxane-based chemotherapy [3]. In patients with completely resectable disease and good performance status, primary debulking surgery (PDS) is the first option to consider, as it has been consistently associated with improved survival outcomes in retrospective studies [4-6]. Neoadjuvant chemotherapy (NACT) is associated with lower morbidity and postoperative mortality [7,8], and it is preferred in medically non-operable patients or in the low likelihood of achieving complete cytoreduction, with non-inferior survival benefit [7,9,10]. Classically, interval debulking surgery (IDS) is performed after three or four cycles of NACT, and 2 or 3 cycles of adjuvant chemotherapy are delivered after CRS to complete a total of 6 cycles of chemotherapy. However, reports evaluating the role of IDS after more than four cycles of NACT are controversial. While some have shown that survival is similar to that of patients undergoing IDS after three cycles of NACT [11-14], other studies have described an impaired prognosis of delayed IDS [15,16].

The incorporation of extensive upper abdominal procedures in CRS has increased the rate of optimal cytoreduction as well as improved the survival of advanced OC patients [17]. However, ultraradical procedures are associated with higher morbidity and postoperative mortality [18-20]. Likewise, high intraabdominal tumor load has a negative impact on survival [21-23]. The aim of our study was to evaluate the survival impact of tumor burden and surgical complexity in relation to the number of NACT cycles in patients with advanced OC with minimal or no residual disease after CRS.

MATERIALS AND METHODS

1. Patients and study design

A computer-generated search in the institutional patient database was performed to identify retrospectively all patients who underwent upfront, interval or closure complete CRS with complete cytoreduction (CC-0) or cytoreduction to minimal residual disease (CC-1) for stage IIIC-IV epithelial ovarian, fallopian, or primary peritoneal cancer between January 2008 and December 2015 in four institutions meeting the requirements of the European Society of Gynaecological Oncology quality indicators from France and Spain. National and Institutional Review Board approval was obtained from our centres (SLN/MFI/AR193997 and HULP code PI-3432).

2. Preoperative assessment, surgery principles and chemotherapy treatment

All patients underwent a preoperative imaging study including a computed tomography (CT) of the chest, abdomen and pelvis. In selected cases of extra-abdominal disease suspicion, a positron emission tomography (PET)/CT was performed. An exploratory laparoscopy was routinely performed at diagnosis to assess resectability and to obtain a histological diagnosis.

All surgical procedures were performed or supervised by experienced oncological surgeons. The surgical technique of CRS was performed following Sugarbaker principles of peritonectomy [24]. The extent and distribution of the disease throughout the 13 abdominopelvic regions were evaluated with the peritoneal cancer index (PCI) [25]. The surgical goal was to achieve complete cytoreduction, evaluated using the Completeness of Cytoreduction score (CC-0: no residual tumor; CC-1: residual disease less than 2.5 mm in diameter; CC-2: residual nodules between 2.5 mm and 2.5 cm; and CC-3 residual nodules greater than 2.5 cm or a confluence of unresectable disease) [25]. Hysterectomy and bilateral salpingo-oophorectomy, infragastric omentectomy and pelvic plus paraaortic lymphadenectomy were the procedures systematically performed during CRS. However, some patients referred from external hospitals had already undergone uni- or bilateral salpingo-oophorectomy with or without hysterectomy at diagnosis. Moreover, as the study period preceded the LION trial [26], lymphadenectomy could be spared only in some selected patients without lymph node involvement at diagnosis to decrease operative time and surgical morbidity. The Aletti score was used to quantify surgical complexity with a cut-off value ≥ 8 being considered as high complexity [27]. Postoperative complications were documented according to the Clavien-Dindo classification [28].

Patients with deep infiltration of the small bowel mesentery, diffuse carcinomatosis involving large parts of the small bowel, stomach, infiltration of the duodenum or pancreas (not limited to the pancreatic tail) were considered non-resectable and were selected for primary chemotherapy. NACT was also indicated in patients unfit to withstand multivisceral resection due to medical co-morbidities or poor performance status, or when too extensive surgery was needed to achieve complete cytoreduction. After three or four cycles of platinum and taxane-based chemotherapy, a clinical, biological and imaging evaluation by thoraco-abdomino-pelvic CT or PET/CT was performed. In the event of poor response or bad performance status, three additional cycles of NACT were administered before IDS. In selected patients with stable disease on CT after NACT, an exploratory laparoscopy was performed before IDS to assess resectability.

Adjuvant chemotherapy was delivered, when feasible, within one or two months after CRS with carboplatin and paclitaxel until a total of six cycles had been completed. In the event of high tumor burden, CC-1 or poor response to NACT, antiangiogenic maintenance treatment with bevacizumab was added after discussion by the tumor board. When surgery was performed after 6 cycles of NACT, two to three additional cycles of chemotherapy were added to the antiangiogenic maintenance treatment with bevacizumab. No maintenance treatment with poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitors was administered during the study period.

Patients with residual disease ≥ 2.5 mm (\geq CC-2) and patients with non-epithelial subtype histology or borderline tumors were excluded from the study.

3. Study data

Medical databases were carefully examined to collect all relevant information. Patient demographic data, World Health Organization (WHO) performance status, cancer

antigen-125 (CA-125) dosage, ascites at diagnosis, NACT, PCI scores recorded during CRS, surgical procedures, surgical complexity according to Aletti score, histologic data, adjuvant treatment and follow-up data were retrieved from medical records.

Patients were classified in 3 groups according to the surgical timing: upfront surgery and 6 cycles of adjuvant chemotherapy (PDS group), IDS after 3–4 cycles of NACT and 2–3 cycles of adjuvant chemotherapy to achieve a total of 6 cycles (early IDS group), and delayed debulking surgery (DDS) after 6 cycles of NACT (DDS group). The latter group included patients undergoing delayed IDS after 6 cycles of NACT and receiving 2 additional cycles of adjuvant chemotherapy due to poor response to NACT, and patients undergoing closure debulking surgery after 6 cycles of NACT without adjuvant chemotherapy.

4. Statistical analysis

Data were summarised by frequency and percentage for categorical variables and by median and range for continuous variables. Comparisons between groups were performed using the χ^2 or Fisher's exact test for categorical variables and the Kruskal-Wallis test for continuous variables. Overall survival (OS) was defined as the time from diagnosis until death from any cause or last follow-up news (censored data) and was estimated using the Kaplan-Meier method. Comparisons between groups were performed using the Logrank test. The Cox proportional hazards model was used to perform multivariable analysis and to estimate hazard ratio (HR) and adjusted hazard ratios (HR_{adj}) with their 95% confidence interval (95% CI). All statistical tests were two-sided and p-values <0.05 were considered statistically significant. Statistical analyses were conducted using STATA 16 (StataCorp, College Station, TX, USA) software.

RESULTS

During the study period, 549 patients met the inclusion criteria (**Fig. S1**). Among them, 175 patients (31.9%) had upfront surgery, 224 (40.8%) underwent early IDS, and 150 (27.3%) had DDS. Within patients undergoing DDS, 106 had a delayed IDS and 44 underwent closure debulking surgery. Baseline characteristics of the three subgroups are shown in **Table 1**. Patients in the PDS group were significantly younger than those in the early IDS and DDS groups and they had a significantly better performance status. CA-125 was significantly higher with the increasing number of cycles of NACT. In the PDS group, there was a higher proportion of patients with stage IIIC disease and non-serous histology, and ascites at diagnosis was significantly lower.

All surgical data is displayed in **Table 2**. Median PCI at CRS was 11.5, 10 and 7 in the PDS, early IDS and DDS groups, respectively ($p < 0.001$). Regarding surgical procedures, patients who received PDS had significantly more large bowel resections than patients who received debulking surgery either after 3–4 or 6 cycles of NACT. Women undergoing DDS had fewer diaphragm stripping and extended peritonectomies compared to patients after PDS or early IDS. The proportion of patients undergoing a CRS with an Aletti score ≥ 8 progressively decreased in the PDS, early IDS and DDS groups ($p = 0.006$).

The overall rate of major surgical complications (grade III–V) according to the Clavien-Dindo classification was higher after PDS (28.6%, 50/175) than after IDS at 3–4 cycles of NACT (23.2%, 52/224) or after DDS (14.0%, 21/150) ($p = 0.007$). **Table S1** shows the overall postoperative complications in the 3 groups. However, among women with a high Aletti score, the major

Table 1. Baseline characteristics of patients.

Characteristics	PDS (n=175)	Early IDS (n=224)	DDS (n=150)	p-value
Age (yr)	58 (22–88)	62 (21–82)	63 (36–88)	0.010
BMI (kg/m ²)	24.2 (16.5–44.1)	24.0 (15.6–52.0)	24.6 (15.6–43.9)	0.484
Missing	7	2	11	
WHO performance status classification				<0.001
0	137 (79.2)	122 (56.2)	96 (65.3)	
1	32 (18.5)	83 (38.2)	44 (29.9)	
≥2	4 (2.3)	12 (5.5)	7 (4.8)	
Missing	2	7	3	
CA-125 (U/mL) at diagnosis	463 (7–23,762)	800 (11–42,956)	1,000 (5–86,000)	<0.001
Missing	24	15	13	
FIGO stage				0.002
IIIC	158 (90.3)	176 (78.6)	115 (76.7)	
IV	17 (9.7)	48 (21.4)	35 (23.3)	
Histological subtype				<0.001
Serous	140 (80.0)	207 (93.2)	142 (95.3)	
Non-serous	35 (20.0)	15 (6.8)	7 (4.7)	
Missing	0	2		
Ascites (liter) at diagnosis	0.1 (0–7)	1 (0–10)	1 (0–8)	<0.001
Missing	15	29	24	

Values are presented as median (range) or number of patients (%). Bold-faced p-values indicate statistical significance.

BMI, body mass index; CA-125, cancer antigen-125; DDS, delayed debulking surgery; Early IDS, early interval debulking surgery; FIGO, International Federation of Gynaecology and Obstetrics; PDS, primary debulking surgery; WHO, World Health Organization.

surgical complication rate was not significantly different between the three groups: 35.8% (34/95) after PDS, 31.3% (31/99) after early IDS, and 18.2% (10/55) after DDS ($p=0.073$).

Furthermore, among patients with a low Aletti score, the rate of major surgical complications was not significantly different in the three groups: 20.0% (16/80) for PDS, 16.8% (21/125) for early IDS and 11.6% (11/96) for DDS ($p=0.302$). Postoperative mortality rates were 1.1% (2/175) after PDS, 2.2% (5/224) after early IDS, and 2.0% (3/150) after DDS ($p=0.723$).

Median follow-up was 63.5 months (95% CI=59.6–70.5) in the PDS group, 62.6 months (95% CI=57.0–69.7) in the early IDS group, and 83.0 months (95% CI=68.1–90.1) in the DDS group. Median OS after PDS, IDS at 3–4 cycles and DDS groups were 84.0 months (95% CI=68.3–111.0), 50.7 months (95% CI=44.6–59.5) and 47.5 months (95% CI=39.3–52.9), respectively ($p<0.001$), without significant differences between the 2 groups of NACT ($p=0.525$). Among patients undergoing DDS, there was no survival difference between patients undergoing delayed IDS (median OS=47.5 months; 95% CI=39.3–52.4) and patients undergoing closure debulking surgery (median OS=51.8 months; 95% CI=25.9–104.9; $p=0.612$).

In multivariable analysis, the number of cycles of NACT (early IDS: HR=1.61; 95% CI=1.18–2.20; $p=0.003$ and DDS: HR=1.88; 95% CI=1.35–2.62; $p<0.001$, respectively), PCI >10 (HR=1.37; 95% CI=1.04–1.81; $p=0.027$), and Aletti score ≥8 (HR=1.36; 95% CI=1.03–1.79; $p=0.028$) were significantly associated with worse OS, while age (HR=1.01; 95% CI=1.00–1.02; $p=0.082$), WHO performance status ≥1 (HR=1.06; 95% CI=0.82–1.37; $p=0.658$), non-serous histological subtype (HR=1.33; 95% CI=0.90–1.96; $p=0.157$), International Federation of Gynaecology and Obstetrics (FIGO) stage IV (HR=0.95; 95% CI=0.69–1.31; $p=0.772$), CC-1 (HR=1.34; 95% CI=0.96–1.88; $p=0.082$), and maintenance treatment with bevacizumab (HR=0.93; 95% CI=0.68–1.29; $p=0.673$) were not significantly associated with OS.

Table 3 shows OS according to surgical timing and surgical complexity measured with the Aletti score. In women with an Aletti score ≥8, median OS at PDS, early IDS and DDS was 80.5, 42.4, and 45.8 months ($p=0.014$), respectively; and in women with an Aletti score <8,

Impact of tumor load and surgical radicality

Table 2. Surgical data of patients

Variables	PDS (n=175)	Early IDS (n=224)	DDS (n=150)	p-value
PCI	11.5 (2–33)	10 (0–39)	7 (0–31)	<0.001
Missing	3	1	2	
PCI				<0.001
PCI ≤10	76 (44.2)	112 (50.2)	99 (66.9)	
PCI >10	96 (55.8)	111 (49.8)	49 (33.1)	
Missing	3	1	2	
Surgical procedures				
Hysterectomy	167 (95.4)	203 (90.6)	121 (80.7)	<0.001
Unilateral or bilateral salpingoophorectomy	164 (93.7)	210 (93.8)	128 (85.3)	0.007
Pelvic lymphadenectomy	158 (90.3)	205 (91.5)	132 (88.0)	0.533
Aortic lymphadenectomy	158 (90.3)	201 (89.7)	129 (86.0)	0.412
Infragastric omentectomy	173 (98.9)	222 (99.1)	145 (96.7)	0.212
Small bowel resection	20 (11.4)	14 (6.3)	10 (6.7)	0.130
Large bowel resection	96 (54.9)	81 (36.2)	48 (32.0)	<0.001
If large bowel resection, rectosigmoid resection (n=225)	86 (89.6)	73 (90.1)	45 (93.8)	0.798
Multiple bowel resection	19 (10.9)	19 (8.5)	10 (6.7)	0.405
Appendectomy	93 (53.1)	111 (49.6)	74 (49.3)	0.724
Right diaphragm stripping	108 (61.7)	150 (67.0)	69 (46.0)	<0.001
Left diaphragm stripping	56 (32.0)	78 (34.8)	29 (19.3)	0.004
If diaphragm stripping, diaphragm resection (n=330)	31 (28.7)	26 (17.1)	15 (21.4)	0.083
Atypical hepatic resection	4 (2.3)	6 (2.7)	5 (3.3)	0.895
Cholecystectomy	20 (11.4)	19 (8.5)	6 (4.0)	0.051
Celiac lymph node resection	24 (13.7)	29 (12.9)	12 (8.0)	0.226
Splenectomy	43 (24.6)	53 (23.7)	31 (20.7)	0.687
Distal pancreatectomy	6 (3.4)	14 (6.3)	11 (7.3)	0.277
Partial gastrectomy	5 (2.9)	4 (1.8)	2 (1.3)	0.689
Extended peritonectomy	89 (50.9)	117 (52.2)	50 (33.3)	<0.001
Glissonectomy	15 (9.5)	16 (8.3)	15 (12.7)	0.447
Mesentery or bowel vaporisation	39 (22.3)	59 (26.3)	27 (18.0)	0.166
Partial abdominal wall resection	15 (8.6)	53 (23.7)	32 (21.3)	<0.001
Partial cystectomy or ureteral resection	4 (2.3)	2 (0.9)	2 (1.3)	0.509
Cardiophrenic lymph node resection	1 (0.6)	3 (1.3)	6 (4.0)	0.085
Inguinal lymph node resection	4 (2.3)	7 (3.1)	2 (1.3)	0.562
Axillary lymph node resection	0 (0)	1 (0.4)	1 (0.7)	0.739
CC-score				0.567
CC-0	157 (89.7)	195 (87.1)	129 (86.0)	
CC-1	18 (10.3)	29 (12.9)	21 (14.0)	
Aletti score				0.006
<8	80 (45.7)	125 (55.8)	95 (63.3)	
≥8	95 (54.3)	99 (44.2)	55 (36.7)	
HIPEC				0.001
No	174 (99.4)	223 (99.6)	142 (94.7)	
Yes	1 (0.6)	1 (0.4)	8 (5.3)	
IP chemotherapy				<0.001
No	156 (89.1)	224 (100)	150 (100)	
Yes	19 (10.9)	0 (0)	0 (0)	
Bevacizumab				<0.001
No	143 (81.7)	164 (73.2)	135 (90.0)	
Yes	32 (18.3)	60 (26.8)	15 (10.0)	

Values are presented as median (range) or number of patients (%). Bold-faced p-values indicate statistical significance.

CC-score, Completeness of Cytoreduction score; DDS, delayed debulking surgery; Early IDS, early interval debulking surgery; Extended peritonectomy, peritonectomy of more than three abdominal regions; HIPEC, hyperthermic intraperitoneal chemotherapy; IP, intraperitoneal; PCI, peritoneal cancer index; PDS, primary debulking surgery; PH, porta hepatis; Partial abdominal wall resection, partial resection of anterior abdominal wall sheath, omphalectomy or port site resection.

median OS was 106.6, 56.7, and 47.5 months ($p=0.013$), respectively. No significant differences between the 2 groups of NACT were observed. In both subsets of patients with an Aletti score <8 and an Aletti score ≥8, the risk of death was increased after early IDS or DDS compared to upfront surgery. The hazard ratios for death with an Aletti score <8 increased progressively

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Table 3. Analysis of OS according to surgical timing and Aletti surgical complexity score

Aletti score	PDS	Early IDS	DDS
Aletti <8			
Median OS (95%CI) (mo)	106.6 (68.0–NR)	56.7 (48.0–80.7)	47.5 (39.3–65.8)
HR (95% CI)	1.00 (ref.)	1.69 (1.08–2.66)	1.96 (1.24–3.10)
HR _{adj} (95% CI)	1.00 (ref.)	1.79 (1.13–2.86)	2.14 (1.32–3.46)
Aletti ≥8			
Median OS (95% CI) (mo)	80.5 (50.5–86.1)	42.4 (36.2–56.8)	45.8 (22.8–52.9)
HR (95% CI)	1.00 (ref.)	1.70 (1.15–2.53)	1.69 (1.08–2.62)
HR _{adj} (95% CI)	1.00 (ref.)	1.66 (1.11–2.47)	1.76 (1.12–2.78)

Bold-faced p-values indicate statistical significance.

CI, confidence interval; DDS, delayed debulking surgery; Early IDS, early interval debulking surgery; HR, hazard ratio; HR_{adj}, adjusted hazard ratio for age, International Federation of Gynaecology and Obstetrics stage, peritoneal cancer index score and Completeness of Cytoreduction score; NR, not reached; OS, overall survival; PDS, primary debulking surgery.

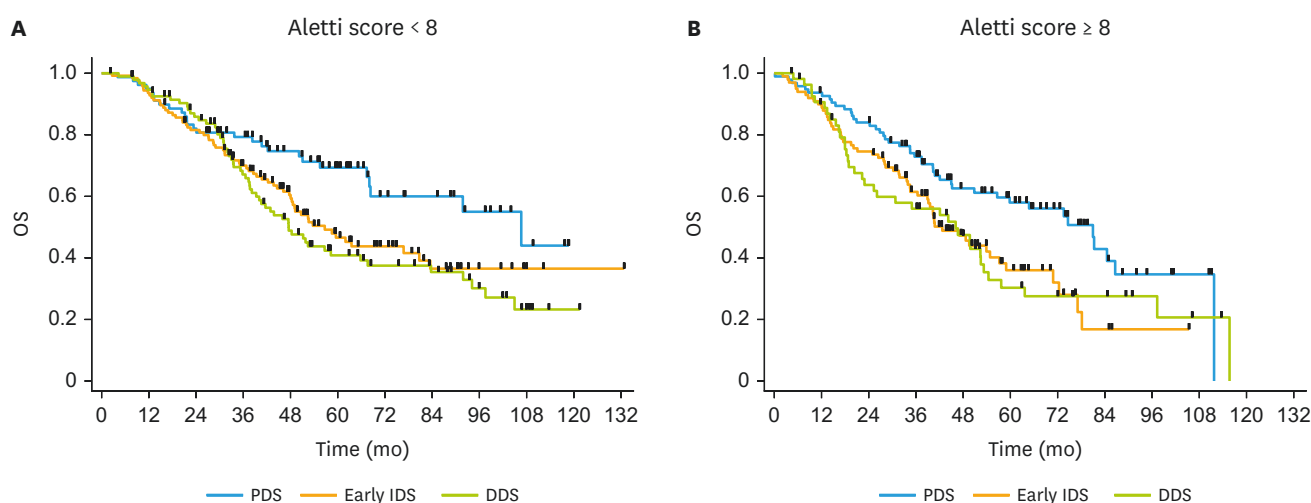


Fig. 1. OS according to surgical timing in patients with an Aletti score <8 (A) and an Aletti score ≥8 (B).

DDS, delayed debulking surgery; Early IDS, early interval debulking surgery; OS, overall survival; PDS, primary debulking surgery.

with the increasing number of cycles. **Fig. 1** shows OS curves of PDS, early IDS and DDS in the subset of patients with an Aletti score <8 and ≥ 8.

Table 4 shows OS according to surgical timing and tumor burden assessed by PCI. In women with PCI >10, median OS at PDS, early IDS and DDS was 67.4, 53.6, and 31.4 months ($p<0.001$), respectively. The difference was significant between early IDS and DDS ($p=0.002$) but not between PDS and early IDS ($p=0.406$). In women with PCI ≤10, median OS was 106.6,

Table 4. Analysis of OS according to surgical timing and PCI

PCI	PDS	Early IDS	DDS
PCI ≤10			
Median OS (95% CI) (mo)	106.6 (80.8–NR)	49.2 (43.7–62.0)	52.9 (46.0–91.9)
HR (95% CI)	1.00 (ref.)	2.57 (1.56–4.23)	2.09 (1.26–3.46)
HR _{adj} (95% CI)	1.00 (ref.)	2.55 (1.53–4.26)	2.06 (1.23–3.46)
PCI >10			
Median OS (95% CI) (mo)	67.4 (44.7–86.1)	53.6 (40.0–76.6)	31.4 (19.8–43.9)
HR (95% CI)	1.00 (ref.)	1.17 (0.80–1.71)	2.16 (1.42–3.29)
HR _{adj} (95% CI)	1.00 (ref.)	1.23 (0.84–1.80)	2.07 (1.36–3.17)

Bold-faced p-values indicate statistical significance.

CI, confidence interval; DDS, delayed debulking surgery; Early IDS, early interval debulking surgery; HR, hazard ratio; HR_{adj}, adjusted hazard ratio for age, International Federation of Gynaecology and Obstetrics stage, Aletti score and Completeness of Cytoreduction score; NR, not reached; OS, overall survival; PCI, peritoneal cancer index; PDS, primary debulking surgery.

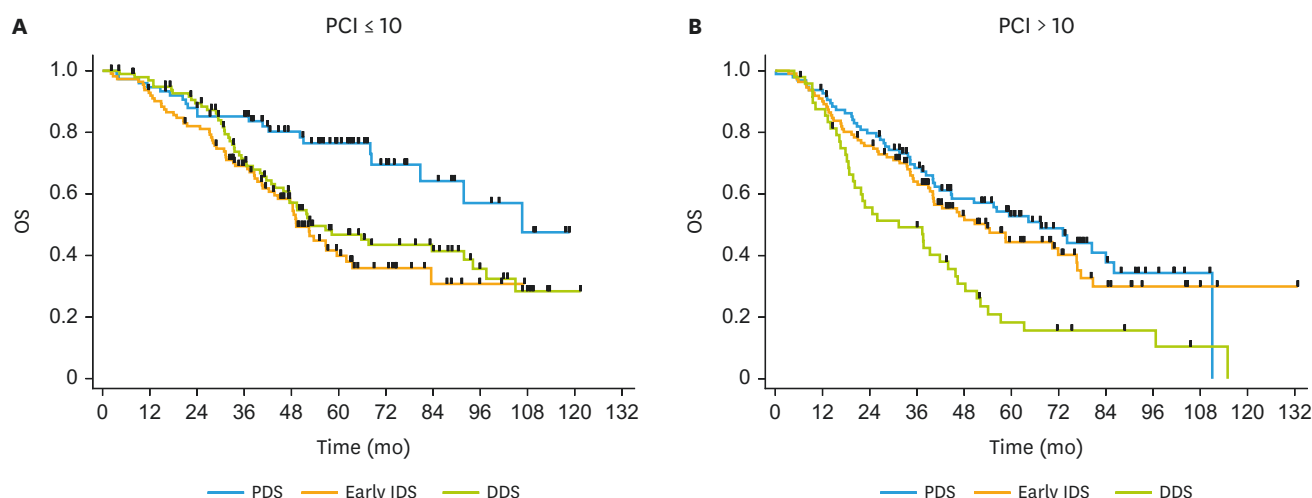


Fig. 2. OS according to surgical timing in patients with PCI ≤ 10 (A) and PCI > 10 (B). DDS, delayed debulking surgery; Early IDS, early interval debulking surgery; OS, overall survival; PCI, peritoneal cancer index; PDS, primary debulking surgery.

49.2, and 52.9 months ($p < 0.001$), respectively. No significant differences were observed between the two groups of NACT in this subset of patients. Among patients with PCI ≤ 10 , the risk of death was increased after debulking surgery, either after 3–4 or 6 cycles of NACT when compared to PDS. Among patients with PCI > 10 , the risk of death was higher after DDS, but early IDS did not yield an increased risk of death. **Fig. 2** displays OS curves of PDS, early IDS and DDS in the subset of patients with a PCI ≤ 10 and > 10 .

DISCUSSION

We found a survival benefit of upfront surgery over NACT, with an additional 33 months of OS in patients undergoing PDS compared with patients undergoing early IDS or DDS. Our findings are concordant with several previous reports showing that upfront cytoreduction offers a survival benefit over IDS [4,5,29,30]. Hypothetically, delaying CRS after NACT promotes the selection of chemoresistant tumor cells, as the probability of developing chemoresistance increases with the increasing number of tumor cells. Therefore, even if IDS were to remove all macroscopic disease, the remaining microscopic residual tumor might have a reduced chemosensitivity [31]. In fact, Petrillo et al. demonstrated a worse disease behavior in terms of timing, pattern, and type of recurrence in patients undergoing IDS compared to patients treated with PDS, as patients treated with NACT more frequently presented platinum-resistant recurrences, carcinomatosis and a shorter platinum-free interval. These findings suggest that upfront surgery reduces the probability of development of resistant tumor clones [32]. However, due to the retrospective design of our series, patients in the PDS group might have had a better baseline prognosis as they were not selected for NACT, so this may have contributed to their improved survival.

Classically, when NACT is indicated, IDS is scheduled after three or four cycles of chemotherapy. However, some reports have assessed the impact of late IDS performed after more than four cycles of NACT [11–14]. In our study, there were no significant differences in survival between IDS at 3–4 cycles or at 6 cycles of NACT. Yoneoka et al. [11] found that in patients with non-resectable disease after three cycles of NACT, delivering 3 additional

cycles before CRS offered a similar survival to that of patients undergoing IDS after 3 cycles of NACT. Similarly, Stoeckle et al. [14] found that survival of late IDS was not worse than with early IDS, and that the rate of complete cytoreduction was higher in patients undergoing late IDS. Other studies reported similar survival rates between patients receiving ≤ 4 or ≥ 5 cycles of NACT before IDS [12,13]. Our findings contrast with those of Colombo et al. [15], whose patients undergoing complete IDS after more than 4 cycles of NACT had a poorer prognosis. Xu et al. [16] reported an impaired oncological outcome of patients undergoing 5 or more cycles of NACT and they recommended not exceeding 4 cycles of NACT before IDS. A previous meta-analysis suggested that there is a gradual development of chemoresistant disease with the cumulative number of NACT cycles. However, most studies included patients undergoing suboptimal surgeries [5]. In contrast, our findings in the overall cohort suggest that when chemoresistant tumor cells have been selected by NACT, additional cycles do not impact survival. Another explanation could be that only patients with minimal or no residual disease were included in the present series.

In our study, surgical radicality was higher in women undergoing upfront surgery (54%) and decreased with the increasing number of cycles of NACT. The proportion of patients with an Aletti score ≥ 8 was 44% after IDS at 3–4 cycles and 37% after 6 cycles, although the difference was not significant. Surgical procedures such as diaphragmatic stripping, extended peritonectomy and large bowel resection were more frequent at PDS. This is concordant with previous studies as NACT is often associated with less extended surgical procedures and lower surgical morbi-mortality [8,10]. In a previous study, we showed that high surgical complexity according to the Aletti score was independently associated with a decreased disease-free survival [6]. In the present study, median OS decreased with the increasing number of NACT cycles in patients with an Aletti score < 8 . The difference in median OS between PDS and early or delayed IDS among patients with an Aletti score < 8 was 50 and almost 60 months, respectively. In patients undergoing more radical surgeries (Aletti score ≥ 8), the benefit of PDS over early or delayed IDS was lower (38 and 35 months, respectively). In other words, the negative impact of a high Aletti score decreased with NACT. The difference in median OS between Aletti ≥ 8 and Aletti < 8 after PDS was 26 months, while this difference was about 14 and less than 2 months after early and delayed IDS, respectively.

Little is known regarding the effect of radical surgery on the survival benefit offered by upfront surgery. Our results contrast with a previous study which did not show a significantly different prognostic outcome between patients receiving radical or simple upfront surgical procedures [21]. This contradiction may be explained by different definitions of radical surgery, as in the current study we assessed surgical complexity with Aletti score, which includes different items to define radical surgery [27]. Extended peritoneal disease requiring ultraradical procedures probably has an adverse tumor biology and surgical efforts may not completely overcome this deleterious effect [33]. Even if the benefit of PDS is impaired by high surgical radicality, we still found a survival advantage of upfront surgery with complete cytoreduction over IDS of almost 40 months in these patients. PDS should remain the mainstay of surgical treatment, even when complex procedures are required to achieve microscopic or no residual tumor.

Concordantly with previous reports, we found that NACT was associated with lower morbidity, 29% after PDS versus 23% after early IDS and 14% after DDS [7,8]. However, among patients with high surgical complexity, the rate of major surgical complications was not associated with NACT.

No residual tumor is widely recognized as the most powerful predictor of clinical outcome in advanced OC [2,34]. However, even in the event of complete cytoreduction, intraabdominal tumor burden still has a negative impact on survival [6,33]. Tentes et al. [35] demonstrated that PCI accurately reflects peritoneal spread and disease burden in advanced OC patients. Some studies have reported that PCI is an independent prognostic factor and that a cut-off value above 10 negatively impacts survival [6,35,36]. Moreover, in the subset of patients with no residual disease, high PCI scores remain associated with poor survival rates [6,37]. Even though the benefit of optimal cytoreduction has been shown to decrease with increasing tumor volume, there is still a significant survival benefit conferred by complete CRS in patients with high disease burden [33]. The impact of high tumor burden on survival according to the number of NACT cycles is unknown. To our knowledge, this is the first study to assess this issue.

In our study, median PCI score at CRS progressively decreased in PDS, early IDS and delayed IDS. The OS advantage of upfront CRS compared to NACT was enhanced in patients with low tumor burden. In this group, there was a survival difference of more than 50 months between upfront surgery and the NACT groups. In addition, our results concordantly showed that among patients with high disease burden, there was no survival difference between PDS and early IDS. Our findings are concordant with the recent randomised SCORPION trial, which included only patients with high tumor load. It reported that PDS and NACT with 3–4 cycles had superimposable survival outcomes in this subset of patients [18]. However, in our study, DDS after 6 cycles of NACT in patients with high PCI at CRS yielded the worst survival rates. Owing to the retrospective nature of our study, it is unclear whether the inferior clinical outcome of this subgroup was due to chemoresistance induced by additional cycles of NACT or to the selection of patients with a poorer prognosis who were not considered good surgical candidates after 3–4 cycles of NACT. In addition, among the patients who underwent DDS, there was no survival difference between those who had delayed IDS and those undergoing closure debulking surgery. It is unclear whether adjuvant chemotherapy after DDS did not improve clinical outcome or if patients receiving adjuvant chemotherapy had a worse prognosis due to the poor response to NACT.

The strengths of our study include a large homogeneous cohort with more than 500 patients with minimal or no residual disease after CRS and a long-term follow-up. Surgical complexity and tumor load were assessed using validated and objective systems such as the Aletti score and PCI [25,27]. The main weakness of the study is its retrospective design with the intrinsic risk of selection bias. As NACT was indicated in medically non-operable patients or in case of non-resectable carcinomatosis, patients with more extended disease were probably included in early IDS and DDS groups, which might have influenced our results. Another important limitation is that PCI was collected at CRS instead of at diagnosis, which would have allowed a more reliable comparison of tumor load between the 3 groups. Unfortunately, although our patients systematically underwent laparoscopy at diagnosis, PCI at this surgery was not available in the surgical report for most patients. The unexpected and uncontrolled significant differences in the baseline characteristics between the three groups could have influenced these findings. The role of early and delayed IDS according to surgical complexity and disease burden needs to be confirmed in prospective multicentric studies.

In conclusion, PDS is associated with higher survival rates than early or delayed IDS. The survival benefit of PDS over NACT is higher in women requiring less complex surgeries, even if radical upfront procedures are still associated with a survival advantage over NACT.

Similarly, low tumor load at CRS enhances the survival benefit of PDS over early or delayed IDS. In patients with high tumor load, delayed IDS yields impairs the oncological outcome.

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SUPPLEMENTARY MATERIALS

Table S1

Postoperative complications according to Clavien-Dindo classification

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Fig. S1

Flow chart of the eligible and the included patients.

[Click here to view](#)

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Article 3

The effect of major postoperative complications on recurrence and long-term survival after cytoreductive surgery for ovarian cancer

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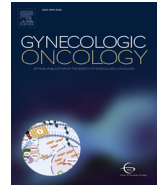
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The effect of major postoperative complications on recurrence and long-term survival after cytoreductive surgery for ovarian cancer

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HIGHLIGHTS

- Major surgical complications have a negative impact on patients' disease-free survival
- Major postoperative complications hinder the delivery of adjuvant chemotherapy
- Extensive peritonectomy and surgical timing are linked to major postoperative morbidity

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ABSTRACT

Objective. To assess the impact on survival of major postoperative complications and to identify the factors associated with these complications in patients with advanced ovarian cancer after cytoreductive surgery.

Methods. We designed a retrospective multicenter study collecting data from patients with IIIC-IV FIGO Stage ovarian cancer who had undergone either primary debulking surgery (PDS), early interval debulking surgery (IDS) after 3–4 cycles of neoadjuvant chemotherapy, or delayed debulking surgery (DDS) after 6 cycles, with minimal or no residual disease, from January 2008 to December 2015. Univariable and multivariable analyses were conducted to identify factors associated with major surgical complications (\geq Grade 3). We assessed disease-free survival (DFS) and overall survival (OS) rates according to the occurrence of major postoperative complications.

Results. 549 women were included. The overall rate of major surgical complications was 22.4%. Patients who underwent PDS had a higher rate of major complications (28.6%) than patients who underwent either early IDS (23.2%) or DDS (14.0%). Multivariable analysis revealed that extensive peritonectomy and surgical timing were associated with the occurrence of major complications. Median DFS and OS were 16.9 months (95%CI = [13.7–18.4]) and 48.0 months (95%CI = [37.2–73.1]) for the group of patients with major complications, and 20.1 months (95%CI = [18.6–22.4]) and 56.7 months (95%CI = [51.2–70.4]) for the group without major complications. Multivariable analysis revealed that major surgical complications were significantly associated with DFS, but not with OS.

Conclusions. Patients who experienced major surgical complications had reduced DFS, compared with patients without major morbidity. Extensive peritonectomy and surgical timing were predictive factors of postoperative morbidity.

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1. Introduction

Absence of residual disease after cytoreductive surgery (CRS) has been described as one of the most important prognostic factors for patients with advanced ovarian cancer [1,2]. Combined with platinum and taxane-based chemotherapy, primary debulking surgery (PDS) is currently the cornerstone of treatment for these patients [3,4]. With the objective of achieving complete cytoreduction, surgical effort has gradually been expanded, by incorporating extensive surgical procedures in the upper abdomen [5,6]. However, surgical radicality has been associated with non-negligible postoperative morbidity and mortality [7–9].

Neoadjuvant chemotherapy (NACT) is usually performed in patients who are not fit to undergo surgery owing to older age, poor performance status or comorbidities, high risk of residual disease, or high surgical complexity expected [10,11]. Interval debulking surgery (IDS) is generally done after three cycles of NACT. However, delivering three additional cycles of chemotherapy and performing delayed IDS is an option for patients who are still non-resectable after the three first cycles of NACT [12–15]. Moreover, it has been demonstrated that primary chemotherapy leads to lower morbidity and postoperative mortality than PDS [10,11].

The impact of postoperative complications on the long-term survival of patients with ovarian cancer is not well established, and current literature on this subject is controversial [9,16,17]. Some authors have reported that major surgical complications do not seem to negatively influence patients' survival [9,16]. Conversely, in other malignancies such as colorectal cancer, major surgical complications have been found to affect oncological outcome [18,19]. Postoperative complications are an independent risk factor for early recurrence, and are also associated with poorer survival [18,19].

The main objective of our study was to evaluate the impact on survival of major surgical complications in patients with advanced ovarian cancer who have undergone CRS leaving minimal or no residual disease, and to identify the factors associated with the occurrence of these complications.

2. Methods

2.1. Patients and study design

We performed a computerized search of patient databases to retrospectively identify patients who had undergone primary, interval or closure debulking surgery with either complete cytoreduction (CC-0) or cytoreduction to minimal residual disease (CC-1) for Stage IIIC-IV epithelial ovarian, fallopian, or primary peritoneal cancer between January 2008 and December 2015 at four institutions meeting the requirements of the European Society of Gynecological Oncology quality indicators from France and Spain. National and institutional review board approvals were obtained (SLN/MFI/AR193997 and HULP code PI-3432).

2.2. Preoperative assessment, surgery principles and chemotherapy treatment

All patients underwent an imaging study at diagnosis that included computed tomography (CT) of the thorax, abdomen, and pelvis. In the case of suspected extra-abdominal disease, positron emission tomography/computed tomography (PET/CT) was performed. An exploratory laparoscopy was routinely performed at diagnosis to assess resectability and perform a histological diagnosis.

All surgical procedures were carried out or supervised by experienced oncological surgeons. CRS was performed according to Sargant's principles of peritonectomy [20]. The extent and distribution of the disease throughout the 13 abdominopelvic regions were evaluated using the Peritoneal Cancer Index (PCI) [21]. The surgical goal was to achieve absence of residual disease, evaluated with the completeness

of cytoreduction score (CC-0: no residual tumor; CC-1: residual disease less than 2.5 mm in diameter; CC-2: residual nodules between 2.5 mm and 2.5 cm; and CC-3: residual nodules greater than 2.5 cm or a confluence of unresectable disease) [21]. Hysterectomy and bilateral salpingo-oophorectomy, infragastric omentectomy and pelvic plus paraaortic lymphadenectomy were systematically performed during debulking surgery. However, some patients referred from external hospitals had already undergone uni- or bilateral salpingo-oophorectomy with or without hysterectomy, and/or omentectomy. Moreover, as the study period preceded the LION trial [22], lymphadenectomy was only spared in some selected patients with no lymph node involvement at diagnosis, to decrease operating time and surgical morbidity. Extensive peritonectomy was defined as peritonectomy procedures performed in more than three anatomical regions [21]. Surgical complexity was quantified using the Aletti score, with a cut-off value ≥ 8 corresponding to high complexity [23].

Patients with deep infiltration of the small bowel mesentery, diffuse carcinomatosis involving large parts of the small bowel, stomach, infiltration of the duodenum or pancreas (not limited to the pancreatic tail) were considered non-resectable and were selected for primary chemotherapy. NACT was also indicated in patients who were not fit enough to withstand multivisceral resection, owing to medical comorbidities or poor performance status, or when the surgery needed to achieve complete cytoreduction was too extensive. After three or four cycles of platinum and taxane-based chemotherapy, a clinical, biological, and imaging (thoraco-abdomino-pelvic CT or PET/CT) assessment was performed. In the event of poor response or poor performance status, three additional cycles of NACT were administered before delayed debulking surgery (DDS). In selected patients with stable disease on CT after NACT, an exploratory laparoscopy was performed before IDS to assess resectability.

Postoperative complications within 30 days of CRS were documented according to the Clavien-Dindo classification (Supplementary Table 1) [24]. Surgical complications were classified according to the following categories: digestive, infectious, respiratory, abdominal wall, lymphatic, hemorrhagic, urinary/renal, cardiac, or neurological.

Adjuvant chemotherapy was delivered, when feasible, within 1 or 2 months of debulking surgery with carboplatin and paclitaxel, until a total of six cycles had been completed. In the event of high tumor burden, CC-1, or poor response to NACT, antiangiogenic maintenance treatment with bevacizumab was added, after discussion by the tumor board. When surgery was performed after six cycles of NACT, two to three additional cycles of chemotherapy were added to the antiangiogenic maintenance treatment with bevacizumab. No maintenance treatment with poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitors was administered during the study period.

Patients were divided into three groups according to the timing of their surgery: primary surgery and six cycles of adjuvant chemotherapy (PDS group); IDS after three to four cycles of NACT, then two to three cycles of adjuvant chemotherapy to achieve a total of six cycles (early IDS group); and DDS after six cycles of NACT (DDS group). The latter group included patients who underwent delayed IDS after six cycles of NACT and received two additional cycles of adjuvant chemotherapy owing to poor response to NACT, and patients who underwent closure debulking surgery after six cycles of NACT with no adjuvant chemotherapy.

Patients with unresectable disease, with residual disease ≥ 2.5 mm (\geq CC-2) and patients with non-epithelial subtype histology or borderline tumors were excluded from the study.

2.3. Study data

Medical databases were carefully examined to collect all relevant information. Patients' demographic data, World Health Organization (WHO) performance status, cancer antigen-125 (CA-125) dosage, ascites at diagnosis, surgical timing, PCI scores recorded during CRS, surgical

procedures, surgical complexity according to Aletti score, histological data, grade and type of postoperative complications according to Clavien-Dindo classification, adjuvant treatment, and follow-up data were retrieved from medical records.

2.4. Statistical analysis

Data were summarized by frequency and percentage for categorical variables, and by median and range for continuous variables. Comparisons between groups were performed using the chi-squared or Fisher's exact test for categorical variables, and the Kruskal-Wallis test for continuous variables. A multivariable logistic regression model was calculated to identify factors associated with major surgical complications. Odds ratios (ORs) were estimated with their 95% confidence intervals (95% CIs). Disease-free survival (DFS) was defined as the time from diagnosis to the date of relapse or death from any cause; patients who were alive and disease-free at last follow-up were censored at this date. Overall survival (OS) was defined as the time from diagnosis to the date of death from any cause; patients alive at last follow-up were censored at this date. Survival data were summarized using the Kaplan-Meier method. Univariable and multivariable analyses were performed using the logrank test and the Cox proportional hazards model. Hazard ratios (HRs) were estimated with their 95% CIs. All statistical tests were two-sided, and a p value <0.05 was considered to be statistically significant. Statistical analyses were carried out using STATA v16 (StataCorp, College Station, TX, USA) software.

3. Results

A total of 549 patients were included in the study. Table 1 shows patients' baseline characteristics. The overall rate of major surgical complications (Grade III–V) according to the Clavien-Dindo classification was 22.4% (123/549), and 10 patients (1.8%, 10/549) died due to postoperative complications (Grade V). There were no complications in 45.7% (251/549) of patients, and 31.9% (175/549) had minor (Grade I–II) postoperative complications. Regarding the type of major postoperative complication, 51 patients (9.3%) had a digestive complication, 49 (8.9%) an infectious complication, 28 (5.1%) a respiratory complication,

24 (4.4%) an abdominal wall complication, 19 (3.5%) a lymphatic complication, 18 (3.3%) a hemorrhagic complication, 13 (2.4%) a urinary or renal complication, 10 (1.8%) a cardiac event, and 2 (0.4%) a neurological event. A total of 66 (12.0%) women had more than one type of major complication. There were no significant differences in baseline characteristics between patients with or without major postoperative complications.

Regarding surgical timing, 175 (31.9%) underwent PDS, 224 (40.8%) had IDS after three to four cycles of NACT, and 150 (27.3%) underwent DDS after six cycles of NACT. Patients who underwent PDS had a significantly higher rate of major complications (50/175, 28.6%) than patients who underwent early IDS (52/224, 23.2%) or DDS (21/150, 14.0%), $p = 0.007$. A PCI score above 10 was described in 72/123 (59.0%) patients with major complications, and in 184/426 (43.7%) patients without major complications, $p = 0.003$. A high Aletti score (≥ 8) was calculated for 75/123 (61.0%) patients with major complications, and for 174/426 (40.8%) patients without major complications, $p < 0.001$. Regarding surgical procedures, the group of patients with major postoperative complications had a significantly higher rate of small and large bowel resection, multiple bowel resection, cholecystectomy, splenectomy, distal pancreatectomy, extended peritonectomy, diaphragmatic stripping, and inguinal lymph node resection than the group with no major complications (Table 2). In the whole sample, 67/549 (12.2%) patients did not receive adjuvant chemotherapy: 26/123 (21.1%) had major surgical complications, and 41/426 (9.6%) did not ($p < 0.001$). In the PDS group, 10/175 (5.7%) women did not receive adjuvant chemotherapy: 6/50 (12.0%) with major surgical complications versus 4/125 (3.2%) without ($p = 0.033$). Among patients who underwent early IDS, 13/224 (5.8%) women did not receive adjuvant chemotherapy: 10/52 (19.2%) with major complications versus 3/172 (1.7%) without ($p < 0.001$). In the DDS group, 44/150 (29.3%) women did not receive adjuvant chemotherapy: 10/21 (47.6%) with major complications versus 34/129 (26.4%) without ($p = 0.047$).

Multivariable analysis revealed that upfront surgery, early IDS, and extensive peritonectomy were associated with the occurrence of major surgical complications (Table 3). A subgroup analysis was conducted in PDS group, and no surgical procedures were associated with postoperative complications (Supplementary Table 2).

Table 1
Baseline characteristics of patients according to occurrence of major postoperative complications.

	Whole sample N = 549	No major surgical complications (Grade < III) n = 426	Major surgical complications (Grade \geq III) n = 123	p value
Median age in years (range)	61 (21–88)	61 (22–88)	62 (21–82)	0.913
Age at diagnosis, n (%)				0.976
≤ 60 years	264 (48.1)	205 (48.1)	59 (48.0)	
> 60 years	285 (51.9)	221 (51.9)	64 (52.0)	
Median BMI (kg/m ²) (range)	24.2 (15.6–52.0)	24.1 (15.6–48.1)	24.2 (17.9–52.0)	0.199
Missing	20 (—)	10 (—)	10 (—)	
WHO performance status classification, n (%)				0.609
0	355 (66.1)	272 (65.5)	83 (68.0)	
≥ 1	182 (33.9)	143 (34.5)	39 (32.0)	
Missing	12 (—)	11 (—)	1 (—)	
Median preoperative CA-125 (UI/ml) (range)	740	700	848	0.106
Missing	(5–86,000)	(5–86,000)	(25–42,110)	
	52 (—)	38 (—)	14 (—)	
FIGO stage, n (%)				0.214
IIIC	449 (81.8)	353 (82.9)	96 (78.0)	
IVA	43 (7.8)	34 (8.0)	9 (7.3)	
IVB (pleural and/or extra-abdominal LN involvement)	57 (10.4)	39 (9.2)	18 (14.6)	
Histological subtype, n (%)				0.778
Serous	489 (89.6)	378 (89.4)	111 (90.2)	
Non-serous	57 (10.4)	45 (10.6)	12 (9.8)	
Missing	3 (—)	3 (—)	0 (—)	
Median ascites (mL) (range)	1000	1000	1000	0.886
Missing	(0–10,000)	(0–10,000)	(0–7000)	
	68 (—)	53 (—)	15 (—)	

Note. BMI: body mass index; WHO: World Health Organization; CA-125: cancer antigen 125; FIGO: International Federation of Gynecology and Obstetrics; LN: lymph node.

Table 2

Surgical data and adjuvant treatment of patients according to occurrence of major postoperative complications.

	Whole sample N = 549	No major surgical complications (Grade < III) n = 426	Major surgical complications (Grade ≥ III) n = 123	p value
Surgical timing, n (%)				0.007
PDS	175 (31.9)	125 (29.3)	50 (40.7)	
Early IDS	224 (40.8)	172 (40.4)	52 (42.3)	
DDS	150 (27.3)	129 (30.3)	21 (17.1)	
PCI, n (%)				0.003
≤10	287 (52.9)	237 (56.3)	50 (41.0)	
>10	256 (47.1)	184 (43.7)	72 (59.0)	
Missing	6 (-)	5 (-)	1 (-)	
Surgical procedure, n (%)				
Hysterectomy	491 (89.4)	378 (88.7)	113 (91.9)	0.319
Unilateral or bilateral salpingoophorectomy	502 (91.4)	385 (90.4)	117 (95.1)	0.098
Pelvic lymphadenectomy	495 (90.2)	383 (89.9)	112 (91.1)	0.706
Aortic lymphadenectomy	488 (88.9)	380 (89.2)	108 (87.8)	0.664
Infragastric omentectomy	540 (98.4)	419 (98.4)	121 (98.4)	1.000
Small bowel resection	44 (8.0)	28 (6.6)	16 (13.0)	0.021
Large bowel resection	225 (41.0)	157 (36.9)	68 (55.3)	< 0.001
If large bowel resection, rectosigmoid resection [n = 225]	204 (90.7)	139 (88.5)	65 (95.6)	0.095
Multiple bowel resection	48 (8.7)	29 (6.8)	19 (15.4)	0.003
Diaphragmatic stripping	330 (60.1)	246 (57.7)	84 (68.3)	0.035
Right diaphragmatic stripping	327 (59.6)	243 (57.0)	84 (68.3)	0.025
Left diaphragmatic stripping	163 (29.7)	112 (26.3)	51 (41.5)	0.001
If diaphragm stripping, diaphragm resection [n = 330]	72 (21.8)	53 (21.5)	19 (22.6)	0.837
Atypical hepatic resection	15 (2.7)	11 (2.6)	4 (3.3)	0.753
Cholecystectomy	45 (8.2)	27 (6.3)	18 (14.6)	0.003
Celiac lymph node resection	65 (11.8)	48 (11.3)	17 (13.8)	0.440
Splenectomy	127 (23.1)	80 (18.8)	47 (38.2)	<0.001
Distal pancreatectomy	31 (5.6)	18 (4.2)	13 (10.6)	0.007
Partial gastrectomy	11 (2.0)	9 (2.1)	2 (1.6)	1.000
Extensive peritonectomy	256 (46.6)	177 (41.5)	79 (64.2)	<0.001
Glissonectomy	46 (8.4)	30 (7.1)	16 (13.0)	0.069
Mesentery or bowel vaporization	125 (22.8)	91 (21.4)	34 (27.6)	0.143
Partial abdominal wall resection	100 (18.2)	79 (18.5)	21 (17.1)	0.710
Partial cystectomy or ureteral resection	8 (1.5)	7 (1.6)	1 (0.8)	0.691
Cardiophrenic lymph node resection	10 (1.8)	9 (2.1)	1 (0.8)	0.470
Inguinal lymph node resection	13 (2.4)	6 (1.4)	7 (5.7)	0.012
Axillary lymph node resection	2 (0.4)	2 (0.5)	0 (0)	1.000
CC score, n (%)				0.701
CC-0	481 (87.6)	372 (87.3)	109 (88.6)	
CC-1	68 (12.4)	54 (12.7)	14 (11.4)	
Aletti score, n (%)				< 0.001
<8	300 (54.6)	252 (59.2)	48 (39.0)	
≥8	249 (45.4)	174 (40.8)	75 (61.0)	
HIPEC, n (%)	10 (1.8)	9 (2.1)	1 (0.8)	0.470
IP chemotherapy, n (%)	19 (3.5)	14 (3.3)	5 (4.1)	0.779
Bevacizumab, n (%)	107 (19.5)	85 (20.0)	22 (17.9)	0.610

Note. PDS: primary debulking surgery; Early IDS: early interval debulking surgery; DDS: delayed debulking surgery; PCI: Peritoneal Cancer Index; Extensive peritonectomy: peritonectomy of more than three abdominal regions; Partial abdominal wall resection: partial resection of anterior abdominal wall sheath, omphalectomy or port site resection; CC score: completeness of cytoreduction score; HIPEC: hyperthermic intraperitoneal chemotherapy; IP: intraperitoneal.

Regarding the type of major postoperative complication, we found that there were more digestive (23/175, 13.1% and 25/224, 11.2% vs. 3/150, 2.0%, $p = 0.001$) and infectious (20/175, 11.4% and 23/224, 10.3% vs. 6/150 4.0%, $p = 0.042$) complications in the PDS and early IDS groups than in the DDS group. Remarkably, the rate of large bowel resection was 54.9% (96/175) in the PDS group, 36.2% (81/224) in early IDS, and 32.0% (48/150) after DDS, $p < 0.001$. There were no significant differences between surgical timing groups on the other types of complications.

Median follow-up was 65.1 months (95% CI = [62.1–70.6]). Median DFS for the whole sample was 19.4 months (95% CI = [18.1–20.6]). For the group of patients who had major surgical complications, it was 16.9 months (95% CI = [13.7–18.4]), compared with 20.1 months (95% CI = [18.6–22.4]) for the group with no major complications, $p = 0.012$. Fig. 1A displays the DFS curves according to the occurrence of major postoperative complications. Median OS for the whole sample was 56.3 months (95% CI = [50.2–67.4]). For the group of patients with major surgical postoperative complications, it was 48.0 months (95% CI = [37.2–73.1]), compared with 56.7 months (95% CI = [51.2–70.4]) for the group of patients with no major surgical postoperative complications,

$p = 0.112$. Fig. 1B illustrates the OS curves according to the presence or absence of major postoperative complications. Table 4 shows the results of the univariable and multivariable analyses for both DFS and OS. Major surgical complications remained significantly associated with DFS (but not OS) in the multivariable analysis.

Among patients who underwent PDS, median DFS was 20.0 months (95% CI = [17.1–25.5]) for those with major surgical complications, and 25.1 months (95% CI = [20.6–33.8]) for those without ($p = 0.042$). Median OS were 73.1 months (95% CI = [40.1–111.0]) and 91.8 months (95% CI = [68.3 – N.R.]), respectively ($p = 0.168$). Among patients who had early IDS, median DFS was 13.8 months (95% CI = [12.3–18.0]) for those with major postoperative complications, and 18.8 months (95% CI = [16.2–20.8]) for those without ($p = 0.085$). Median OS were 40.4 months (95% CI = [20.6–56.8]) and 53.7 months (95% CI = [47.7–71.9]), respectively ($p = 0.051$). Among patients who underwent DDS, median DFS was 12.3 months (95% CI = [7.8–18.3]) for those with major postoperative complications, and 18.8 months (95% CI = [15.9–22.2]) for those without ($p = 0.148$). Median OS were 33.4 months (95% CI = [13.3 – N.R.]) and 47.5 months (95% CI = [40.6–52.9]), respectively ($p = 0.908$). Fig. 2 displays the DFS

Table 3

Multivariable logistic regression analysis to identify factors associated with major surgical complications in the whole sample.

	OR	95% CI	p value
Surgical timing			0.434
PDS	1.00	Ref.	0.011
Early IDS	0.82	[0.51–1.34]	
DDS	0.46	[0.25–0.84]	
PCI			0.380
≤10	1.00	Ref.	
>10	0.77	[0.43–1.38]	
Aletti score			0.863
<8	1.00	Ref.	
≥8	0.93	[0.42–2.07]	
Small bowel resection			0.415
No	1.00	Ref.	
Yes	1.44	[0.60–3.47]	
Large bowel resection			0.205
No	1.00	Ref.	
Yes	1.57	[0.78–3.18]	
Multiple bowel resection			0.754
No	1.00	Ref.	
Yes	1.15	[0.48–2.77]	
Diaphragmatic stripping			0.072
No	1.00	Ref.	
Yes	0.52	[0.25–1.06]	
Cholecystectomy			0.614
No	1.00	Ref.	
Yes	1.21	[0.58–2.51]	
Splenectomy			0.057
No	1.00	Ref.	
Yes	1.80	[0.98–3.28]	
Distal pancreatectomy			0.251
No	1.00	Ref.	
Yes	1.66	[0.70–3.96]	
Extensive peritonectomy			0.003
No	1.00	Ref.	
Yes	2.98	[1.45–6.15]	

Note. OR: odds ratio; 95% CI: 95% confidence interval; PDS: primary debulking surgery; IDS: interval debulking surgery; DDS: delayed debulking surgery; PCI: Peritoneal Cancer Index.

and OS curves for the groups of patients who underwent PDS, early IDS and DDS, according to the presence or absence of major postoperative complications.

4. Discussion

4.1. Factors associated with major postoperative complications

In our patient series, the rate of major surgical complications was 22.4%, with mortality below 2%, which is in line with previous published studies [7,16,25]. This non-negligible rate of major postoperative complications in our study can be explained by the number of extensive procedures performed in our institutions. Chi et al. described a 22% incidence of Grade III–V postoperative complications after extensive upper abdominal surgical procedures during PDS for advanced ovarian cancer, with a postoperative mortality of 1.4% [7]. Similarly, Patankar et al. reported a rate of postoperative complications of around 30% in women with ovarian cancer who underwent two or more extensive procedures during CRS [25].

We found that the rate of major postoperative complications was significantly associated with surgical timing. The rate of complications decreased as the number of NACT cycles increased, falling from 28.6% after PDS to 23.2% after early IDS, and 14% after DDS. Similarly, Lomnyska et al. observed a higher rate of Grade 3 or more postoperative complications after PDS (32%) than after IDS (12%) [16]. This is not surprising, as upfront procedures usually involve greater surgical complexity than IDS [26]. The multivariable analysis revealed that upfront surgery was significantly associated with postoperative complications. Interestingly, in our study, digestive and infectious complications

were significantly more common in patients who had undergone upfront or early interval CRS than in patients who had had delayed surgery. This can be explained by the significantly higher rate of large bowel resections in women who underwent PDS.

Tumor burden (PCI > 10) and surgical complexity (Aletti score ≥ 8) were higher in the group of patients with postoperative complications, but this association did not remain significant in the multivariable analysis. By contrast, Lomnyska et al. found that a PCI of 21 or more was an independent predictor of high-grade complications after surgery for ovarian cancer [16]. Aletti et al. reported that their surgical complexity score was an independent predictor of 30-day morbidity [9], and in another study, high-complexity surgery was found to be a predictor of severe complications after CRS for ovarian cancer [27]. The absence of significant associations in our study between high tumor burden or surgical complexity and major postoperative complications can be attributed to the lower tumor burden and surgical complexity of the patients who underwent delayed surgery, which was also included in the multivariable analysis.

Surgical procedures such as extensive peritonectomy were significantly associated with major postoperative complications. Furthermore, there was a higher rate of diaphragmatic stripping and splenectomy among patients with major morbidity that almost reached statistical significance. Pantakar et al. found that the number of extended cytoreductive procedures (e.g., small or large bowel resection, hepatic resection, bladder resection, diaphragm resection, lymphadenectomy or cytoreduction) was the strongest risk factor for postoperative complications [25]. In our study, we did not find that bowel resection was associated with major postoperative complications, but this may be because of the higher rate of large bowel resection during PDS, both variables included in the multivariable analysis. Nevertheless, Lomnyska et al. found that large bowel resection, colectomy and bowel anastomosis were not associated with high-grade postoperative complications in their study [16].

4.2. Impact on survival of postoperative complications

Our findings suggest that major postoperative complications negatively impact oncological outcome. DFS was significantly reduced with the occurrence of major surgical complications, with a decrease of 3 months in median DFS in patients with major postoperative complications. There was a non-significant trend toward reduced OS in patients presenting with major complications, with a decrease of almost 9 months in median OS. However, in subgroup analyses, we observed that this impact on survival was greater in patients who underwent upfront surgery, with a decrease of 5 months in median DFS. In patients with early IDS and DDS, there was only a non-significant trend toward decreased DFS and OS with the occurrence of major postoperative complications. This seems logical, as PDS usually requires more complex procedures, with a higher rate of postoperative complications.

Similarly, in a study including almost 4000 women with advanced ovarian cancer who underwent CRS, Wright et al. reported that the occurrence of two or more major perioperative complications increased the risk of death from ovarian cancer [17]. By contrast, two other studies reported that severe postoperative complications did not seem to have a negative impact on OS [9,16]. Aletti et al. demonstrated that short-term morbidity in patients with Stage IIIC–IV ovarian cancer undergoing debulking surgery did not translate into an independent predictor of OS [9]. Similarly, Lomnyska et al. showed that high-grade complications (Grade ≥ 3) did not impair OS [16]. However, these two studies both had smaller patient samples than ours, which could explain why there was no significant impact on survival. Moreover, the impact of major postoperative complications on DFS was not assessed in these studies, and DFS is known to require less statistical power than OS to show significant differences [28]. Another study including patients with ovarian cancer showed that postoperative complications such as

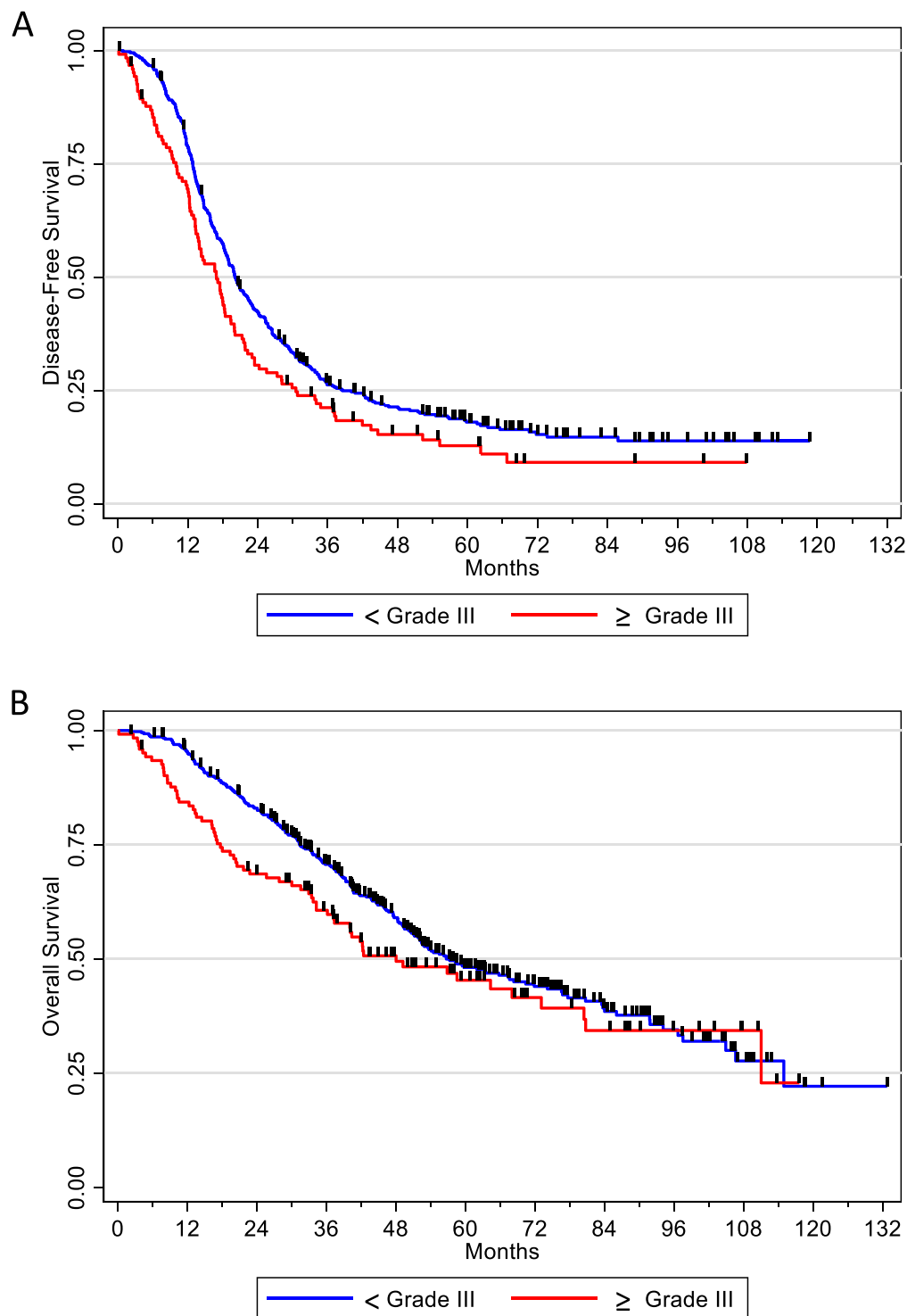


Fig. 1. Disease-free survival (A) and overall survival (B) curves according to the occurrence of major postoperative complications.

anastomotic leakage after bowel resection did not have a negative impact on OS [29].

Although the impact of postoperative morbidity has seldom been studied in ovarian cancer, this subject has been extensively explored in patients with colorectal cancer undergoing surgery, in whom major surgical complications seem to impair oncological outcome [18,19]. Baratti et al. showed that major postoperative morbidity

after cytoreduction plus hyperthermic intraperitoneal chemotherapy (HIPEC) in patients with peritoneal carcinomatosis of colorectal origin was correlated with both overall and disease-specific survival, with a 5-year OS of 12% in patients who had experienced major complications, compared with almost 60% for those who had a complication-free recovery [18]. Simkens et al. identified postoperative complications requiring a further intervention as the only significant risk factor for

Table 4
Univariable and multivariable analyses for disease-free and overall survival in the whole sample.

	Disease-free survival						Overall survival					
	Univariable			Multivariable			Univariable			Multivariable		
	HR	95% CI	p value	HR	95% CI	p value	HR	95% CI	p value	HR	95% CI	p value
Age at diagnosis												
≤60 years	1.00	Ref.[0.89–1.29]	0.445				1.00	Ref.[0.95–1.51]	0.125			
>60 years	1.07						1.20					
Surgical timing												
PDS	1.00	Ref.[1.21–1.89]	<0.001	1.00	Ref.[1.22–1.92]	<0.001	1.00	Ref.[1.19–2.14]	<0.001	1.00	Ref.[1.23–2.23]	0.001
Early IDS	1.51			1.53			1.60			1.65		
DDS	1.43	[1.12–1.83]		1.65	[1.27–2.15]		1.73	[1.27–2.35]		2.04	[1.47–2.81]	
FIGO stage			0.044			0.185			0.953			
IIIC	1.00	Ref.[1.01–1.60]		1.00	Ref.[0.93–1.50]		1.00	Ref.[0.75–1.37]				
IV	1.27			1.18			1.01					
PCI			<0.001			0.004			0.002			0.038
≤10	1.00	Ref.[1.26–1.83]		1.00	Ref.[1.11–1.75]		1.00	Ref.[1.13–1.80]		1.00	Ref.[1.02–1.77]	
>10	1.52			1.40			1.43			1.34		
Aletti score			0.002			0.071			0.017			0.103
<8	1.00	Ref.[1.12–1.62]		1.00	Ref.[0.98–1.53]		1.00	Ref.[1.05–1.67]		1.00	Ref.[0.96–1.63]	
≥8	1.35			1.23			1.33			1.25		
CC score			0.001			0.004			0.013			0.078
CC-0	1.00	Ref.[1.19–2.04]		1.00	Ref.[1.13–1.95]		1.00	Ref.[1.08–2.04]		1.00	Ref.[0.97–1.86]	
CC-1	1.56			1.49			1.49			1.34		
Postoperative complications			0.012			0.010			0.112			0.056
<Grade III	1.00	Ref.[1.06–1.64]		1.00	Ref.[1.07–1.69]		1.00	Ref.[0.95–1.64]		1.00	Ref.[0.99–1.74]	
≥Grade III	1.32			1.35			1.25			1.31		

Note. HR: hazard ratio; 95% CI: 95% confidence interval; PDS: primary debulking surgery; IDS: interval debulking surgery; DDS: delayed debulking surgery; FIGO: International Federation of Gynecology and Obstetrics; PCI: Peritoneal Cancer Index; CC score: completeness of cytoreduction score.

early recurrence, regardless of peritoneal extension. A decrease in OS of 9 months was observed in patients who experienced major complications [19]. Another study among patients with peritoneal malignancies (including 8% with ovarian cancer) who underwent CRS plus HIPEC found that early postoperative complications had a negative impact on short-term postoperative and long-term cancer-related survival [30].

Although it is difficult to elucidate the exact mechanisms behind the correlation between major surgical complications and decreased DFS, there is probably a synergy between the immunosuppressive and pro-inflammatory effects of postoperative complications [31], which may allow minimal residual disease to proliferate. In most postoperative complications, there is an increased systemic inflammatory response that stimulates the proliferation and survival of malignant cells by activating pro-inflammatory cascades [32]. It has been suggested that the use of preoperative corticosteroids could reduce the magnitude of the postoperative systemic inflammatory response, thus decreasing postoperative complications in patients with gastrointestinal cancer [33]. Moreover, the innate immune system, which chronically inhibits cancer proliferation, is less effective in the presence of a systemic infection [34]. Lastly, increased expression of proangiogenic factors, which are released in response to surgical stress and magnified by postoperative complications, may facilitate the survival and growth of residual tumor cells after surgery for colorectal cancer [35]. Another possible explanatory factor for reduced DFS is the inability of patients with major postoperative complications to receive adjuvant chemotherapy.

In our series, we found that the occurrence of major surgical complications had a negative impact on adjuvant treatment, as the proportion of patients who did not receive adjuvant chemotherapy was significantly higher for those who had major complications than for those who did not (21% vs. 10%). Wright et al. reported that the occurrence of postoperative complications was associated not with omission of chemotherapy, but with delayed chemotherapy. In their study, initiation of chemotherapy more than 12 weeks after surgery was associated with decreased survival [17]. Similarly, Singh et al. found that a delay in chemotherapy initiation was associated with shorter progression-free survival [36].

The notion that major surgical complications may impair the oncological outcome, and that some of these complications may be preventable, highlights the importance of adhering to evidence-based practice

guidelines. Perioperative practices such as avoiding hypothermia, minimizing blood loss, and optimizing nutritional status should be implemented, as they are known to prevent surgical complications, particularly infections [37]. However, all these strategies were not evaluated in our study. It is also essential to adequately select the patients who will benefit most from CRS. In our study, there was already a high selection of patients with good performance status (WHO 0) and with a CC score of 0 or 1 after CRS, so all patients with macroscopic tumor residue were excluded. Although the effort should focus on how to decrease postoperative complications, our findings should not be misinterpreted. Even if the occurrence of postoperative complications was associated with upfront surgery, this approach was still associated with better OS and should remain the first option offered to patients with advanced ovarian cancer.

The main strength of our study was the large and homogeneous sample of patients, including only patients whose CRS left them with minimal or no residual disease. To our knowledge, there are only a few patient series studies in the literature that have assessed the impact of postoperative morbidity on the long-term survival of patients with ovarian cancer. Nonetheless, in addition to the limitations arising from the retrospective design of our study, several other weaknesses need to be mentioned. First, although we established strict definitions for each type of complication before retrieving data from medical records, the diagnosis of each complication may not have been uniform across institutions. Second, despite having information about the omission of adjuvant chemotherapy, the timing of initiation and the possible need for dose reductions, which can both have an impact on survival, were not recorded. Third, among the patients with major postoperative complications in the DDS group who did not receive adjuvant chemotherapy, we do not know if this was due to the occurrence of surgical complications or following a decision of the tumor board, based on histological response to NACT. Fourth, some factors that may increase the risk of postoperative complications, such as nutritional status, comorbidities, and smoking, were not assessed in our series.

It is essential to continue improving the perioperative management of patients undergoing cytoreductive procedures, to limit major postoperative complications. Moreover, understanding the prognostic implications of these complications for long-term survival may help us to

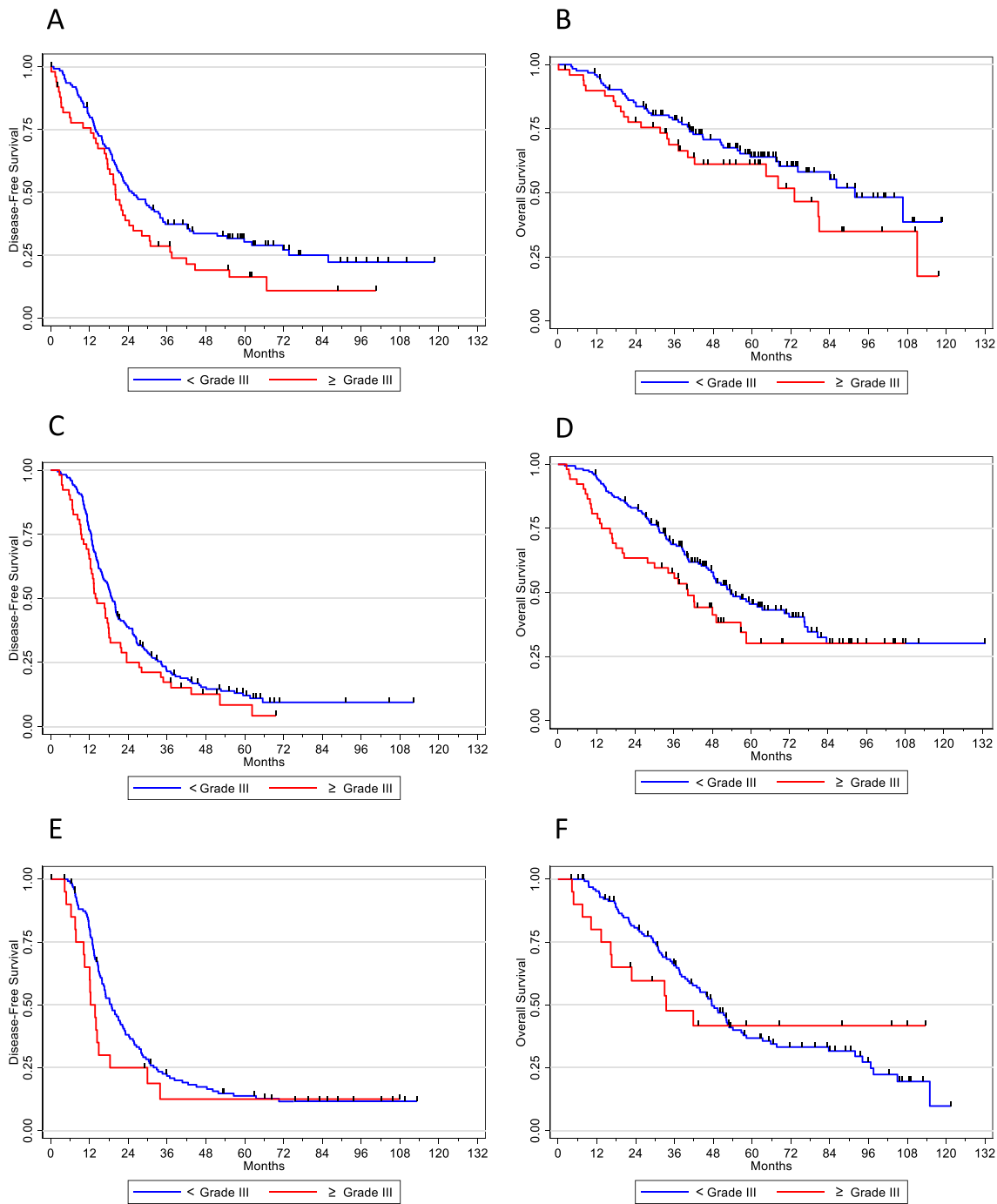


Fig. 2. Disease-free survival (DFS) and overall survival (OS) curves according to the occurrence of major postoperative complications in the group of patients with primary debulking surgery (A and B); early interval debulking surgery (C and D); and delayed debulking surgery (E and F).

identify potential key points of intervention to improve oncological outcomes, such as considering further adjuvant treatment and individualizing follow-up strategies in patients presenting with major surgical complications.

5. Conclusion

In conclusion, patients who had major postoperative complications had poorer DFS than patients with no major morbidity. This negative impact was greater after PDS, with a decrease of 5 months in median

DFS. Furthermore, the occurrence of major surgical complications had a negative impact on adjuvant therapy. Surgical procedures such as extensive peritonectomy and surgical timing were associated with major postoperative morbidity.

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Credit authorship contribution statement

Martina Aida Angeles: Conceptualization, Data curation, Methodology, Writing – original draft. **Alicia Hernández:** Conceptualization, Project administration, Methodology, Writing – review & editing. **Asunción Pérez-Benavente:** Conceptualization, Project administration, Methodology, Writing – review & editing. **Bastien Cabarro:** Conceptualization, Data curation, Methodology, Writing – review & editing. **Emanuela Spagnolo:** Conceptualization, Data curation, Methodology, Writing – review & editing. **Agnieszka Rychlik:** Conceptualization, Data curation, Methodology, Writing – review & editing. **Amel Daboussi:** Conceptualization, Data curation, Methodology, Writing – review & editing. **Federico Migliorelli:** Conceptualization, Project administration, Methodology, Writing – review & editing. **Sarah Bétrian:** Conceptualization, Project administration, Methodology, Writing – review & editing. **Gwénaél Ferron:** Conceptualization, Project administration, Methodology, Writing – review & editing. **Antonio Gil-Moreno:** Conceptualization, Project administration, Methodology, Writing – review & editing. **Frédéric Guyon:** Conceptualization, Project administration, Methodology, Writing – review & editing. **Alejandra Martinez:** Conceptualization, Project administration, Methodology, Writing – review & editing.

Declaration of Competing Interest

The authors declare no conflict of interest.

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Article 4

Survival impact of histological response to neoadjuvant chemotherapy according to number of cycles in patients with advanced ovarian cancer

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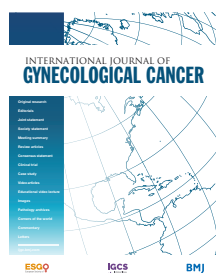
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Survival impact of histological response to neoadjuvant chemotherapy according to number of cycles in patients with advanced ovarian cancer

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ABSTRACT

Objective We sought to evaluate the impact of chemotherapy response score according to the number of cycles of neoadjuvant chemotherapy, on disease-free survival and overall survival, in patients with advanced epithelial ovarian cancer ineligible for primary debulking surgery.

Methods This multicenter retrospective study included patients with International Federation of Gynecology and Obstetrics (FIGO) stage IIIC-IV epithelial ovarian cancer who underwent 3–4 or 6 cycles of a platinum and taxane-based neoadjuvant chemotherapy, followed by complete cytoreduction surgery (CC-0) or cytoreduction to minimal residual disease (CC-1), between January 2008 and December 2015, in four institutions. Disease-free survival and overall survival were assessed according to the histological response to chemotherapy defined by the validated chemotherapy response score.

Results A total of 365 patients were included: 219 (60.0%) received 3–4 cycles of neoadjuvant chemotherapy, and 146 (40.0%) had 6 cycles of neoadjuvant chemotherapy before cytoreductive surgery. There were no significant differences in early relapses, disease-free survival, and overall survival according to the number of neoadjuvant chemotherapy cycles. However, regardless of the number cycles of neoadjuvant chemotherapy, persistent extensive histological disease (chemotherapy response score 1–2) was significantly associated with a higher peritoneal cancer index, minimal residual disease (CC-1), and early relapses. Median disease-free survival in patients with complete or near-complete response (score 3) was 28.3 months (95% CI 21.6 to 36.8), whereas it was 16.3 months in patients with chemotherapy response score 1–2 (95% CI 14.7 to 18.0, $p < 0.001$).

Conclusion In our cohort, the number of neoadjuvant chemotherapy cycles was not associated with disease-free survival or overall survival. Chemotherapy response score 3 improved oncological outcome regardless of the number of neoadjuvant chemotherapy cycles.

INTRODUCTION

Primary debulking surgery to achieve complete cytoreduction of all macroscopic visible disease,

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Chemotherapy response score assessed on interval debulking specimen reflects chemosensitivity and is associated with survival in advanced high grade serous carcinoma. The impact of histological response on survival according to the number of neoadjuvant chemotherapy cycles remains unknown.

WHAT THIS STUDY ADDS

⇒ Chemotherapy response score is associated with survival, regardless of the number of cycles of neoadjuvant chemotherapy.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

⇒ Chemotherapy response score may be used as a surrogate for chemosensitivity and as a useful end-point for clinical trials, irrespective of the number of cycles of neoadjuvant chemotherapy.

followed by platinum and taxane-based chemotherapy and appropriate maintenance therapy, are the standard treatment for advanced epithelial ovarian cancer.^{1 2} Neoadjuvant chemotherapy followed by interval debulking surgery is an alternative for patients with specific medical conditions precluding them from surgery, or in case of unresectable disease.^{3–5} Neoadjuvant chemotherapy allows higher rates of complete cytoreduction, less extensive surgical procedures, fewer postoperative complications, and assessment of chemosensitivity.^{6 7} However, the optimal duration of neoadjuvant chemotherapy is not yet established. Usually, three cycles of neoadjuvant chemotherapy is the standard of care according the EORTC 55971 and CHORUS trials.^{3 8} Reports evaluating the role of interval debulking surgery after more than four cycles of neoadjuvant chemotherapy are controversial. While some have shown that survival is similar to that of patients undergoing interval debulking surgery after three cycles of neoadjuvant chemotherapy,^{9–12} others have reported poorer prognosis of delayed

Original research

surgery.^{13–16} To date, there has been no randomized controlled trial to determine the best timing for interval debulking surgery.

Neoadjuvant chemotherapy allows *in vivo* tumor chemosensitivity assessment according to histopathologic response. Complete histopathological response, defined as the absence of surgical residual disease, is achieved in fewer than 10% of patients receiving neoadjuvant chemotherapy, and is associated with significantly longer survival.^{17,18} Thus, a chemotherapy response score has been developed to describe the response to neoadjuvant chemotherapy in high-grade serous carcinomas. This score is obtained on interval debulking specimens, it has been associated with platinum-sensitivity, and has shown a prognostic role.^{19–22} However, most previous studies have limitations such as small sample size, heterogeneity between participants, the number of neoadjuvant chemotherapy cycles, and regimens used.^{23–25} To date, the impact of histological response on survival according to the number of neoadjuvant chemotherapy cycles remains unknown.

This study evaluated survival outcome according to the type of histopathological response (measured by the chemotherapy response score) and the number of neoadjuvant chemotherapy cycles received in advanced ovarian cancer patients.

METHODS

Patients and Study Design

Using a computer-generated search of our institutional patient database, we retrospectively identified all patients who underwent neoadjuvant chemotherapy with three to four or six cycles, followed by complete cytoreduction surgery (CC-0) or cytoreduction to minimal residual disease (CC-1), for International Federation of Gynecology and Obstetrics (FIGO) stage IIIC-IV epithelial ovarian cancer, between January 2008 and December 2015, in four institutions meeting the requirements of the European Society of Gynecological Oncology quality indicators from France and Spain. National and Institutional Review Board approvals were obtained (SLN/MFI/AR193997 and HULP code PI-3432). A flow chart of eligible and included patients is available in Online supplemental figure 1.

Surgical and Chemotherapy Treatment Regimens

At diagnosis, all patients underwent imaging including thoraco-abdomino-pelvic computed tomography (CT). In patients with a suspicion of extra-abdominal disease, positron emission tomography/CT was performed. Patients with deep infiltration of the small bowel mesentery, diffuse carcinomatosis involving large parts of the small bowel and stomach, and infiltration of the duodenum or pancreas, were considered unresectable and were selected for primary chemotherapy. Neoadjuvant chemotherapy was also indicated in patients unfit for extensive resection due to medical co-morbidities or poor performance status, or when too extensive surgery was needed to achieve complete cytoreduction. Neoadjuvant chemotherapy was platinum- and taxane-based chemotherapy, according to our institutional recommendations (carboplatin with area under the curve (AUC) 5–6 and paclitaxel 175 mg/m², once every 3 weeks).

Response to neoadjuvant chemotherapy and resectability to neoadjuvant chemotherapy was assessed on imaging after three to four neoadjuvant chemotherapy cycles and according to cancer antigen (CA) 125 dosage. Patients with stable disease on CT scan or

at exploratory laparoscopic assessment underwent three additional cycles. If peritoneal carcinomatosis was stable compared with initial assessment, interval debulking surgery was delayed to six cycles. Criteria for non-resectable disease were the same as those at diagnosis. All surgical procedures were performed by experienced oncological surgeons. The extent and distribution of the disease were evaluated with the peritoneal cancer index. Surgery aimed to obtain a complete cytoreduction, using the Completeness of Cytoreduction score (CC-0: no residual tumor; CC-1: residual disease <2.5 mm in diameter; CC-2: residual nodules between 2.5 mm and 2.5 cm; and CC-3: residual nodules >2.5 cm or a confluence of unresectable disease).²⁶ We used the Aletti Score to quantify surgical complexity.²⁷

Pathology examination was performed by an expert gynecologic oncology pathologist in each participating institution. However, omental chemotherapy response score was assessed retrospectively for this study by two experts, using the pathology reports. Chemotherapy response score 3 was defined as good response and chemotherapy response score 1–2 as no significant response (Online supplemental table 1).

When feasible, adjuvant chemotherapy was delivered within 1 or 2 months after cytoreductive surgery with carboplatin and paclitaxel until a total of at least six cycles had been completed. In the event of high tumor burden, minimal residual disease (CC-1) or poor response to neoadjuvant chemotherapy, antiangiogenic maintenance treatment with bevacizumab was added after discussion by the tumor board. When surgery was performed after six cycles of neoadjuvant chemotherapy, two to three additional cycles of chemotherapy were added to the antiangiogenic maintenance treatment with bevacizumab. No maintenance treatment with poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitors was administered during the study period.

Patients with unresectable disease, with residual disease ≥2.5 mm (CC-2), and those with non-epithelial subtype histology or borderline tumors were excluded from the study. Patients' demographic data, performance status, CA125 dosage, neoadjuvant chemotherapy treatment details, peritoneal cancer index scores recorded during cytoreductive surgery, surgical procedures, histologic data, and follow-up data were recorded. Follow-up was conducted according to each center's protocol. Globally, it included clinical examination, CA125 dosage, with or without a thoraco-abdomino-pelvic CT scan every 4 to 6 months for 5 years. Afterwards, the follow-up visits were scheduled annually.

Statistical Analysis

Data were summarized by median and range for quantitative variables and by frequency and percentage for qualitative variables. Comparisons between groups were performed using the Mann-Whitney test for quantitative variables and the χ^2 or Fisher's exact test for qualitative variables. Disease-free survival was defined as the time from the diagnosis to relapse or death from any cause. Patients who were alive and disease-free were censored at last follow-up news. Overall survival was defined as the time from the diagnosis to death from any cause. Patients who were alive were censored at last follow-up news. Survival data were summarized using the Kaplan-Meier method. Univariable and multivariable analyses were performed using the Log rank test and the Cox model. Hazard ratios (HR) were estimated with their 95% confidence

Table 1 Baseline characteristics of overall population (n=365) and according to chemotherapy response score (CRS)

	Overall (n=365)	CRS 1–2 (n=277)	CRS 3 (n=88)	P value
Age (years), n (%)				0.770
≤60	161 (44.1)	121 (43.7)	40 (45.5)	
>60	204 (55.9)	156 (56.3)	48 (54.5)	
Median (range)	62 (21–88)	63 (21–88)	62 (38–83)	0.953
BMI (kg/m ²), median (range)	24.1 (15.6–52.0)	24.1 (15.6–52.0)	24.3 (16.4–44.6)	0.795
Missing	13 (-)	8 (-)	5 (-)	
WHO performance status, n (%)				0.163
0	211 (59.4)	159 (59.3)	52 (59.8)	
1	125 (35.2)	98 (36.6)	27 (31.0)	
≥2	19 (5.4)	11 (4.1)	8 (9.2)	
Missing	10 (-)	9 (-)	1 (-)	
Preoperative CA125 (U/mL), median (range)	885.0 (5–86000)	868.5 (11–42110)	896.5 (5–86000)	0.750
Missing	27 (-)	21 (-)	6 (-)	
FIGO stage, n (%)				0.314
IIIC	282 (77.3)	219 (79.1)	63 (71.6)	
IV	83 (22.7)	58 (20.9)	25 (28.4)	
Histological subtype, n (%)				0.578
Serous carcinoma	341 (94.2)	258 (93.8)	83 (95.4)	
High-grade	275 (93.9)	211 (92.5)	64 (98.5)	
Low-grade	18 (6.1)	17 (7.5)	1 (1.5)	
Grade N/A	48 (-)	30 (-)	18 (-)	
Endometrioid carcinoma	10 (2.8)	7 (2.5)	3 (3.4)	
Carcinosarcoma	6 (1.7)	6 (2.2)	0 (0.0)	
Clear cell carcinoma	2 (0.6)	2 (0.7)	0 (0.0)	
Mucinous carcinoma	1 (0.3)	1 (0.4)	0 (0.0)	
Others	2 (0.6)	1 (0.4)	1 (1.1)	
Missing	3 (-)	2 (-)	1 (-)	
Ascites (liter), median (range)	1 (0–10)	1 (0–10)	1 (0–7.5)	0.045
Missing	51 (-)	36 (-)	15 (-)	

BMI, body mass index; CA125, cancer antigen 125; CRS, chemotherapy response score; FIGO, International Federation of Gynecology and Obstetrics; N/A, not available; WHO, World Health Organization.

intervals (95% CI). Significant variables in the univariable analysis and variables judged clinically relevant were selected for the multivariable analysis. All statistical tests were two-sided and p values <0.05 were considered statistically significant. Statistical analyses were conducted using STATA v16 software.

RESULTS

A total of 365 patients were included in the study. Demographic and clinical baseline characteristics are summarized in [Table 1](#). Among the 365 patients, 219 (60.0%) received three to four cycles of neoadjuvant chemotherapy followed by early interval debulking surgery, and 146 (40.0%) had six cycles of neoadjuvant chemotherapy before delayed debulking surgery. Median peritoneal cancer index (assessed in 363/365 patients) at the time of debulking surgery was 9 (range 0–39). Complete cytoreduction was achieved in 318 patients (87.1%) and cytoreduction to minimal

residual disease was performed in 47 (12.9%) patients. Surgical procedures and post-operative data according to chemotherapy response score are presented in [Table 2](#). In total, 105/146 (71.9%) patients who received six cycles of neoadjuvant chemotherapy were also treated with adjuvant chemotherapy, with a median three cycles of adjuvant chemotherapy (range 1–6).

With a median follow-up of 69.0 months (95% CI 62.6 to 74.5), 300 patients relapsed (82.2%). In the total population, 79 patients (22.5%) were considered to be platinum resistant (patients who experienced a relapse within 6 months after the last cycle of carboplatin). Median disease-free survival was 18.1 months (95% CI 16.5 to 19.8) and median overall survival was 49.4 months (95% CI 46.2 to 54.5) in the total population.

In univariable analysis, high peritoneal cancer index and Aletti scores, chemotherapy response score 1–2, and residual disease were significantly associated with worse disease-free survival. Peritoneal cancer index, Aletti scores, and chemotherapy response

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Table 2 Surgical and post-operative data for overall population (n=365) and according to chemotherapy response score (CRS)

	Overall (n=365)	CRS 1-2 (n=277)	CRS 3 (n=88)	P value
PCI, n (%)				
≤10	205 (56.5)	132 (47.8)	73 (83.9)	<0.001
>10	158 (43.5)	144 (52.2)	14 (16.1)	
Median (range)	9 (0–39)	11 (0–39)	4 (0–19)	
Missing	2 (-)	1 (-)	1 (-)	
NACT, n (%)				
3–4 cycles	219 (60.0)	174 (62.8)	45 (51.1)	0.051
6 cycles	146 (40.0)	103 (37.2)	43 (48.9)	
CC-score				
CC-0	318 (87.1)	231 (83.4)	87 (98.9)	<0.001
CC-1	47 (12.9)	46 (16.6)	1 (1.1)	
Aletti score, n (%)				
<8	213 (58.4)	139 (50.2)	74 (84.1)	<0.001
≥8	152 (41.6)	138 (49.8)	14 (15.9)	
Post-operative complications*, grade III/IV, n (%)				
No	294 (80.5)	218 (78.7)	76 (86.4)	0.114
Yes	71 (19.5)	59 (21.3)	12 (13.6)	
Bevacizumab maintenance, n (%)				
No	290 (79.5)	213 (76.9)	77 (87.5)	0.032
Yes	75 (20.5)	64 (23.1)	11 (12.5)	
Platinum resistance†, n (%)				
*No	272 (77.5)	194 (73.5)	78 (89.7)	0.002
Yes	79 (22.5)	70 (26.5)	9 (10.3)	
Missing	14 (-)	13 (-)	1 (-)	

*Platinum resistance defined as early relapse within 6 months after last cycle of carboplatin.

†Clavien-Dindo classification.

CC, complete cytoreduction; CRS, chemotherapy response score; NACT, neoadjuvant chemotherapy; PCI, peritoneal cancer index.

score 1–2 were also significantly associated with worse overall survival (Online supplemental table 1). In the overall cohort, 277 patients (75.9%) had a chemotherapy response score 1–2 after neoadjuvant chemotherapy, and 88 patients (24.1%) had a complete or extensive response to neoadjuvant chemotherapy (score 3). Median disease-free survival in patients with chemotherapy

response score 3 was 28.3 months (95% CI 21.6 to 36.8), whereas it was 16.3 months in patients with score 1–2 (95% CI 14.7 to 18.0, $p<0.001$). Median overall survival in chemotherapy response score 3 patients was 104.9 months (95% CI 63.5 to not reached) and 45.8 months (95% CI 40.0 to 49.2) in chemotherapy response score 1–2 patients ($p<0.001$) (Figure 1).

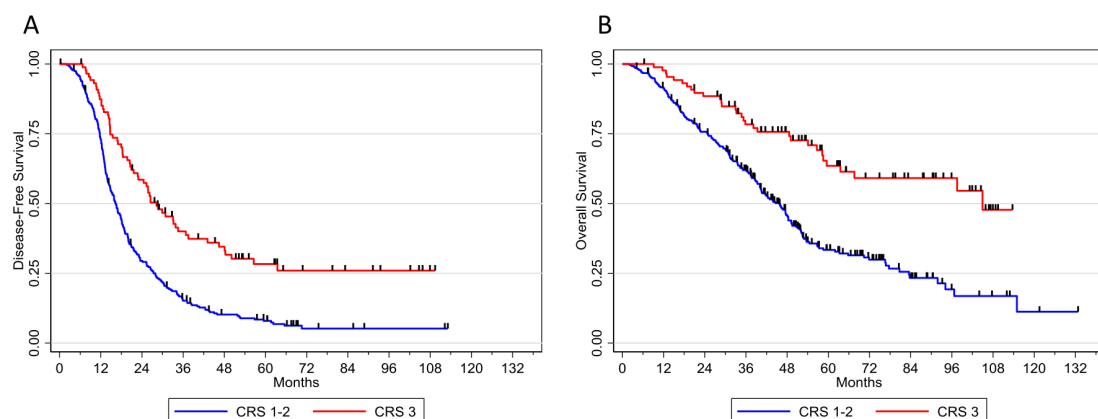


Figure 1 Disease-free survival (A) and overall survival (B) according to histological response to neoadjuvant chemotherapy assessed by chemotherapy response score (CRS).

Table 3 Multivariable disease-free survival and overall survival analysis of total population (n=365)

	Disease-free survival			Overall survival		
	HR	95% CI	P value	HR	95% CI	P value
Age (years)						
≤60	1.00	Ref	0.852	1.00	Ref	0.489
>60	0.98	(0.78 to 1.23)		1.10	(0.84 to 1.45)	
FIGO stage						
IIIC	1.00	Ref	0.100	1.00	Ref	0.413
IV	1.25	(0.96 to 1.64)		1.15	(0.82 to 1.62)	
Cycles of NACT						
3–4	1.00	Ref	0.498	1.00	Ref	0.145
6	1.09	(0.85 to 1.38)		1.24	(0.93 to 1.65)	
PCI						
≤10	1.00	Ref	0.098	1.00	Ref	0.542
>10	1.25	(0.96 to 1.64)		1.10	(0.80 to 1.51)	
Aletti score						
<8	1.00	Ref	0.209	1.00	Ref	0.248
≥8	1.18	(0.91 to 1.54)		1.20	(0.88 to 1.64)	
CC-score						
CC-0	1.00	Ref	0.362	1.00	Ref	0.726
CC-1	1.16	(0.84 to 1.61)		1.07	(0.73 to 1.58)	
CRS						
CRS 1–2	1.00	Ref	<0.001	1.00	Ref	<0.001
CRS 3	0.53	(0.39 to 0.71)		0.42	(0.28 to 0.63)	

CC, complete cytoreduction; CRS, chemotherapy response score; FIGO, International Federation of Gynecology and Obstetrics; NACT, neoadjuvant chemotherapy; PCI, peritoneal cancer index; Ref, reference.

In multivariable analysis, chemotherapy response score 3 was the only factor independently associated with better disease-free survival (HR 0.53, 95% CI 0.39 to 0.71, $p<0.001$) and overall survival (HR 0.42, 95% CI 0.28 to 0.63, $p<0.001$) (Table 3). Among the 219 patients treated with three to four cycles of neoadjuvant chemotherapy, 20.5% (45 patients) achieved chemotherapy response score 3. A total of 146 patients received six cycles of neoadjuvant chemotherapy before delayed debulking surgery, and 43 patients (29.5%) achieved chemotherapy response score 3 ($p=0.051$). Response score 1 or 2 was significantly associated with

a higher peritoneal cancer index, more extensive surgery, minimal residual disease, higher post-operative complications, and use of bevacizumab maintenance therapy. It was also associated with a higher early relapse rate within the 6 months (Table 2).

Regardless of the number of neoadjuvant chemotherapy cycles, score 1 or 2 was significantly associated with worse disease-free survival and overall survival (Figure 2, Online supplemental table 3). Median disease-free survival was 16.5 months (95% CI 13.9 to 18.4) and 15.9 months (95% CI 14.0 to 18.8) for patients with chemotherapy response score 1–2 and who received three to four

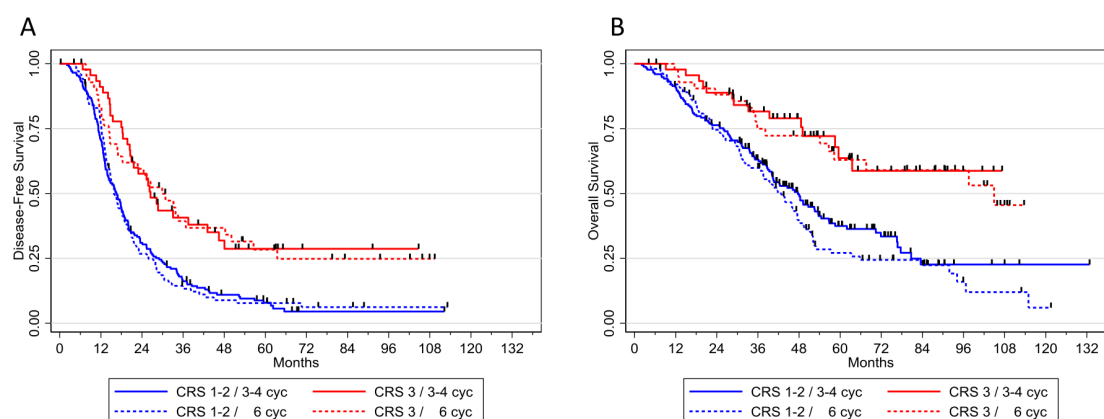


Figure 2 Disease-free survival (A) and overall survival (B) according to number of cycles and histological response assessed by chemotherapy response score (CRS) to neoadjuvant chemotherapy.

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neoadjuvant chemotherapy cycles and six neoadjuvant chemotherapy cycles, respectively. Median disease-free survival was 26.5 months (95% CI 20.6 to 43.1) and 29.9 months (95% CI 17.0 to 48.3) for patients with score 3 and who received three to four neoadjuvant chemotherapy cycles and six neoadjuvant chemotherapy cycles, respectively. Disease-free survival rates were 29.5% and 58.6% (HR 0.47, 95% CI 0.36 to 0.63, $p < 0.001$) in chemotherapy response score 1–2 and score 3 groups, respectively. Similarly, 24 months overall survival rates were 75.7% and 88.5% (HR 0.39, 95% CI 0.26 to 0.57, $p < 0.001$) in chemotherapy response score 1–2 and chemotherapy response score 3 groups, respectively. Moreover, there were no significant differences in early relapses, disease-free survival or overall survival according to the number of neoadjuvant chemotherapy cycles in the subset of patients with chemotherapy response score 1–2 and chemotherapy response score 3 (Figure 2, online supplemental table 3, 4).

DISCUSSION

Summary of Main Results

The main finding of our study was that histopathological response, measured by the chemotherapy response score, has a survival impact irrespective of the number of neoadjuvant chemotherapy cycles. There was no significant difference in the rate of early relapses, disease-free and overall survival rates according to the number of neoadjuvant chemotherapy cycles. Regardless of the surgical timing, persistent extensive histological disease was significantly associated with a higher peritoneal cancer index, more extensive surgery, minimal residual disease, early relapses, and disease-free and overall survival rates. Indeed, patients with near complete or complete pathological response had approximately a 50% increase in disease-free survival compared with patients with omental tumor residue. These results validate the prognostic role of histopathologic response assessed by the chemotherapy response score after neoadjuvant chemotherapy, and support other findings.^{21 22}

Furthermore, the 9% increase in pathologic response after six cycles did not translate into an increase in overall survival.

Results in the Context of Published Literature

Our results regarding the number of neoadjuvant chemotherapy cycles are in keeping with a retrospective study which showed that six cycles of neoadjuvant chemotherapy were safe, had equivalent survival rates to three cycles, and did not increase perioperative complications.⁹ Similarly, Akladios et al reported that the number cycles of neoadjuvant chemotherapy did not seem to affect overall survival in patients with advanced ovarian cancer.¹⁰ Phillips et al reported survival in patients undergoing ≤ 4 cycles and ≥ 5 cycles of neoadjuvant chemotherapy, showing that patients treated with > 5 cycles achieved a lower rate of complete cytoreduction, with a higher rate of suboptimal cytoreduction, which was associated with a worse survival.¹¹ Yoneoka et al also compared patients undergoing interval debulking surgery after three cycles of neoadjuvant chemotherapy with those who had six cycles before delayed surgery without postoperative chemotherapy, showing equivalent survival in both groups.¹²

In contrast, other studies found that the number of preoperative chemotherapy cycles was negatively correlated with survival,

suggesting that surgery should be performed as early as possible.²⁸ They hypothesized the progressive emergence of chemoresistant disease with the increasing number of neoadjuvant chemotherapy cycles. Colombo et al and Xu et al reported poorer prognosis in patients undergoing late surgery after more than four neoadjuvant chemotherapy cycles, even in the event of complete cytoreduction.^{13 14} Moreover, in a recent study, Nitecki et al showed that residual disease, defined by an incomplete resection (but not by histopathological score), after neoadjuvant chemotherapy was associated with worse survival outcomes, regardless of the number of neoadjuvant chemotherapy cycles.²⁹ Thus, there appears to be a complex relationship between the number of neoadjuvant chemotherapy cycles, the completeness of resection, and survival outcomes. Our study only included patients with complete or near complete (CC-0 or CC-1) resection, with no significant difference in resection rates according to the number of cycles of neoadjuvant chemotherapy. However, the decision regarding the number of cycles of neoadjuvant chemotherapy was impacted by the clinical, biological, and imaging response to neoadjuvant chemotherapy and may have introduced a selection bias between both groups (3–4 vs > 6 cycles). Achieving an optimal resection of all macroscopic disease should always be the ultimate goal in advanced ovarian cancer treatment, regardless of the number of neoadjuvant chemotherapy cycles. We decided to exclude patients with ≥ 2.5 mm (CC-2) residue to avoid the negative survival impact of tumor residue, which could influence the prognostic effect of other variables. We wanted a homogeneous cohort, but not including ≥ 2.5 mm (CC-2) residue may have led to a selection bias. We do not know if patients with delayed interval debulking surgery would have had more CC-2 residue. Indeed, our selection criteria probably affected the results of the study, as patients with a poor response to neoadjuvant chemotherapy and CC-2 resection were excluded.

The ongoing CHRONO (NCT03579394) prospective multi-institutional randomized study aims to define the best timing for cytoreductive surgery by comparing disease-free survival when surgery is performed after three or six courses of neoadjuvant chemotherapy, in patients initially unsuitable for primary surgery.

Concerning the chemotherapy response score, our results are in keeping with a recent study by Lontos et al assessing lymphocytic infiltration and the chemotherapy response score as prognostic markers in ovarian cancer patients treated with neoadjuvant chemotherapy followed by delayed surgery.³⁰ They showed the predictive value of the chemotherapy response score in epithelial ovarian cancer patients treated with neoadjuvant chemotherapy and interval debulking surgery, but also demonstrated the prognostic significance of lymphocytic infiltration. The chemotherapy response score assessed at the omentum predicted progression-free survival when adjusted for age, stage, debulking status, and bevacizumab maintenance.

Our study confirms that the chemosensitivity of advanced epithelial ovarian carcinoma may be assessed by the chemotherapy response score. These results are in line with a meta-analysis conducted by Cohen et al including almost 900 patients. They reported that the chemotherapy response score was significantly associated with progression-free and overall survival and that patients with *BRCA1/2* mutations were more likely to achieve chemotherapy response score 3. They suggested that this score is a very useful biomarker and could be incorporated as a new

endpoint in clinical trials.³¹ Similarly and recently, You et al also described that CA125 longitudinal kinetics strongly reflects chemosensitivity to first-line treatment and may be used as highly predictive and prognostic information for progression-free and overall survival.^{32 33} No association between CA125 kinetics and chemotherapy response score was evaluated in our study.

Strengths and Weaknesses

This study included a large homogeneous cohort with 365 patients with long-term follow-up. To our knowledge, it is the first to demonstrate the prognostic value of histopathologic response irrespective of the number of neoadjuvant chemotherapy cycles. Histopathological responses were assessed using the validated and objective chemotherapy response score.^{19 20} The main limitation is its retrospective design with the intrinsic risk of selection bias. Pathology reports were also reviewed retrospectively. Moreover, the chemotherapy response score was developed to reproducibly describe the response to neoadjuvant chemotherapy only in high-grade serous carcinomas, and our cohort had 24.7% of patients with a different subtype. Its value remains to be confirmed in other histological types. Indeed, given the relative chemoresistance of low-grade, clear-cell and mucinous ovarian cancer, our results may have been influenced by our selected population. Moreover, BRCA status was not collected and may also influence pathologic response and survival outcomes.

Implications for Practice and Future Research

This work may implement the current literature by showing that the histopathological response is associated with survival outcome, irrespective of the number of neoadjuvant chemotherapy cycles. This 'retrospective' information obtained after surgery adds additional prognostic information to adapt/intensify the treatment strategy and follow-up. Moreover, our findings confirm the strong prognostic relationship between the chemotherapy response score and survival, and that the chemotherapy response score may be used as a surrogate for chemosensitivity and as a useful endpoint for clinical trials.

CONCLUSION

Our study demonstrates the prognostic value of the validated chemotherapy response score in epithelial ovarian cancer patients treated with neoadjuvant chemotherapy. It also shows that histopathological response is significantly associated with disease-free and overall survival, irrespective of the number of neoadjuvant chemotherapy cycles.

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Article 5

Impact of pattern of recurrence on post-relapse survival according to surgical timing in patients with advanced ovarian cancer

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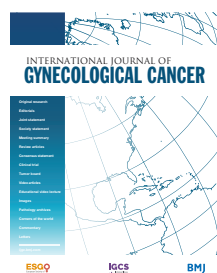
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Impact of pattern of recurrence on post-relapse survival according to surgical timing in patients with advanced ovarian cancer

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ABSTRACT

Objective Our study aimed to evaluate the association between timing of cytoreductive surgery and pattern of presentation of the first recurrence in patients with advanced ovarian cancer. We also aimed to assess the impact of the pattern of recurrence on post-relapse overall survival according to surgical timing.

Methods This retrospective multicenter study evaluated patients with International Federation of Gynecology and Obstetrics (FIGO) stage IIIC-IV ovarian cancer. Patients had undergone either primary debulking surgery, early interval debulking surgery after 3–4 cycles of neoadjuvant chemotherapy, or delayed debulking surgery after 6 cycles, with minimal or no residual disease, between January 2008 and December 2015. Survival analyses were conducted using the Log-rank test and the Cox model. Cumulative incidences of the different patterns of recurrence were estimated using a competing risks methodology.

Results A total of 549 patients were included: 175 (31.9%) patients had primary, 224 (40.8%) early interval, and 150 (27.3%) delayed debulking surgery. The cumulative incidence of peritoneal recurrences at 2 years was higher with increasing neoadjuvant cycles (24.4%, 30.9% and 39.2%; $p=0.019$). For pleural or pulmonary recurrences, it was higher after early interval surgery (9.9%, 13.0% and 4.1%; $p=0.022$). Median post-relapse overall survival was 33.5 months (95% confidence interval (CI) (24.3 to 44.2)), 26.8 months (95% CI (22.8 to 32.6)), and 24.5 months (95% CI (18.6 to 29.4)) for primary, early interval, and delayed debulking surgery groups, respectively ($p=0.025$). The pattern of recurrence in a lymph node (hazard ratio (HR) 0.42, 95% CI (0.27 to 0.64)), delayed surgery (HR 1.53, 95% CI (1.11 to 2.13)) and time to first recurrence (HR 0.95, 95% CI (0.93 to 0.96)) were associated with post-relapse overall survival. For primary and early interval surgery, lymph node recurrences were associated with significantly longer post-relapse overall survival.

Conclusions The pattern of first recurrence was associated with timing of surgery, with peritoneal recurrences being more frequent with the increasing number of cycles of neoadjuvant chemotherapy. Lymph node recurrences were associated with better prognosis, having higher post-relapse overall survival. This improved prognosis of lymphatic recurrences was not observed in patients who underwent delayed surgery.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Despite being adequately treated, most patients with advanced ovarian cancer will experience recurrence. However, the influence of the timing of cytoreductive surgery on the natural history of recurrent ovarian cancer remains unknown.

WHAT THIS STUDY ADDS

⇒ We found that the pattern of presentation of the first recurrence was associated with timing of surgery, with peritoneal recurrences being more frequent after neoadjuvant chemotherapy. Lymph node recurrences were those with the best prognosis with a longer survival after the first relapse. This better prognosis was not observed in patients who had delayed surgery.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The findings of this study help us to better understand the natural history of recurrent ovarian cancer. The prognosis of recurrence depends not only on the pattern of recurrence but also on the timing of cytoreductive surgery. The pattern of recurrence may also be a marker of disease biology.

INTRODUCTION

Primary debulking surgery followed by adjuvant chemotherapy is the standard of care for advanced ovarian cancer in patients with completely resectable disease and good performance status.^{1,2} An alternative strategy for medically non-operable patients or with unresectable disease is neoadjuvant chemotherapy followed by interval debulking surgery, which has shown similar survival outcomes.^{3–5} Nonetheless, despite maximal surgical effort and improved survival with the addition of maintenance treatment strategies, most patients with advanced ovarian cancer experience recurrence, irrespective of the timing of surgical cytoreduction.⁶

It has been hypothesized that chemo-resistant clonal cells can be selected with neoadjuvant chemotherapy,² meaning that surgery after neoadjuvant treatment would be less effective than upfront surgery,



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leading to a higher rate of recurrences. Post-relapse survival can be affected by the length of the interval between the end of treatment and recurrence, and also by the pattern of recurrence.⁷ However, there is little robust data in the literature assessing the influence of the timing of surgical cytoreduction on the natural history of recurrent ovarian cancer. We aimed to evaluate if the timing of cytoreductive surgery was associated with the pattern of presentation of first recurrence and to assess the impact of the pattern of recurrence on post-relapse overall survival, according to the timing of surgery.

METHODS

Patients and Study Design

We performed a computer-generated search of the patient databases of four institutions recognized as referral centers in the treatment of ovarian cancer in France and Spain. Our search captured all patients who had upfront or interval debulking surgery with minimal (CC-1) or no residual (CC-0) disease. This was according to Completeness of Cytoreduction score⁸ for the International Federation of Gynecology & Obstetrics (FIGO) stage IIIc-IV epithelial ovarian cancer and dated between January 2008 and December 2015. National and institutional review board approvals were obtained (SLN/MFI/AR193997 and HULP code PI-3432).

Preoperative Assessment, Surgical and Chemotherapy Treatment

At diagnosis, all patients underwent an imaging workup including a thoraco-abdomino-pelvic CT. In the case of suspected extra-abdominal disease, positron emission tomography/computed tomography (PET/CT) was performed. An exploratory laparoscopy was performed to assess resectability and histology.⁹ Surgical procedures were performed according to Sargant's principles of peritonectomy.¹⁰ The abdominal tumorous load was assessed with the peritoneal cancer index and the main goal of the surgery was to obtain complete cytoreduction.⁸ Surgical complexity was quantified using the Aletti score, with a cut-off value ≥ 8 corresponding to high complexity (23).

Patients with deep infiltration of the mesentery, diffuse carcinomatosis involving large parts of the small bowel or the stomach, infiltration of the duodenum or the pancreas (not limited to the pancreatic tail) were considered non-resectable and were selected for neoadjuvant chemotherapy. Neoadjuvant strategy was also indicated in patients who were not fit to withstand multivisceral resection, owing to medical comorbidities or poor performance status, or when the surgery needed to achieve complete cytoreduction was too extensive (more than three bowel or visceral resections).¹¹ After three to four cycles of neoadjuvant chemotherapy, a clinical, biological, and imaging assessment was performed before interval debulking surgery. In the event of poor response or poor performance status, three additional cycles of neoadjuvant chemotherapy were administered before delayed debulking surgery after discussion at tumor board. In selected patients with stable disease on CT after neoadjuvant chemotherapy, an exploratory laparoscopy was performed before interval surgery to assess resectability.

Adjuvant chemotherapy with carboplatin and paclitaxel was delivered, when feasible, within 1–2 months of debulking surgery, for 6 cycles. In the event of high tumor burden, CC-1, or poor response

to neoadjuvant chemotherapy, antiangiogenic maintenance treatment with bevacizumab was added after discussion at tumor board. When surgery was performed after 6 cycles of neoadjuvant chemotherapy, two to three additional cycles of chemotherapy were added to the antiangiogenic maintenance treatment with bevacizumab. No maintenance treatment with PARP inhibitors was administered during the study period.¹¹

Patients were divided into three groups according to the surgical timing: primary surgery and 6 cycles of adjuvant chemotherapy (group 1); early interval surgery after 3–4 cycles of neoadjuvant chemotherapy, then 2–3 cycles of adjuvant chemotherapy to achieve a total of 6 cycles (group 2); and delayed debulking surgery after 6 cycles of neoadjuvant chemotherapy (group 3).

Follow-up was conducted according to each center's protocol. Globally, this included clinical examination, cancer antigen-125 (CA-125) dosage with or without a chest, abdominal, and pelvic CT scan every 4 to 6 months for 5 years. Thereafter, follow-up visits were scheduled annually. All recurrences were confirmed by imaging and localization was classified into four subgroups: lymph node involvement; peritoneal; pleural or pulmonary; and other (metastatic localization). We defined recurrence as unique or as multiple if disease was identified in only one or in more than one of the four defined localizations, respectively. The date of recurrence was defined as the date when recurrence was confirmed by CT scan or PET/CT. We defined an early relapse as a recurrence within 6 months after last cycle of carboplatin (platinum resistance).

Study Data

Medical databases were carefully examined to collect all relevant information. Patients' demographic data, World Health Organization performance status, CA-125 dosage, ascites at diagnosis, surgical timing, peritoneal cancer index recorded during debulking surgery, Aletti score, histological data, adjuvant treatment, and follow-up data (date and pattern of recurrence) were retrieved from medical records. In accordance with the journal's guidelines, we will provide our data for independent analysis or for reproducibility of this study in other centers if such is requested.

Statistical Analysis

Data were summarized by frequency and percentage for categorical variables and by median and range for continuous variables. Comparisons between groups were performed using the Chi-squared or Fisher's exact test for categorical variables and the Kruskal-Wallis test for continuous variables. Disease-free survival was defined as the time between the date of diagnosis and the date of recurrence or death from any cause; patients alive and disease-free were censored at last follow-up. Overall survival was defined as the time between the date of diagnosis and the date of death from any cause; patients alive were censored at last follow-up. Post-relapse overall survival was defined as the time between the date of diagnosis of the first recurrence and the date of death from any cause; patients alive were censored at last follow-up. Survival data were estimated using the Kaplan-Meier method. Univariable and multivariable analyses were performed using the Log-rank test and the Cox proportional hazards model. Multivariable analysis was performed including those variables with a significant association with the outcome as well as those considered clinically relevant. Hazard ratios (HR) were estimated with their 95% confidence

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intervals (95% CI). Cumulative incidences of the different patterns of recurrence were estimated using competing risks methodology with other patterns of recurrence and death from any cause considered as competing events. In the case of multiple first recurrences, the pattern of the recurrence was defined as the worst one according to the following order: other (metastatic), pleural or pulmonary, peritoneal and lymph node. Comparisons between groups were performed using the Gray test. All statistical tests were two-sided and p-values <0.05 were considered statistically significant. Statistical analyses were conducted using STATA v16 (StataCorp, College Station, TX, USA) software.

RESULTS

A total of 549 women were included, 175 (31.9%) in group 1, 224 (40.8%) in group 2, and 150 (27.3%) in group 3. Baseline characteristics, surgical, and treatment data are shown in [Table 1](#).

The median follow-up was 68.1 months (95% CI (62.9; 73.3)). During the study period, 438/549 patients (79.8%) relapsed, 128/175 (73.1%) in group 1, 188/224 (83.9%) in group 2, and 122/150 (81.3%) in group 3. Median disease-free survival was 19.4 months (95% CI (18.0; 20.6)). It was 23.0 months (95% CI (20.0; 29.3)), 18.0 months (95% CI (15.7 20.0)), and 17.0 months (95% CI (15.0; 20.9)) for primary, early interval, and delayed debulking surgery, respectively ($p<0.001$).

The pattern of first recurrence at any time during follow-up is shown in [Table 2](#). The cumulative incidence of peritoneal recurrences at 2 years was 31.1%, 9.6% for pleural or pulmonary recurrences, 6.5% for lymph node recurrences, and 10.9% for other metastatic recurrences ([Figure 1A](#)). Cumulative incidence of peritoneal recurrences at 2 years was 24.4% (95% CI (18.2; 31.0)) in primary surgery, 30.9% (95% CI (24.9; 37.0)) in early interval, and 39.2% (95% CI (31.2; 47.1)) in delayed surgery, $p=0.019$. Cumulative incidence of pleural or pulmonary recurrences at 2 years was 9.9% (95% CI (6.0; 14.9)) in upfront surgery group, 13.0% (95% CI (8.9; 17.7)) in early interval and 4.1% (95% CI (1.7; 8.3)) in delayed surgery, $p=0.022$ ([Figure 1B](#)). Remarkably, the rate of diaphragmatic stripping was significantly different between the three groups (61.7%, 67.9%, vs 46.7%; $p<0.001$). There was no significant difference in the rate of early relapse between group 1 (19.5%), group 2 (22.9%), and group 3 (23.1%) ($p=0.671$).

There were 293 (53.4%) deaths, 73/175 (41.7%) in the upfront surgery group, 124/224 (55.4%) in the early interval group, and 96/150 (64.0%) in the delayed surgery group. Median overall survival was 56.7 months (95% CI (50.2; 65.8)). It was 84.0 months (95% CI (67.4; 111.0)), 50.7 months (95% CI (44.6; 59.5)), and 47.5 months (95% CI (39.3; 52.9)) in groups 1, 2 and 3, respectively ($p<0.001$). Median post-relapse overall survival was 26.5 months (95% CI (24.0; 31.3)), with 33.5 months (95% CI (24.3; 44.2)), 26.8 months (95% CI (22.8; 32.6)), and 24.5 months (95% CI (18.6; 29.4)) for primary, early interval, and delayed debulking surgery groups, respectively ($p=0.025$).

Median post-relapse overall survival for patients with peritoneal, lymph node, pleural or pulmonary, and other recurrences was 26.5 months (95% CI (23.2; 31.2)), 68.1 months (95% CI (39.3; 88.8)), 20.5 months (95% CI (14.3; 23.5)), and 23.2 months (95% CI (18.1; 31.3)), respectively ($p<0.001$) ([Figure 2](#)). In multivariable analysis,

the pattern of recurrence (lymph node: HR 0.42, 95% CI (0.27; 0.64), $p<0.001$), surgical timing (delayed surgery: HR 1.53, 95% CI (1.11; 2.13), $p=0.010$), and time to recurrence (HR 0.95, 95% CI (0.93; 0.96), $p<0.001$) remained significantly associated with post-relapse overall survival ([Table 3](#)).

In subgroup analyses, lymph node recurrences (HR adjusted for time to first relapse (adj)=0.34, 95% CI (0.14; 0.83), $p=0.018$) and multiple recurrences (HR_{adj} 1.66, 95% CI (1.03; 2.69), $p=0.037$) were significantly associated with post-relapse overall survival in the upfront surgery group. In early interval surgery, lymph node recurrences were associated with improved post-relapse overall survival (HR_{adj} 0.34, 95% CI (0.16; 0.73), $p=0.005$), but not in the delayed surgery group (HR_{adj} 0.54, 95% CI (0.29; 1.04), $p=0.064$).

DISCUSSION

Summary of Main Results

We found an increasing rate of peritoneal recurrences with the increasing number of cycles of neoadjuvant chemotherapy (primary: 24%, early interval: 31%, and delayed surgery: 39%), and a higher rate of pleural or pulmonary recurrences after early interval debulking surgery (13%) compared with primary (10%) and delayed surgery (4%). The second main finding was that lymph node recurrences were associated with a longer post-relapse overall survival. Survival benefit of lymphatic recurrences was not observed in women who underwent delayed surgery.

Results in the Context of Published Literature

Surgical Timing and Pattern of First Recurrence

It is known that most patients with advanced ovarian cancer will experience disease recurrence, independently of the timing of surgery.⁶ Reports in the literature on the impact of the number of cycles of neoadjuvant chemotherapy on the type of recurrences are scarce.^{6 12 13} Gadducci et al found a non-significantly higher rate of abdominal and pelvic recurrences after interval surgery compared with primary surgery (26% vs 20% and 19% vs 16%).⁶ Likewise, Petrillo et al reported more aggressive behavior of recurrent disease in patients receiving neoadjuvant chemotherapy, with an increased proportion of patients presenting with peritoneal carcinomatosis compared with patients who underwent upfront surgery (57% vs 20%).¹³

Himoto et al also showed that the distribution of disease at the time of the first recurrence varied with the choice of primary treatment. Neoadjuvant chemotherapy followed by interval debulking surgery was associated with a higher rate of overlapping locations between baseline and first recurrence and with a lower rate of new disease locations compared with primary debulking surgery.¹² One possible explanation for the increased rate of peritoneal recurrences after neoadjuvant treatment in our study is that microscopic tumor regions might be more difficult to identify during interval surgery due to their more benign visual appearance and due to tumor scarring following chemotherapy. Therefore, a neoadjuvant strategy may interfere with the perioperative visual evaluation of tumor spread and lead to incomplete resection of tumor in potentially resectable areas.¹⁴ Another hypothesis is that microscopic non-visible disease, likely remaining after any cytoreductive surgery, could contain selected chemo-resistant clonal cells after neoadjuvant chemotherapy,² leading to a higher rate of abdominal

Table 1 Baseline characteristics, surgical and treatment data according to surgical timing

	Overall n=549	PDS n=175	Early IDS n=224	DDS n=150	p-value
Age (years), median (range)	61 (21–88)	58 (22–88)	62 (21–82)	63 (36–88)	0.01
Age (years), n (%)					0.016
≤ 60	264 (48.1)	101 (57.7)	102 (45.5)	61 (40.7)	
> 60	285 (51.9)	74 (42.3)	122 (54.5)	89 (59.3)	
BMI (kg/m ²), median (range)	24.2 (15.6–52.0)	24.2 (16.5–44.1)	24 (15.6–52.0)	24.6 (15.6–43.9)	0.484
Missing	20 (-)	7 (-)	2 (-)	11 (-)	
WHO performance status, n (%)					
0	355 (66.1)	137 (79.2)	122 (56.2)	96 (65.3)	<0.001
1	159 (29.6)	32 (18.5)	83 (38.2)	44 (29.9)	
≥ 2	23 (4.3)	4 (2.3)	12 (5.5)	7 (4.8)	
Missing	12 (-)	2 (-)	7 (-)	3 (-)	
CA-125 (U/ml) at diagnosis, median (range)	740 (5–86,000)	463 (7–23,762)	800 (11–42,956)	1000 (5–86,000)	<0.001
Missing	52 (-)	24 (-)	15 (-)	13 (-)	
FIGO stage, n (%)					
IIIC	449 (81.8)	158 (90.3)	176 (78.6)	115 (76.7)	0.002
IV	100 (18.2)	17 (9.7)	48 (21.4)	35 (23.3)	
Histological subtype, n (%)					
Serous	489 (89.6)	140 (80.0)	207 (93.2)	142 (95.3)	<0.001
Non-serous	57 (10.4)	35 (20.0)	15 (6.8)	7 (4.7)	
Missing	3 (-)	0 (-)	2 (-)	1 (-)	
Ascites volume (L) at diagnosis, median (range)					<0.001
Missing	1 (0–10) 68 (-)	0.1 (0–7) 15 (-)	1 (0–10) 29 (-)	1 (0–8) 24 (-)	
PCI, median (range)	10 (0–39)	11.5 (2–33)	10 (0–39)	7 (0–31)	<0.001
Missing	6 (-)	3 (-)	1 (-)	2 (-)	
CC-score					0.567
CC-0	481 (87.6)	157 (89.7)	195 (87.1)	129 (86.0)	
CC-1	68 (12.4)	18 (10.3)	29 (12.9)	21 (14.0)	
Aletti Score, n (%)					0.006
< 8	300 (54.6)	80 (45.7)	125 (55.8)	95 (63.3)	
≥ 8	249 (45.4)	95 (54.3)	99 (44.2)	55 (36.7)	
HIPEC, n (%)	10 (1.8)	1 (0.6)	1 (0.4)	8 (5.3)	0.001
IP chemotherapy, n (%)	19 (3.5)	19 (10.9)	0 (0)	0 (0)	<0.001
Bevacizumab, n (%)	107 (19.5)	32 (18.3)	60 (26.8)	15 (10.0)	<0.001

BMI, body mass index; CA-125, cancer antigen 125; CC-score, completeness of cytoreduction score; DDS, delayed debulking surgery; FIGO, International Federation of Gynecology and Obstetrics; HIPEC, hyperthermic intraperitoneal chemotherapy; Early IDS, early interval debulking surgery; IP, intraperitoneal; PCI, peritoneal cancer index; PDS, primary debulking surgery; WHO, World Health Organization.

recurrences after interval surgery. However, this higher rate of peritoneal recurrences in our study may also be partially explained by the fact that patients who underwent neoadjuvant chemotherapy had a higher intra-abdominal tumor burden or unresectable diffuse carcinomatosis at diagnosis, or by the fact that the group of patients

who underwent upfront surgery received more frequently intraperitoneal chemotherapy.

In our study, early interval surgery was associated with a higher rate of pleural or pulmonary recurrences. This subgroup of patients had a significantly higher rate of diaphragmatic stripping, meaning

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Table 2 Pattern of recurrence during follow-up in the 549 patients included in the study

Pattern of recurrence	Overall n=549	PDS n=175	Early IDS n=224	DDS n=150
Lymph node, n (%)	181 (33.0)	58 (33.1)	73 (32.6)	50 (33.3)
Peritoneal, n (%)	313 (57.0)	88 (50.3)	135 (60.3)	90 (60.0)
Pleural or pulmonary, n (%)	71 (12.9)	24 (13.7)	38 (17.0)	9 (6.0)
Other*, n (%)	80 (14.6)	22 (12.6)	36 (16.1)	22 (14.7)
Unique recurrence, n (%)	270 (49.2)	80 (45.7)	110 (49.1)	80 (53.3)
Multiple recurrence, n (%)	168 (30.6)	48 (27.4)	78 (34.8)	42 (28.0)

*Other included metastatic localizations such as intra-parenchymatous hepatic (n=53), cerebral (n=8), intra-parenchymatous splenic (n=4), adrenal gland (n=3), bone (n=3), mammary gland (n=3), renal (n=1), and multiple metastatic localization (n=5).
DDS, delayed debulking surgery; IDS, early interval debulking surgery; PDS, primary debulking surgery.

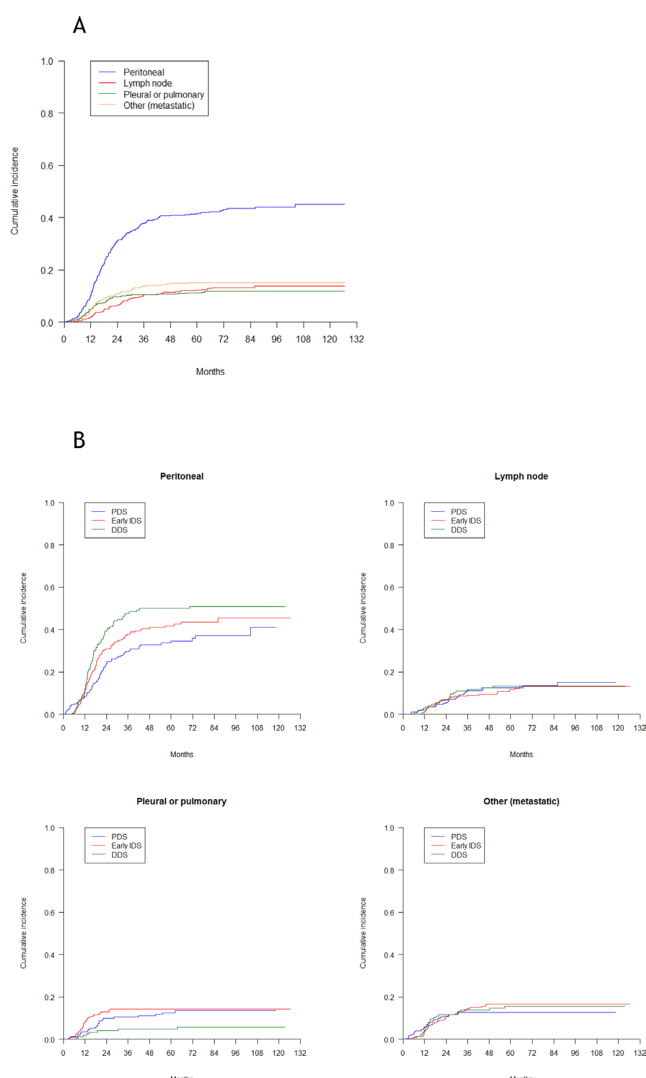


Figure 1 (A.) cumulative incidence of the pattern of recurrence by tumor location in the overall cohort. (B.) cumulative incidence of recurrences according to surgical timing for the four patterns of recurrence: peritoneal (p=0.019); lymph node (p=0.922); pleural or pulmonary (p=0.022); other (metastatic) (p=0.683).

that these patients had a higher rate of pleural disease at diagnosis, which could explain the higher rate of recurrences at this site.

Impact of the Pattern of Recurrence on Post-relapse Survival

It is known that exclusive lymph node involvement at diagnosis has a more indolent course of disease with better survival than peritoneal carcinomatosis.¹⁵ However, studies comparing survival outcomes of different types of recurrence have reported controversial results.^{16–18} Delangle et al did not show a better prognosis of patients with isolated nodal recurrences compared with peritoneal carcinomatosis,¹⁶ and Gadducci et al did not find that the pattern of recurrence (pelvis vs retroperitoneal lymph nodes) was an independent prognostic factor.¹⁷ Conversely, Levy et al showed better survival for patients with retroperitoneal lymph node recurrences compared with patients with peritoneal carcinomatosis or combined recurrences,¹⁸ which is concordant with our findings. Moreover, we specifically assessed post-relapse survival and found that once the recurrence is diagnosed, posterior survival will vary according to the type of recurrence. It would be interesting to evaluate if certain patterns of recurrence are markers of tumor biology and if they are associated with genetic or molecular factors.

Our data also showed that the impact of the recurrence pattern on post-relapse survival was present in patients who underwent primary or early interval surgery, but was not significant in those

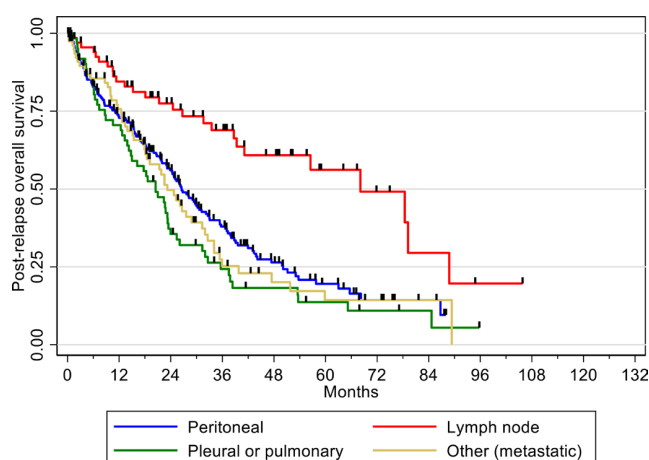


Figure 2 Post-relapse overall survival according to the pattern of recurrence (p<0.001).

Table 3 Multivariable analysis for overall survival after first relapse in the overall cohort.

	Post-relapse overall survival		
	HR	95% CI	p-value
Age at first relapse (years)			0.4
≤ 60	1	Ref.	
> 60	0.9	(0.70 to 1.15)	
FIGO stage			0.525
IIIC	1	Ref.	
IV	0.9	(0.66 to 1.23)	
Cycles of NACT			
0	1	Ref.	
3–4	1.31	(0.96 to 1.79)	0.084
6	1.53	(1.11 to 2.13)	0.01
Time to first recurrence	0.95	(0.93 to 0.96)	<0.001
Pattern of recurrence			
Peritoneal	1	Ref.	
Lymph node	0.42	(0.27 to 0.64)	<0.001
Pleural or pulmonary	1.13	(0.81 to 1.58)	0.462
Other (metastatic)	1.02	(0.74 to 1.40)	0.91

CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; NACT, neoadjuvant chemotherapy; Ref., reference? please confirm.

who had delayed surgery. This could be explained by the fact that delayed surgery was per se associated with a higher risk of death after the first relapse. The negative impact of performing delayed surgery is maintained over time and goes beyond the first recurrence, erasing the benefit of having a more indolent recurrence that is found with exclusive lymph node involvement. To the best of our knowledge, the impact on survival of the recurrence pattern according to surgical timing has not previously been reported.

Finally, our results showed that shorter time to first relapse was associated with an increased risk of death. This has been reported by Ferrandina et al who showed that post-relapse survival was affected not only by the type of recurrence, but also by the length of the interval between the end of primary treatment and the occurrence of first recurrence.⁷ This interval is widely considered the most relevant factor in determining the natural history of recurrent ovarian cancer.¹⁹

Strengths and Weaknesses

To our knowledge, this is the largest series of advanced ovarian cancer patients evaluating the association between the pattern of recurrence and oncological outcome according to the timing of surgical cytoreduction. We included a cohort of more than 500 women who underwent cytoreductive surgery with minimal or no residual disease and who had a long median follow-up of almost 6 years. Among the limitations of our study, we highlight its retrospective design and the associated inherent risk of selection bias. Medically non-operable patients and those with non-resectable

disease at diagnosis were included in early interval and delayed surgery groups. Therefore, the poorer prognosis of these patients compared with those who underwent primary surgery might have influenced the results of our study. Moreover, patients in the delayed surgery group may also have an inherent worse prognosis compared with the early interval group, as they were not candidates for surgery after 3–4 cycles of chemotherapy. All patients without a good response after 3 or 4 cycles of neoadjuvant chemotherapy and non-resectable at delayed debulking surgery, and all those with ≥CC-2 at cytoreductive surgery were excluded from our study, which undoubtedly improved the overall survival of our cohort.

Implications for Practice and Future Research

Our findings suggest that the type of recurrence may vary depending on the timing of surgical cytoreduction, and that the better survival outcome of patients with lymphatic recurrences may be erased by delayed surgery. Further prospective multicenter studies need to confirm our results.

CONCLUSIONS

We found that the pattern of presentation of the first recurrence was associated with the timing of surgery, with peritoneal recurrences being more frequent after neoadjuvant chemotherapy. Lymph node recurrences showed a better prognosis, with increased overall survival after relapse. This improved outcome of lymphatic recurrences was more evident after primary and early interval surgery. Shorter time to first relapse and delayed debulking surgery were significantly associated with decreased overall survival after relapse. Further prospective studies are needed to confirm our findings regarding the impact on oncological outcome of the pattern of the first recurrence in ovarian cancer patients.

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SUMMARY OF THE RESULTS

SUMMARY OF THE RESULTS

The articles published and presented for this Doctoral Thesis aimed to define the best timing to schedule cytoreductive surgery to obtain the maximal survival benefit in patients with advanced ovarian cancer. We studied some important aspects which can help guiding the decision on the optimal timing for debulking surgery.

The first article entitled "**A multivariate analysis of the prognostic impact of tumor burden, surgical timing and complexity after complete cytoreduction for advanced ovarian cancer**" studied the survival benefit of primary debulking surgery compared to interval debulking surgery (either early or delayed) after complete cytoreduction (CC-0) or cytoreduction to minimal residual disease (CC-1) in advanced ovarian cancer.

A total of 549 patients were included: 175 (31.9%) underwent primary debulking surgery, 224 (40.8%) had early interval debulking surgery after 3-4 cycles of neoadjuvant chemotherapy, and 150 (27.3%) underwent delayed debulking surgery after 6 cycles. Median disease-free survival in primary, early interval and delayed debulking surgery were 23.0 months (95% CI = [20.0–29.3]), 18.0 months (95% CI = [15.9–20.0]) and 17.1 months (95% CI = [15.0–20.9]), respectively; $p < 0.001$. Median overall survival were 84.0 months (95% CI = [68.3–111.0]), 50.7 months (95% CI = [44.6–59.5]) and 47.5 months (95% CI = [39.3–52.9]), respectively; $p < 0.001$. In multivariable analysis, high peritoneal cancer index (PCI) score and neoadjuvant chemotherapy were negatively associated to disease-free and overall survival. Surgical complexity and CC-1 were negatively associated to disease-free survival.

We concluded that upfront surgery offered a survival gain of almost three years compared to either interval or delayed debulking surgery in patients with minimal or no residual disease after cytoreductive surgery. Primary debulking surgery should remain the standard of care for advanced ovarian cancer.

The second article entitled "**Effect of tumor burden and radical surgery on survival difference between upfront, early interval or delayed cytoreductive surgery in ovarian cancer**" evaluated the impact of PCI score and Aletti score on the survival benefit of primary debulking surgery over neoadjuvant chemotherapy.

Regardless of Aletti score, median overall survival after primary debulking surgery was significantly higher than after early interval or delayed debulking surgery, but the survival difference was higher in women with an Aletti score <8. Among patients with a PCI score ≤ 10 , median overall survival after primary debulking surgery was significantly higher than after early interval or delayed debulking surgery. In women with PCI score >10, there were no differences between primary and early interval debulking surgery, but delayed surgery was associated with decreased overall survival.

We concluded that the benefit of complete upfront debulking surgery compared with neoadjuvant chemotherapy was maximal in patients with a low complexity score. In patients with low tumor burden, there was a survival benefit of primary over either early interval or delayed debulking surgery. In women with high tumor load, delayed debulking surgery impaired the oncological outcome.

The third article entitled "**The effect of major postoperative complications on recurrence and long-term survival after cytoreductive surgery for ovarian cancer**" assessed the impact on survival of major postoperative complications and studied the factors associated with the occurrence of such complications.

The overall rate of major surgical complications was 22.4%. Patients who underwent upfront surgery had a higher rate of major complications (28.6%) than patients who underwent either early interval (23.2%) or delayed debulking surgery (14.0%). Multivariable analysis revealed that extensive peritonectomy and surgical

timing were associated with the occurrence of major complications. Median disease-free and overall survival were 16.9 months (95% CI = [13.7-18.4]) and 48.0 months (95% CI = [37.2-73.1]) for the group of patients with major complications, and 20.1 months (95% CI = [18.6-22.4]) and 56.7 months (95% CI = [51.2-70.4]) for the group without major complications. Multivariable analysis revealed that major surgical complications were significantly associated with disease-free survival, but not with overall survival.

We concluded that patients who experienced major surgical complications had an impaired oncological outcome compared with those patients without major morbidity. Extensive peritonectomy and surgical timing were predictive factors of major postoperative morbidity.

The fourth article entitled "**Survival impact of histological response to neoadjuvant chemotherapy according to number of cycles in patients with advanced ovarian cancer**" aimed to evaluate the impact on survival of chemotherapy response score according to the number of cycles of neoadjuvant chemotherapy in patients with advanced ovarian cancer ineligible for primary debulking surgery.

Out of the 549 patients of the whole cohort, 365 receiving neoadjuvant chemotherapy were included (in 9 of the 374 who received neoadjuvant chemotherapy, data on chemotherapy response score was not available): 219 (60%) received 3-4 cycles of neoadjuvant chemotherapy and 146 (40%) had 6 cycles of neoadjuvant chemotherapy before cytoreductive surgery. There were no significant differences in early relapses, disease-free and overall survival according to the number of neoadjuvant chemotherapy cycles. However, regardless of the number of neoadjuvant chemotherapy cycles, persistent extensive histological disease (chemotherapy response score of 1-2) was significantly associated with a higher PCI score, minimal residual disease (CC-1) and early relapses. Median disease-free survival in patients with complete or near-complete response (chemotherapy response score of 3) was 28.3 months (95%

CI = [21.6-36.8]), whereas it was 16.3 months in patients with chemotherapy response score 1-2 (95% CI = [14.7-18.0]), ($p < 0.001$).

We concluded that complete or near-complete histological response improved oncological outcome regardless of the number of neoadjuvant chemotherapy cycles.

The fifth article entitled **"Impact of pattern of recurrence on post-relapse survival according to surgical timing in patients with advanced ovarian cancer"** studied the association between timing of cytoreductive surgery and the pattern of presentation of the first recurrence in patients with advanced ovarian cancer. We also aimed to assess the impact of the pattern of recurrence on post-relapse overall survival according to surgical timing.

The cumulative incidence of peritoneal recurrences at two years was higher with increasing neoadjuvant chemotherapy cycles (24.4% for primary, 30.9% for early interval, and 39.2% for delayed debulking surgery; $p=0.019$). For pleural or pulmonary recurrences, it was higher after early interval surgery (9.9%, 13.0%, and 4.1%; $p=0.022$). Median post-relapse overall survival was 33.5 months (95% CI = [24.3-44.2]), 26.8 months (95% CI = [22.8-32.6]), and 24.5 months (95%CI [18.6-29.4]) for primary, early interval, and delayed debulking surgery groups, respectively ($p=0.025$). The pattern of recurrence within a lymph node (HR 0.42, 95% CI = [0.27-0.64]), delayed surgery (HR 1.53, 95% CI = [1.11-2.13]) and time to first recurrence (HR 0.95, 95% CI = [0.93-0.96]) were associated with post-relapse overall survival. For primary and early interval surgery, lymph node recurrences were associated with significantly longer post-relapse overall survival.

We concluded that the pattern of the first recurrence was associated with surgical timing, with peritoneal recurrences being more frequent with the increasing number of cycles of neoadjuvant chemotherapy. Lymph node recurrences were associated with better prognosis, having higher post-relapse overall survival. This

improved prognosis of lymphatic recurrences was not observed in patients who underwent delayed surgery.

DISCUSSION

DISCUSSION

The best timing to schedule debulking surgery -*primary, interval or delayed*- to obtain the maximal survival benefit has been largely debated and despite many studies published on this topic with conflicting results, it currently remains an unanswered question. With this thesis, we aimed to provide more information to understand what factors should be considered when deciding the optimal timing to schedule cytoreductive surgery.

Optimal timing for cytoreductive surgery

The principal objective of our **first study** was to assess the survival benefit of primary debulking surgery compared to early interval and delayed debulking surgery in patients with minimal or no residual disease. We found significantly different overall survival in these three groups of patients, with a median overall survival of 84 months for primary, 51 months for early interval, and 48 months for delayed debulking surgery. Survival rates in our series are in line with previous reports. Most series describe median survival rates below 80 months for patients undergoing primary debulking surgery, ranging from 45 months to 86 months⁵³. Regarding interval debulking surgery, the majority of studies report median survival rates below 50 months, ranging from 28 months to 78 months⁵³.

Since the publication of the two randomized controlled trials of Vergote et al. and Kehoe et al., which reported that neoadjuvant chemotherapy confers a non-inferior survival benefit^{91,92}, a decrease of postoperative morbidity and mortality, and an increase in the rate of complete or optimal cytoreduction, a spread of its use has been observed in current clinical practice^{91,92,96,97,106,115}. Nevertheless, these randomized controlled trials have been extensively criticized due to their excessively low rate of complete cytoreduction after primary debulking surgery, of 20.4% and 17% in EORTC trial and CHORUS trial, respectively^{91,92}. For this reason, two randomized controlled trials were launched in high-volume hospitals with expert surgical teams which aim to define the optimal timing of cytoreductive surgery for maximal survival benefit in patients with advanced ovarian cancer. SCORPION trial (Surgical Complications Related to

Primary or Interval debulking in Ovarian Neoplasm, NCT01461850) was a single-institution trial randomizing FIGO stage IIIC patients with high tumoral load to primary debulking surgery followed by adjuvant chemotherapy or to 3-4 cycles of neoadjuvant chemotherapy followed by interval surgery and adjuvant chemotherapy up to 6 cycles¹¹⁶. This study including 171 patients was recently published, and showed that in patients with high tumor load primary debulking surgery and neoadjuvant chemotherapy have similar progression-free and overall survival outcomes⁹³. In these series, median progression-free and overall survival were 15 and 41 months for patients assigned to primary debulking surgery, compared with 14 and 43 months for patients assigned to neoadjuvant chemotherapy, respectively. The survival rates described in this study are inferior to the rates found in our series, but this could be explained by the fact that only patients with CC-0 and CC-1 were included in our study. TRUST trial (Trial of Radical Upfront Surgical Therapy in advanced ovarian cancer (ENGOT ov33/AGO-OVAR OP7, NCT02828618) is a multicentric international trial with almost 800 patients that randomizes FIGO stage IIIB-IVB ovarian cancer patients to upfront surgery followed by adjuvant chemotherapy or to 3 cycles of neoadjuvant chemotherapy followed by interval debulking surgery and 3 cycles of adjuvant chemotherapy; overall survival is the primary endpoint. Moreover, only centers fulfilling a preestablished requirement regarding the rate of primary debulking surgery and CC-0 are allowed to participate. The results of this study are expected in 2024¹¹⁷.

There is strong evidence in the literature supporting a survival advantage of primary debulking surgery. Bristow et al. conducted a meta-analysis reporting that neoadjuvant chemotherapy was associated with inferior overall survival compared to upfront surgery. In a more recent meta-analysis, Qin et al. reported from multiple observational studies that primary debulking surgery yielded better overall survival than interval debulking surgery, and that this benefit remained even in patients with low residual disease⁹⁴. Similar findings were described by Xiao et al., with a significantly improved overall survival in patients undergoing upfront surgery⁹⁵.

Biologic rationale for starting the treatment by upfront debulking surgery is based on the removal of bulky disease before starting chemotherapy, which would allow better perfusion of microscopic residual tumor and, therefore, an improved effect of chemotherapy. As well, the removal of bulky tumor would allow an improvement of host immunocompetence¹¹⁸. Neoadjuvant chemotherapy may also promote the selection of chemoresistant tumoral clones, as the probability of developing chemoresistance increases with the increasing number of tumor

cells. Therefore, even if interval surgery were to remove all macroscopic disease, the remaining microscopic residual tumor might already have a reduced chemosensitivity and the outgrowth of these chemoresistant cells would explain the platinum resistance¹¹⁹. In fact, Petrillo et al. demonstrated a worse disease behavior in terms of timing, pattern, and type of recurrence in patients undergoing interval surgery compared to patients treated with upfront surgery, as patients treated with neoadjuvant chemotherapy more frequently presented platinum-resistant recurrences, carcinomatosis, and a shorter platinum-free interval. These findings suggest that upfront surgery reduces the probability of developing resistant tumor clones¹²⁰.

In our series, the effect of delay on surgical timing after neoadjuvant chemotherapy was traduced by loss of median survival of almost three years in patients undergoing CC-0 or CC-1 cytoreduction, evidencing that the absence of residual tumor after interval surgery does not overcome the deleterious effect of delaying the surgery. Our results are in keeping with a review published by Chiva et al., which selected multiple studies including data from patients with complete cytoreduction after primary and interval surgeries. They showed that complete cytoreduction after interval debulking surgery had a reduced survival benefit of almost two years compared with complete cytoreduction after upfront surgery⁵³.

Regarding the impact of the timing of cytoreductive surgery after neoadjuvant chemotherapy *-early interval or delayed debulking surgery-*, we did not find significant differences in survival between patients undergoing early interval surgery after 3-4 cycles or delayed surgery after 6 cycles of chemotherapy. This might be biologically plausible, as once the chemoresistant clones have been selected, delivering different number of cycles of neoadjuvant chemotherapy would not modify survival outcomes. Another explanation could be that only patients with minimal or no residual disease were included in the present series. Yoneoka et al. compared patients undergoing interval cytoreductive surgery after 3 cycles of neoadjuvant chemotherapy with patients receiving 3 additional cycles of neoadjuvant chemotherapy before surgery without postoperative chemotherapy. They found that 6 cycles of neoadjuvant chemotherapy followed by cytoreductive surgery exhibited equivalent effects on survival than interval debulking surgery after 3 cycles followed by 3 cycles of postoperative chemotherapy⁹⁹. Similarly, Akladios et al. found that the number cycles did not seem to play a role in the overall survival of patients with advanced ovarian cancer¹⁰⁰. Phillips et al. reported an equivalent survival in patients undergoing ≤ 4 cycles and ≥ 5 cycles of neoadjuvant chemotherapy¹⁰¹; and Nitecki et al. showed that delivering >4 cycles of neoadjuvant chemotherapy was not associated with poorer progression-free and overall survival than delivering 3-4 cycles¹⁰⁵. Stoeckle et al.

stated that late interval debulking surgery yielded higher complete resection rates than early interval debulking surgery with similar survival outcomes¹⁰². Contrarily, Bristow et al. found that the number of preoperative chemotherapy cycles was negatively correlated with survival. They hypothesized a gradual and progressive emergence of chemoresistant disease with the cumulative number of neoadjuvant chemotherapy cycles. However, most studies included patients undergoing suboptimal surgeries⁵⁴. Other studies have also reported poorer prognosis in patients undergoing more than 4 cycles of neoadjuvant chemotherapy, even in case of complete cytoreduction^{103,104}. Colombo et al. showed that patients who underwent complete interval debulking surgery after more than 4 cycles of neoadjuvant chemotherapy had a poorer prognosis¹⁰³. Xu et al. reported an impaired oncological outcome of patients undergoing 5 or more cycles of neoadjuvant chemotherapy and they recommended not exceeding 4 cycles of neoadjuvant chemotherapy before interval debulking surgery¹⁰⁴. The ongoing CHRONO (NCT03579394) prospective multi-institutional randomized study will provide a definitive answer to the question of the optimal timing for interval cytoreductive surgery. The study aims to compare the disease-free survival of patients initially deemed unsuitable for primary surgery who receive surgery after either three or six cycles of neoadjuvant chemotherapy.

Prognostic factors in advanced ovarian cancer

The secondary objective of our first study was to evaluate the effect of tumor load and surgical complexity on patients' survival. Understanding factors influencing the long-term survival of patients with complete cytoreduction or with minimal residual disease may help to tailor the decision on the ideal surgical timing. We found that high peritoneal cancer index score and neoadjuvant chemotherapy were negatively associated with disease-free and overall survival. High surgical complexity and CC-1 were negatively associated with disease-free survival.

Absence of residual tumor after cytoreductive surgery has been described as the single most important prognostic factor in advanced ovarian cancer patients⁴⁷⁻⁴⁹. Our series also showed that patients with CC-1 after cytoreductive surgery yielded a statistically significant decrease in median survival of 16 months when compared to patients with CC-0. Median overall survival for patients with CC-0 and CC-1 were 60 months and 44 months, respectively.

The effect of disease burden on survival after complete cytoreductive surgery is still debated in the literature^{121–124}. Some authors hypothesize that bulky and diffuse spread of the disease may reflect a high biological aggressiveness of the tumor or the existence of the disease for a longer period of time, allowing for advanced growth and implantation¹²². It is unknown if the complete removal of all macroscopic disease can completely overcome the negative effect of high tumor load and if it can "reset the clock". In our series, together with the number of cycles of neoadjuvant chemotherapy, peritoneal cancer index was the main prognostic factor for decreased overall survival, meaning that even in patients with no residual or minimal residual disease, tumor burden remains a prognostic factor. This is in line with a previous study published by our group in which tumor extension measured by peritoneal cancer index was the only significant prognostic factor associated with decreased disease-free survival in patients who underwent complete cytoreduction after upfront surgery¹²⁵. In a large series of patients with complete or optimal cytoreduction, patients with more extensive disease -defined as upper abdominal disease- had a worse survival outcome¹²¹. High initial disease burden had a persistent negative effect even when complete surgery was achieved^{121,123}. Zivanovic et al. demonstrated that even if there was a survival benefit of optimal cytoreduction in patients with high initial tumor burden, it was less marked in patients with large-volume disease¹²². However, Eisenkop et al. showed that complete surgical cytoreduction had more significant independent influence on survival than total extent of intra-abdominal tumor burden. They stated that the surgical effort during cytoreductive surgery has not to be abbreviated on the presumption of extensive intra-abdominal disease¹²⁴. In our series, the median overall survival of patients with high tumor burden (peritoneal cancer index >10) was 48 months, which is similar to other series¹²¹. Patients with high tumor burden (peritoneal cancer index >10) undergoing primary debulking surgery have a survival benefit of almost 24 months compared to patients undergoing interval debulking surgery. Therefore, even if high disease burden is a negative prognostic factor, complete primary debulking surgery should remain the mainstay of surgical treatment.

In our study, there were not survival differences between patients with a FIGO stage IIIC and IVA or IVB, suggesting that surgical maximal effort should also be done in these last patients if complete cytoreduction can be achieved.

Complex surgical procedures are performed in approximately 40-50% of cytoreductive surgery^{64,126}. In our series, 29% of patients underwent an ultraradical surgery, and 45% underwent a high complexity surgery according to Aletti score.

Extensive and radical procedures have increased the rate of complete cytoreduction and improved patients' survival^{64,65,126}. Nonetheless, ultraradical procedures have also been associated with longer operative time, increased blood loss, higher morbidity and postoperative mortality^{64,127,128}. In our study, higher Aletti score values were associated with decreased disease-free survival. Some authors suggest that disease requiring ultraradical surgery in order to obtain complete cytoreduction would reflect a more aggressive infiltrative behavior of the disease and, therefore, the surgical effort would not be enough to compensate tumor biology¹²². In a previous study of our workgroup, we found that patients who needed complex surgical procedures involving two or more visceral resections in order to achieve complete cytoreduction had worse survival outcome than patients with less extensive procedures. This negative impact of surgical complexity was not significant in patients who underwent upfront procedures. On the contrary, Horowitz et al. found that patients with low and moderate disease distribution had an improved survival when surgery was complete, even if complex procedures were required. Therefore, it was not complex surgery which affected patients' survival when accounting for other confounding factors¹²¹. According to our definition of ultraradical surgery -which includes at least two digestive or visceral procedures-, we did not find that ultraradical procedures were associated to decreased survival. However, our definition and Aletti score do not use the same criteria to assess surgical complexity.

As previously demonstrated by our first study and other reports in the literature, tumor burden and surgical complexity are associated with an impaired prognosis. The aim of our **second study** was to evaluate if these known negative prognostic factors -high tumor burden and high surgical complexity- modify the benefit conferred by primary debulking surgery in patients with advanced ovarian cancer with minimal (CC-1) or no residual disease (CC-0) after cytoreductive surgery. We found that in women with an Aletti score ≥ 8 , median overall survival at primary, early interval and delayed debulking surgery was 81 months, 42 months, and 46 months ($p=0.014$), respectively; and in women with an Aletti score < 8 , median overall survival was 107 months, 57 months, and 48 months ($p=0.013$), respectively. The differences were not significant between the two groups of neoadjuvant chemotherapy. In women with peritoneal cancer index > 10 , median overall survival at primary debulking surgery, early interval debulking surgery, and delayed debulking surgery were 67 months, 54 months, and 31 months ($p<0.001$), respectively (the difference was significant between early interval and delayed debulking surgery, but not between primary and early interval debulking surgery). In women with peritoneal cancer index ≤ 10 , median overall survival was 107 months, 49 months, and 53

months ($p < 0.001$), respectively (no significant differences were observed between the two groups of neoadjuvant chemotherapy).

Impact of surgical complexity on survival benefit gained by upfront over interval surgery

In our study, surgical radicality was higher in women undergoing upfront surgery (54%) and decreased with the increasing number of cycles of neoadjuvant chemotherapy. The proportion of patients with an Aletti score ≥ 8 was 44% after interval debulking surgery at 3-4 cycles and 37% after 6 cycles. Surgical procedures such as diaphragmatic stripping, extended peritonectomy, and large bowel resection were more frequent at upfront surgery. This is concordant with previous studies as neoadjuvant chemotherapy is often associated with less extended surgical procedures and lower surgical morbidity and mortality^{90,106}.

In the present study, median overall survival decreased with the increasing number of neoadjuvant chemotherapy cycles in patients with an Aletti score < 8 . The difference in median overall survival between primary debulking surgery and early interval or delayed debulking surgery among patients with an Aletti score < 8 was 50 and almost 60 months, respectively. In patients undergoing more radical surgeries (Aletti score ≥ 8), the benefit of primary debulking surgery over early interval or delayed debulking surgery was lower (38 and 35 months, respectively). In other words, in our series, the benefit of primary debulking surgery over early interval or delayed debulking surgery was more notorious in patients undergoing less complex cytoreductive surgeries.

The effect of radical surgery on the survival benefit offered by upfront surgery has been scarcely studied. Our results contrast with a previous study which did not show a significantly different prognostic outcome between patients receiving radical or simple upfront surgical procedures¹²⁵. This contradiction may be explained by different definitions of radical surgery, as in the current study we assessed surgical complexity with Aletti score, which includes different items to define radical surgery¹²⁹. Extended peritoneal disease requiring ultraradical procedures probably has an adverse tumor biology and surgical efforts may not completely overcome this deleterious effect¹²². Even if the benefit of primary debulking surgery is impaired by high surgical radicality, we still found a survival advantage of upfront surgery with complete cytoreduction over interval debulking surgery of almost 40 months in these patients. We believe that primary

debulking surgery should remain the mainstay of surgical treatment, even when complex procedures are required to achieve microscopic or no residual tumor.

Impact of high tumor load on survival benefit reached with upfront surgery over interval surgery

Even if no residual tumor is widely recognized as the most powerful predictor of clinical outcome in advanced ovarian cancer^{49,130}, in the event of complete cytoreduction, intraabdominal tumor burden still has a negative impact on survival^{87,122}. Tentes et al. demonstrated that peritoneal cancer index accurately reflects peritoneal spread and disease burden in advanced ovarian cancer patients¹³¹. Some studies have reported that peritoneal cancer index is an independent prognostic factor and that a cut-off value above 10 negatively impacts survival^{87,131,132}. Moreover, in the subset of patients with no residual disease, high peritoneal cancer index scores remain associated with poor survival rates^{87,133}. Even though the benefit of optimal cytoreduction has been shown to decrease with increasing tumor volume, there is still a significant survival benefit conferred by complete cytoreductive surgery in patients with high disease burden¹²². The impact of high tumor burden on survival according to the number of neoadjuvant chemotherapy cycles is unknown. To our knowledge, this is the first study to assess this issue.

In our study, median peritoneal cancer index score at cytoreductive surgery progressively decreased in primary, early interval, and delayed debulking surgery. The overall survival advantage of upfront cytoreductive surgery compared to neoadjuvant chemotherapy was enhanced in patients with low tumor burden. In this group, there was a survival difference of more than 50 months between upfront surgery and the neoadjuvant chemotherapy groups. In addition, our results concordantly showed that among patients with high disease burden, there was no survival difference between upfront and early interval debulking surgery. Our findings are concordant with the recent randomized SCORPION trial, which included only patients with high tumor load. The authors reported that primary and interval debulking surgery with 3-4 cycles had superimposable survival outcomes in this subset of patients⁹³. However, in our study, delayed debulking surgery after 6 cycles of neoadjuvant chemotherapy in patients with high peritoneal cancer index yielded the worst survival rates. Owing to the retrospective nature of our study, it is unclear whether the inferior clinical outcome of this subgroup was due to chemoresistance induced by additional cycles of neoadjuvant chemotherapy or to the selection of patients with a poorer prognosis who were not considered good surgical candidates

after 3-4 cycles of neoadjuvant chemotherapy. In addition, among the patients who underwent delayed debulking surgery, there was no survival difference between those who had delayed interval debulking surgery and those undergoing closure debulking surgery. It is unclear whether adjuvant chemotherapy after delayed debulking surgery did not improve clinical outcome or if patients receiving adjuvant chemotherapy had a worse prognosis due to the poor response to neoadjuvant chemotherapy.

With the general belief among gynecologic oncologists that primary surgery is superior to interval surgery, the surgical effort to achieve complete cytoreduction in primary setting has increased over the last decades. This increase in surgical radicality has also increased postoperative morbidity due to more extensive and complex surgical procedures. In the **third study** of this thesis, we aimed to increase the evidence regarding the impact on survival of major postoperative complications, and to identify which factors are associated with the occurrence of these complications. We found that extensive peritonectomy and surgical timing were associated with major postoperative morbidity, and that the occurrence of major surgical complications were associated with a negative impact on adjuvant therapy. Major postoperative complications were associated with a decreased disease-free survival (median disease-free survival of 17 months for the group who had major complications vs. 20 months for the group with no major complications) and that this negative impact of major complications was more important after primary debulking surgery (median disease-free survival of 20 months for those patients with major surgical complications vs. 25 months for those without).

Factors associated with major postoperative complications

In our patient series, the rate of major surgical complications was 22.4%, with a mortality rate below 2%, which is in line with previous published studies^{127,134,135}. This non-negligible rate of major postoperative complications in our study can be explained by the number of extensive procedures performed in our institutions. Chi et al. described a 22% incidence of Grade III-V postoperative complications after extensive upper abdominal surgical procedures during upfront cytoreductive surgery for advanced ovarian cancer, with a postoperative mortality of 1.4%¹²⁷. Similarly, Patankar et al. reported a rate of postoperative complications of around 30% in women with ovarian cancer who underwent two or more extensive procedures during cytoreductive surgery¹³⁵.

We found that the rate of major postoperative complications was significantly associated with surgical timing. The rate of complications decreased as the number of neoadjuvant chemotherapy cycles increased, falling from 29% after upfront surgery to 23% after early interval surgery, and 14% after delayed debulking surgery. Similarly, Lomnytska et al. observed a higher rate of Grade 3 or more postoperative complications after primary debulking surgery (32%) than after interval debulking surgery (12%)¹³⁴. This is not surprising, as upfront procedures usually involve greater surgical complexity than interval procedures¹¹⁶. The multivariable analysis revealed that upfront surgery was significantly associated with postoperative complications. Interestingly, in our study, digestive and infectious complications were significantly more common in patients who had undergone upfront or early interval cytoreductive surgery than in patients who had delayed surgery. This can be explained by the significantly higher rate of large bowel resections in women who underwent primary debulking surgery.

Tumor burden (peritoneal cancer index >10) and surgical complexity (Aletti score ≥8) were higher in the group of patients with major postoperative complications, but this association did not remain significant in the multivariable analysis. By contrast, Lomnytska et al. found that a peritoneal cancer index of 21 or more was an independent predictor of high-grade complications after surgery for ovarian cancer¹³⁴. Aletti et al. reported that their surgical complexity score was an independent predictor of 30-day morbidity¹³⁶, and in another study, high-complexity surgery was found to be a predictor of severe complications after cytoreductive surgery for ovarian cancer¹³⁷. The absence of significant associations in our study between high tumor burden or surgical complexity and major postoperative complications can be attributed to the lower tumor burden and surgical complexity of the patients who underwent delayed surgery, which was also included in the multivariable analysis.

Surgical procedures such as extensive peritonectomy were significantly associated with major postoperative complications. Furthermore, there was a higher rate of diaphragmatic stripping and splenectomy among patients with major morbidity that almost reached statistical significance. Pantakar et al. found that the number of extended cytoreductive procedures (e.g., small or large bowel resection, hepatic resection, bladder resection, diaphragm resection, lymphadenectomy or cytoreduction) was the strongest risk factor for postoperative complications¹³⁵. In our study, we did not find that bowel resection was associated with major postoperative complications, but this may be because of the higher rate of large bowel resection during primary debulking surgery, both variables included in the multivariable analysis.

Nevertheless, Lomnytska et al. found that large bowel resection, colectomy, and bowel anastomosis were not associated with high-grade postoperative complications in their study¹³⁴.

Impact on survival of postoperative complications

The findings of this study suggest that major postoperative complications negatively impact oncological outcome. Disease-free survival was significantly reduced with the occurrence of major surgical complications, with a decrease of 3 months in median disease-free survival in patients with major postoperative complications. There was a non-significant trend toward reduced overall survival in patients presenting with major complications, with a decrease of almost 9 months in median overall survival. In subgroup analyses, we observed that this impact on survival was only significant in patients who underwent upfront surgery, with a decrease of 5 months in median disease-free survival. In patients with early interval and delayed debulking surgery, there was only a non-significant trend toward decreased disease-free and overall survival with the occurrence of major postoperative complications. This seems logical, as primary debulking surgery usually requires more complex procedures, with a higher rate of postoperative complications.

Similarly, in a study including almost 4000 women with advanced ovarian cancer who underwent cytoreductive surgery, Wright et al. reported that the occurrence of two or more major perioperative complications increased the risk of death from ovarian cancer¹³⁸. By contrast, two other studies reported that severe postoperative complications did not seem to have a negative impact on overall survival^{134,136}. Aletti et al. demonstrated that short-term morbidity in patients with Stage IIIC-IV ovarian cancer undergoing debulking surgery did not translate into an independent predictor of overall survival¹³⁶. Similarly, Lomnytska et al. showed that high-grade complications (Grade ≥ 3) did not impair overall survival¹³⁴. However, these two studies both had smaller patient samples than ours, which could explain why there was no significant impact on survival. Moreover, the impact of major postoperative complications on disease-free survival was not assessed in these studies, and disease-free survival is known to require less statistical power than overall survival to show significant differences¹³⁹. Another study including patients with ovarian cancer showed that postoperative complications such as anastomotic leakage after bowel resection did not have a negative impact on overall survival¹⁴⁰.

Although the impact of postoperative morbidity has seldom been studied in ovarian cancer, this subject has been extensively explored in patients with colorectal cancer undergoing surgery, in whom major surgical complications seem to impair oncological outcome^{141,142}. Baratti et al. showed that major postoperative morbidity after cytoreduction plus hyperthermic intraperitoneal chemotherapy in patients with peritoneal carcinomatosis of colorectal origin was correlated with both overall and disease-specific survival. The 5-year overall survival was of 12% in patients who had experienced major complications, compared with almost 60% for those who had a complication-free recovery¹⁴¹. Simkens et al. identified postoperative complications requiring further intervention as the only significant risk factor for early recurrence, regardless of peritoneal extension. A decrease in overall survival of 9 months was observed in patients who experienced major complications¹⁴². Another study among patients with peritoneal malignancies (including 8% with ovarian cancer) who underwent cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy found that early postoperative complications had a negative impact on short-term postoperative and long-term cancer-related survival¹⁴³.

Although it is difficult to elucidate the exact mechanisms behind the correlation between major surgical complications and decreased disease-free survival, there is probably a synergy between the immunosuppressive and proinflammatory effects of postoperative complications¹⁴⁴, which may allow minimal residual disease to proliferate. In most postoperative complications, there is an increased systemic inflammatory response that stimulates the proliferation and survival of malignant cells by activating pro-inflammatory cascades¹⁴⁵. It has been suggested that the use of preoperative corticosteroids could reduce the magnitude of the postoperative systemic inflammatory response, thus decreasing postoperative complications in patients with gastrointestinal cancer¹⁴⁶. Moreover, the innate immune system, which chronically inhibits cancer proliferation, is less effective in the presence of a systemic infection¹⁴⁷. Lastly, increased expression of proangiogenic factors, which are released in response to surgical stress and magnified by postoperative complications, may facilitate the survival and growth of residual tumor cells after surgery for colorectal cancer¹⁴⁸. Another possible explanatory factor for reduced disease-free survival is the inability of patients with major postoperative complications to receive adjuvant chemotherapy.

In our series, we found that the occurrence of major surgical complications had a negative impact on adjuvant treatment, as the proportion of patients who did not receive adjuvant chemotherapy was significantly higher for those who had major complications than for those who did not (21% vs. 10%). Wright et al. reported that the occurrence of postoperative

complications was associated not with the omission of chemotherapy, but with delayed chemotherapy. In their study, initiation of chemotherapy more than 12 weeks after surgery was associated with decreased survival¹³⁸. Similarly, Singh et al. found that a delay in chemotherapy initiation was associated with shorter progression-free survival¹⁴⁹.

Neoadjuvant chemotherapy has been increasingly employed with the dual purpose of reducing tumor burden to improve the likelihood of complete resection, while also lowering the risk of major complications due to less extensive surgical procedures^{88,106}. The response to neoadjuvant chemotherapy is a recognized prognostic factor associated with survival^{109–112}. In the **fourth study** of this thesis, we aim to assess the impact on survival of this response (measured by chemotherapy response score) according to the number of cycles of neoadjuvant chemotherapy delivered. The main finding of our study was that the histopathological response measured by the chemotherapy response score had a survival impact, irrespective of the number of neoadjuvant chemotherapy cycles. Regardless of the surgical timing after neoadjuvant chemotherapy, persistent extensive histological disease was significantly associated with a higher peritoneal cancer index, more extensive surgery, minimal residual disease, early relapses, and disease-free and overall survival rates. Indeed, patients with near complete or complete pathological response had approximately a 50% increase in disease-free survival compared to patients with omental tumor residue. Furthermore, the 9% increase in pathologic response after 6 cycles did not translate to an increase in overall survival.

Chemotherapy response score

Concerning chemotherapy response score, our results are in keeping with a recent study by Lontos et al. assessing lymphocytic infiltration and chemotherapy response score as prognostic markers in ovarian cancer patients treated with neoadjuvant chemotherapy followed by delayed surgery. They showed the predictive value of chemotherapy response score in ovarian cancer patients treated with neoadjuvant chemotherapy and interval debulking surgery, but also demonstrated that the presence of lymphocytic infiltration was associated with improved overall survival. Chemotherapy response score assessed at the omentum predicted progression-free survival when adjusted by age, stage, debulking status, and bevacizumab maintenance¹⁵⁰.

Our study confirmed that the chemosensitivity of advanced ovarian cancer may be assessed by chemotherapy response score, and that the impact on survival of this response did not vary according to the cycles of neoadjuvant chemotherapy. These results are in line with a meta-analysis conducted by Cohen et al. including almost 900 patients. They reported that chemotherapy response score was significantly associated with progression-free and overall survival, and that patients with BRCA1 or BRCA2 mutations were more likely to achieve chemotherapy response score of 3. They suggested that this score is a very useful biomarker and could be incorporated as a new endpoint in clinical trials¹⁵¹. Similarly, You et al. also described that CA 125 longitudinal kinetics strongly reflects chemosensitivity to first-line treatment and may be used as a high predictive and prognostic information for progression-free and overall survival^{152,153}. No association between CA 125 kinetic and chemotherapy response score was observed in our study.

Despite the maximal surgical effort and improved survival with the addition of maintenance treatment strategies, most patients with advanced ovarian cancer will experience a recurrence of their disease, irrespective of the timing of surgical cytoreduction¹⁵⁴. It is unknown if the surgical timing may modify the natural history of ovarian cancer concerning the pattern of the first recurrence. In the **fifth and last study** of this thesis, we evaluated if the pattern of the first recurrence varies according to the timing of cytoreductive surgery. As well, we also studied if the pattern of the first recurrence had an impact on patients' post-relapse survival. We found an increasing rate of peritoneal recurrences with the increasing number of cycles of neoadjuvant chemotherapy (primary: 24%, early interval: 31%, and delayed surgery: 39%), and a higher rate of pleural or pulmonary recurrences after early interval debulking surgery (13%) compared to primary (10%) and delayed surgery (4%). The second main finding of the study was that lymph node recurrences were associated with a longer post-relapse overall survival. The survival benefit of lymphatic recurrences was not observed in women who underwent delayed surgery.

Surgical timing and pattern of the first recurrence

Reports in the literature on the impact of the number of cycles of neoadjuvant chemotherapy on the type of recurrences are scarce^{120,154,155}. Gadducci et al. found a non-significantly higher rate of abdominal and pelvic recurrences after interval surgery compared to primary surgery (26% vs. 20% and 19% vs. 16%)¹⁵⁴. Likewise, Petrillo et al. reported more

aggressive behavior of recurrent disease in patients receiving neoadjuvant chemotherapy, with an increased proportion of patients presenting with peritoneal carcinomatosis compared to patients who underwent upfront surgery (57% vs 20%)¹²⁰.

Himoto et al. also showed that the distribution of disease at the time of the first recurrence varied with the choice of primary treatment. Neoadjuvant chemotherapy followed by interval debulking surgery was associated with a higher rate of overlapping locations between baseline and first recurrence and with a lower rate of new disease locations compared to primary debulking surgery¹⁵⁵. One possible explanation for the increased rate of peritoneal recurrences after neoadjuvant treatment in our study is that microscopic tumor regions might be more difficult to identify during interval surgery due to their more benign visual appearance and due to tumor scarring following chemotherapy. Therefore, neoadjuvant strategy may interfere with the perioperative visual evaluation of tumor spread and lead to incomplete resection of tumor in potentially resectable areas¹⁵⁶. Another hypothesis is that microscopic non-visible disease, likely remaining after any cytoreductive surgery, could contain selected chemo-resistant clonal cells after neoadjuvant chemotherapy⁵⁴, leading to a higher rate of abdominal recurrences after interval surgery. However, this higher rate of peritoneal recurrences in our study may also be partially explained by the fact that patients who underwent neoadjuvant chemotherapy had a higher intraabdominal tumor burden or unresectable diffuse carcinomatosis at diagnosis, or by the fact that the group of patients who underwent upfront surgery received more frequently intraperitoneal chemotherapy.

In our study, early interval surgery was associated with a higher rate of pleural or pulmonary recurrences. This subgroup of patients had a significantly higher rate of diaphragmatic stripping, meaning that these patients had a higher rate of pleural disease at diagnosis, which could explain the higher rate of recurrences at this site. To our knowledge, this finding has not been previously reported in the literature.

In our series, we did not find that platinum-resistant disease was associated with surgical timing, and no association was found in the subgroup analysis of patients with FIGO stage IIIC or IV disease. On the other hand, Gadducci et al. showed a significantly higher recurrence rate within 6 months after interval debulking surgery (11.3%) than after primary debulking surgery (3.1%), and a trend to a higher recurrence rate between 6 and 12 months (30.6% vs. 19.9%)¹⁵⁴. Similarly, Petrillo et al. documented a significantly lower rate of platinum-resistant recurrences (≤ 6 months) in the primary debulking surgery group (5%) compared to the interval debulking

surgery group (36%)¹²⁰. This higher rate of early recurrence in these previous reports could be explained by the selection of chemo-resistant clonal cells after neoadjuvant chemotherapy, as has been suggested by other studies⁵⁴.

Impact of the pattern of recurrence on post-relapse survival

It is known that exclusive lymph node involvement at diagnosis has a more indolent course of disease with better survival than peritoneal carcinomatosis¹⁵⁷. However, studies comparing survival outcomes of different types of recurrence have reported controversial results^{158–160}. Delangle et al. did not show a better prognosis of patients with isolated nodal recurrences compared to peritoneal carcinomatosis¹⁵⁸, and Gadducci et al. did not find that the pattern of recurrence (pelvis vs. retroperitoneal lymph nodes) was an independent prognostic factor¹⁵⁹. Conversely, Levy et al. showed better survival for patients with retroperitoneal lymph node recurrences compared to patients with peritoneal carcinomatosis or combined recurrences¹⁶⁰, which is concordant with our findings. Moreover, we specifically assessed post-relapse survival and found that once the recurrence is diagnosed, posterior survival will vary according to the type of recurrence. It would be interesting to evaluate if certain patterns of recurrence are markers of tumor biology and if they are associated to genetic or molecular factors. Other studies have also evaluated the impact on long-term survival of tumor burden at recurrence, Ferrandina et al. showed that patients suffering from recurrence with a prevalent pattern of diffuse abdominal carcinomatosis had an unfavorable prognosis compared to patients presenting with discrete lesions¹⁶¹. However, this was not assessed in our study, as peritoneal recurrences were not distinguished according to disease burden.

Our data also showed that the impact of the recurrence pattern on post-relapse survival was present in patients who underwent primary or early interval surgery but was not significant in those who had delayed surgery. This could be explained by the fact that delayed surgery was per se associated with a higher risk of death after the first relapse. The negative impact of performing delayed surgery is maintained over time and goes beyond the first recurrence, erasing the benefit of having a more indolent recurrence that is found with exclusive lymph node involvement. To the best of our knowledge, the impact on survival of the recurrence pattern according to surgical timing has not previously been reported.

Finally, our results showed that shorter time to first relapse was associated with an increased risk of death. This has been reported by Ferrandina et al. who showed that post-relapse survival was affected not only by the type of recurrence, but also by the length of the interval between the end of primary treatment and the occurrence of first recurrence¹⁶¹. This interval is widely considered the most relevant factor in determining the natural history of recurrent ovarian cancer, with patients who present with platinum-sensitive recurrences having better response to second-line platinum-therapy¹⁶².

Concerning the **strengths** of the studies of our thesis, we included a large and homogeneous cohort with more than 500 women, including only those patients with minimal or no residual disease after cytoreductive surgery. Our patients had a long-term follow-up of almost six years. To our knowledge, this is the largest series performed in high-volume ovarian cancer institutions evaluating the following issues: the impact on survival of surgical complexity and tumor load according to surgical timing, the impact of postoperative morbidity on the long-term survival according to surgical timing, the prognostic value of histopathologic response on survival according to the number of neoadjuvant chemotherapy cycles, and the association between the pattern of recurrence and oncological outcome according to the timing of surgical cytoreduction. Moreover, surgical complexity and tumor load were assessed using validated and objective systems such as the Aletti score and peritoneal cancer index score^{129,163}, and histopathological responses were assessed using the validated and objective chemotherapy response score^{109,110}.

Regarding the **limitations** of our studies, the most remarkable is the retrospective design of our work and the inherent risk of selection bias due to a better performance status and operability of patients undergoing primary debulking surgery, as they were not selected for neoadjuvant chemotherapy, and this may have contributed to their improved survival. Moreover, adjuvant treatment with intraperitoneal chemotherapy or hyperthermic intraperitoneal chemotherapy was heterogeneous among the three groups and the improved survival in primary debulking surgery could be partially explained by intraperitoneal chemotherapy. However, due to the low number of patients receiving these types of treatment in our cohort, statistical analyses regarding this issue were not conducted. Patients with more extended disease were probably included in early interval and delayed debulking surgery groups, which might have influenced our results. As well, patients in delayed surgery group may also have an inherent worse prognosis compared to early interval group, as they were not candidates for surgery after 3-4 cycles of chemotherapy. Even though, our group of patients

with delayed debulking surgery may have an improved prognosis compared to those undergoing delayed surgery in real clinical practice as only women with CC-0 or CC-1 after debulking surgery were included. The unexpected and uncontrolled significant differences in the baseline characteristics between the three groups could have influenced these findings. All patients without a good response after neoadjuvant chemotherapy and with non-resectable disease at delayed debulking surgery, and all those with \geq CC-2 at cytoreductive surgery were excluded from our study, which undoubtedly improved the overall survival of our cohort. We did not retrieve from records all patients in whom the cytoreductive surgery was not possible or with CC-2 after cytoreductive surgery, therefore, we could not assess our rates of complete cytoreduction. Another weakness of our study may be the low number of patients in the primary debulking surgery group (32%). This could be explained by the fact that most patients with an initial external evaluation had already initiated neoadjuvant chemotherapy, and that a non-negligible number of these patients would have been presumably candidates for upfront surgery. Another important limitation is that peritoneal cancer index was collected at cytoreductive surgery instead of at diagnosis, which would have allowed a more reliable comparison of tumor load between the three groups. Unfortunately, although our patients systematically underwent laparoscopy at diagnosis, peritoneal cancer index at this surgery was not available in the surgical report for most patients.

Regarding the study of postoperative complications, although we established strict definitions for each type of complication before retrieving data from medical records, the diagnosis of each complication may not have been uniform across institutions. Despite having information about the omission of adjuvant chemotherapy, the timing of initiation and the possible need for dose reductions, which can both have an impact on survival, were not recorded. Among the patients with major postoperative complications in the delayed surgery group who did not receive adjuvant chemotherapy, we do not know if this was due to the occurrence of surgical complications or following a decision of the tumor board, based on a good histological response to neoadjuvant chemotherapy. Moreover, some factors that may increase the risk of postoperative complications, such as nutritional status, comorbidities, and smoking, were not assessed in our series.

Concerning the study of histopathologic response, pathology reports were also reviewed retrospectively. The chemotherapy response score was developed to reproducibly describe the response to neoadjuvant chemotherapy only in high-grade serous carcinomas, and our cohort had 24.7% of patients with a different subtype. Indeed, given the relative

chemoresistance of low-grade, clear-cell and mucinous ovarian cancer, our results may have been influenced by our selected population. Moreover, BRCA status was not collected and may also influence pathologic response to chemotherapy, survival outcomes, and the impact of chemotherapy response score on survival.

Following the results of this thesis, the main **implications for clinical practice** need to be mentioned, as well as the **future perspectives**. We found that upfront surgery provided an increase in overall survival of almost three years over neoadjuvant chemotherapy and, therefore, upfront complete cytoreduction should remain the standard of care until the publication of the results of TRUST trial. The survival benefit of upfront surgery over interval surgery decreased with increasing extensive peritoneal disease and high Aletti scores, but radical upfront procedures are still associated with a survival advantage over neoadjuvant chemotherapy. High Aletti score should not preclude primary debulking surgery if complete cytoreduction can be achieved. In patients with high tumor burden, early interval debulking surgery is a valid alternative to primary debulking surgery with similar survival benefit and fewer major postoperative complications. Delayed debulking surgery should be avoided in this subgroup of patients.

On the other hand, the notion that major surgical complications may impair the oncological outcome, and that some of these complications may be preventable, highlights the importance of adhering to evidence-based practice guidelines. Perioperative practices such as avoiding hypothermia, minimizing blood loss, and optimizing nutritional status should be implemented, as they are known to prevent surgical complications, particularly infections¹⁶⁴. It is also essential to adequately select the patients who will benefit most from cytoreductive surgery. Although the effort should focus on how to decrease postoperative complications, our findings should not be misinterpreted. Even if the occurrence of postoperative complications was associated with upfront surgery, this approach was still associated with better overall survival and should remain the first option offered to patients with advanced ovarian cancer, particularly in those with low tumor burden. It is essential to continue improving the perioperative management of patients undergoing cytoreductive procedures, to limit major postoperative complications. Moreover, understanding the prognostic implications of these complications for long-term survival may help us to identify potential key points of intervention to improve oncological outcomes, such as considering further adjuvant treatment and individualizing follow-up strategies in patients presenting with major surgical complications.

Regarding histopathological response, this work may expand the current literature by showing that the histopathological response is associated with survival outcome, irrespective of the number of neoadjuvant chemotherapy. This 'retrospective' information obtained after surgery adds additional prognostic information to adapt or intensify treatment strategy and follow-up. Moreover, our findings confirm the strong prognostic relationship between chemotherapy response score and survival, and that chemotherapy response score may be used as a surrogate of chemosensitivity and as a useful endpoint for clinical trials. BRCA mutation and homologous recombination deficiency status was not collected in our study, and patients did not receive PARPi maintenance treatment due to the study period. However, the benefit of primary debulking surgery over interval surgery may be modulated by genetic status, chemosensitivity of the disease, and also by maintenance treatment with PARPi. These factors could decrease or even erase the survival benefit of upfront surgery and, therefore, this needs to be evaluated in future studies.

Finally, our findings suggest that the type of recurrence may vary depending on the timing of surgical cytoreduction, and that the better survival outcome of patients with lymphatic recurrences may be erased by delayed surgery. Further prospective multicenter studies are needed to confirm our findings regarding the impact on oncological outcome of the pattern of the first recurrence in ovarian cancer patients.

CONCLUSIONS

CONCLUSIONS

FIRST STUDY

1. **Primary debulking surgery** offered a **survival gain** of **almost three years** compared to **early interval debulking surgery** at 3-4 cycles of neoadjuvant chemotherapy or **delayed debulking surgery** at 6 cycles after complete cytoreduction (CC-0) or cytoreduction to minimal residual disease (CC-1) in patients with advanced ovarian cancer (IIIC-IVB).
2. **High tumor burden** (peritoneal cancer index >10) and **high surgical complexity** (Aletti score ≥8) were associated with **decreased disease-free survival** (DFS), and **high peritoneal cancer index** was associated with **decreased overall survival** (OS).

SECOND STUDY

3. **Regardless of Aletti score, OS after primary debulking surgery** was **higher** than after early interval or delayed debulking surgery, but **survival difference** was **higher** in women with **Aletti score <8**. In patients with **low tumor burden** (peritoneal cancer index ≤10), **OS after primary debulking surgery** was higher than after early interval or delayed debulking surgery. In patients with **high tumor burden** (peritoneal cancer index >10), there were **no differences** in terms of OS between **primary and early interval debulking surgery**, but **delayed debulking surgery** was associated with **decreased OS**.

THIRD STUDY

4. **Major postoperative complications** were associated with a **reduced DFS**, but **not** with decreased **OS**, in patients who underwent a cytoreductive surgery with CC-0 or CC-1 for advanced ovarian cancer (IIIC-IVB).

5. **Extensive peritonectomy and surgical timing** were **predictive factors of major postoperative complications** in patients who underwent a cytoreductive surgery with CC-0 or CC-1 for advanced ovarian cancer (IIIC-IVB).

FOURTH STUDY

6. **Chemotherapy response score of 3 improved DFS and OS regardless of the number of cycles of neoadjuvant chemotherapy** in patients with advanced ovarian cancer (IIIC-IVB) non-eligible for primary debulking surgery who underwent interval debulking surgery after 3-4 cycles or delayed debulking surgery after 6 cycles of neoadjuvant chemotherapy.

FIFTH STUDY

7. **Pattern of first recurrence** was **associated** with **surgical timing**, with **peritoneal recurrences** being **more frequent** with the **increasing number of cycles of neoadjuvant chemotherapy** in patients who underwent a cytoreductive surgery with CC-0 or CC-1 for advanced ovarian cancer (IIIC-IVB).
8. **Lymph node recurrences** were associated with **longer post-relapse overall survival** in patients who underwent a cytoreductive surgery with CC-0 or CC-1 for advanced ovarian cancer (IIIC-IVB). This **improved prognosis of lymphatic recurrences** was **not observed** in patients who underwent **delayed debulking surgery**.

CONCLUSIONES

CONCLUSIONES

PRIMER ESTUDIO

1. La **cirugía citorreductora primaria** ofrece un **aumento de la supervivencia** de casi **tres años** en **comparación** con la **cirugía de intervalo precoz** después de 3-4 ciclos de quimioterapia neoadyuvante o con la **cirugía citorreductora tardía** después de 6 ciclos, en pacientes con cáncer de ovario avanzado (IIIC-IVB) sin enfermedad residual (CC-0) o con enfermedad residual mínima (CC-1).
2. La **alta carga tumoral** (*peritoneal cancer index* >10) y la **alta complejidad quirúrgica** (score de Aletti ≥8) están asociados con una **disminución** de la **supervivencia libre de enfermedad**. La **alta carga tumoral** está también asociada con una **disminución** de la **supervivencia global**.

SEGUNDO ESTUDIO

3. **Independientemente** del score de **Aletti**, la **supervivencia global** tras **cirugía citorreductora primaria** es **más elevada** que tras **cirugía citorreductora de intervalo precoz** o **tardía**. Esta **diferencia** es **más marcada** en pacientes con un score de **Aletti** <8. En pacientes con **baja carga tumoral** (*peritoneal cancer index* ≤10), la **supervivencia global** tras **cirugía citorreductora primaria** es **más elevada** que tras **cirugía citorreductora de intervalo precoz** o **tardía**. En pacientes con **alta carga tumoral** (*peritoneal cancer index* >10), **no** hay **diferencias** en términos de supervivencia global entre pacientes con **cirugía citorreductora primaria** o de **intervalo precoz**. Sin embargo, la **cirugía citorreductora tardía** está asociada con una **menor supervivencia global**.

TERCER ESTUDIO

4. Las **complicaciones posoperatorias mayores** están asociadas con una **disminución** de la **supervivencia libre de enfermedad**, pero **no** de **supervivencia global**, en pacientes con una cirugía citorreductora (CC-0 o CC-1) por un cáncer de ovario avanzado (IIIC-IVB).
5. La **peritonectomía extendida** y el **momento de la cirugía citorreductora** son **factores predictivos** de **complicaciones posoperatorias mayores** en pacientes con una cirugía citorreductora (CC-0 o CC-1) por un cáncer de ovario avanzado (IIIC-IVB).

CUARTO ESTUDIO

6. Una **puntuación de 3** en el **score de respuesta a la quimioterapia** está asociada con un **aumento** de la **supervivencia libre de enfermedad y global**, **independientemente** del **número de ciclos de quimioterapia neoadyuvante**, en las pacientes con cáncer de ovario avanzado (IIIC-IVB) no candidatas a cirugía citorreductora primaria que son operadas después de 3-4 o 6 ciclos de quimioterapia.

QUINTO ESTUDIO

7. El **patrón de la primera recurrencia** está **asociado** al **momento de la cirugía**, siendo las **recurrencias peritoneales más frecuentes** con el **incremento** del **número de ciclos de quimioterapia neoadyuvante**, en pacientes con cirugía citorreductora (CC-0 o CC-1) por cáncer de ovario avanzado (IIIC-IVB).
8. Las **recurrencias en ganglios linfáticos** están asociadas con una **mayor supervivencia global posterior a la recurrencia** en pacientes con cirugía citorreductora (CC-0 o CC-1) por cáncer de ovario avanzado (IIIC-IVB). Este **mejor pronóstico** de las **recurrencias linfáticas no es observado** en pacientes con **cirugía citorreductora tardía**.

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