VNIVERSITAT DE VALÈNCIA

EXPLORING NEW PERSPECTIVES IN THE EVALUATION AND TREATMENT IN ADVANCED OVARIAN CANCER

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PROGRAMA DE DOCTORADO 3139 EN MEDICINA

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PRODUCCIÓN CIENTÍFICA DE LA DOCTORANDA.

Las publicaciones científicas generadas por María Teresa Climent Martí durante su doctorado y directamente asociadas a la presente Memoria de Tesis Doctoral de la Universidad de Valencia son:

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"Dolor, placer y muerte no son más que el proceso de la existencia. La lucha revolucionaria en este proceso es una puerta abierta a la inteligencia"

Frida Kahlo (1907 - 1954)

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RESUMEN:

El cáncer de ovario es una causa significativa de muerte en los tumores ginecológicos. Su diagnóstico se produce entre un 70 – 80% en estadios avanzados.
El pilar del tratamiento en esta situación es la cirugía citorreductora sin residuo macroscópico tumoral asociado al tratamiento quimioterápico. No obstante, pese al tratamiento, un 80% de las pacientes presentan una recaída con una supervivencia menor al 20% a los cinco años.

En este escenario, el cáncer de ovario se muestra como una patología en la que es necesaria implementar mejoras diagnósticas y terapéuticas con el objetivo de mejorar el pronóstico de estas pacientes.

Los estudios publicados establecen avances en las diferentes estrategias en el tratamiento del cáncer de ovario avanzado, focalizándose en las diferentes estrategias quirúrgicas, el uso de herramientas diagnósticas que permiten mejorar los resultados quirúrgicos y, por tanto, el pronóstico, y los diferentes regímenes quimioterápicos.

- La citorreducción completa es el principal factor pronóstico en cirugía primaria y en cirugía secundaria. Bajo esta premisa radica la importancia de la correcta selección de las pacientes mediante el uso de herramientas diagnósticas, como la aplicación del índice de carcinomatosis peritoneal de Sugarbaker, para la planificación quirúrgica en casos de cáncer de ovario avanzado y en la recurrencia de estas pacientes, reduciendo las laparotomías innecesarias y optimizando el manejo integral de estas pacientes.
  Además de la predicción de los resultados quirúrgicos, la aplicación de este índice asocia un valor pronóstico en las pacientes con carcinomatosis peritoneal comparado con el índice de Fagotti.

- La citorreducción secundaria en el cáncer de ovario recurrente mejora la supervivencia global y el intervalo libre de enfermedad, particularmente cuando se consigue la citorreducción completa. Es por ello por lo que el beneficio depende de la cuidadosa selección de pacientes basándose en diferentes algoritmos como el AGO score (buen estado basal de la paciente, ascitis menor de 500 mL, citorreducción completa en primera cirugía) o el iModel (estadio FIGO, ascitis ausente o mínima, ausencia de residuo tumoral en primera cirugía, intervalo libre de platino, estado basal y nivel de Ca 125).
  El meta – análisis realizado basándose en tres estudios randomizados confirma que la combinación de la cirugía de citorreductora asociado a quimioterapia es más efectiva que la quimioterapia sola.

- El uso de la quimioterapia intraperitoneal utilizada asociada al tratamiento intravenoso estándar demuestra una mejoría significativa en la supervivencia global y el intervalo libre de enfermedad en el cáncer de ovario avanzado en el que se realiza cirugía citorreductora primaria sin residuo tumoral o ≤ 1 cm. No obstante, los efectos secundarios y los retos logísticos han limitado la adopción generalizada de este tratamiento. Sin embargo, la evidencia científica disponible evaluada en el artículo a través del meta – análisis de 6 artículos impresiona que la tolerancia es comparable a la quimioterapia sólo.
  Es necesario estandarizar los regímenes de quimioterapia intraperitoneal e identificar las pacientes candidatas en las que aplicar este tratamiento.

Las conclusiones extraídas de los estudios presentados nos lleva a establecer la necesidad de un tratamiento personalizado que integre herramientas diagnósticas como el índice de carcinomatosis peritoneal que asociadas al estudio prequirúrgico en la cirugía primaria, y a los diferentes algoritmos de selección de pacientes para la cirugía tras la recurrencia permita seleccionar aquellas pacientes en las que la ausencia de residuo tumoral sea el objetivo, ya que ha demostrado ser un determinante en la supervivencia de las pacientes con diagnóstico de cáncer de ovario avanzado y en la recurrencia.
Es necesario realizar más estudios que permitan definir la correcta selección de pacientes para los diferentes tratamientos, la estandarización de los distintos regímenes quimioterápicos y el papel de la vía intraperitoneal en las pacientes con carcinomatosis peritoneal, además de evaluar el beneficio a largo plazo de los tratamientos emergentes disponibles.

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ABREVIATURAS

CP	Carcinomatosis peritoneal.
BRCA 1	Breast cancer gene 1
BRCA 2	Breast cancer gene 2
HRD	Defectos en los genes de recombinación homóloga.
CCNE – 1	Ciclina E1
PTEN:	Fosfatasa y homólogo de la tensina.
Rb – 1	Retinoblastoma 1
MMR	Mismatch repair (reparación de errores de emparejamiento.
RAD51C	Gen activador de la recombinación homóloga 51 C
RAD51D	Gen activador de la recombinación homóloga 51 D
BRIP1	BRCA 1 – interacting protein 1.
TP 53	Proteína tumoral 53.
ROS	Especies reactivas de oxígeno.
ARID1A	AT – rich interactive domain 1A.
KRAS	Kirsten Rat Sarcoma viral oncogene homolog.
PiK3CA	Fosfatidinositol – 4, 5 – bifosfato 3 Kinasa subunidad catalítica alfa.
IMC	Índice de masa corporal.
IL6	Interleukina 6.
TNFα	Factor de necrosis tumoral alfa.
NK	Natural Killer
THS	Terapia hormonal sustitutiva.
ACOG	Colegio Americano de Obstetricia y Ginecología.
HGSC	Carcinoma seroso de alto grado.
LGSC	Carcinoma seroso de bajo grado.
BRAF	V – Raf murine sarcoma viral oncogene homolog B1
ERBB2	Erb B2 receptor tyrosine Kinasa 2 (conocido como HER2)
HER 2	Human epidermal growth factor receptor 2.
AFP	Alfa – fetoproteína.
hCG	Human chorionic gonadotropin.
ADN	Ácido desoxirribonucleico.
STIC	Carcinoma intraepitelial seroso en trompa
FAS	Fas Cell Surface Death receptor
Rsf – 1	Remodeling and spacing factor 1
PAX – 8	Paired Box 8
MAPK	Mitogen – activated protein kinase.
AKT	Protein Kinase B (conocido como PKB)
FIGO	Federación Internacional de Ginecología y Obstetricia.
TNM	Tumor, Node, Metastasis Classification System
UICC	Union for International Cancer Control
ICAM-1	Intercellular Adhesion Molecule 1
VCAM-1	Vascular Cell Adhesion Molecule 1
VEGF	Vascular endothelial growth factor
MMT	Transición mesotelial a mesenquimal
TGF-β	Factor de crecimiento transformante beta
ECM	Remodelación de la Matriz Extracelular
MMPs	Metaloproteinasas de matriz
Ca 125	Antígeno del Cáncer 125

CEA	Antígeno carcinoembrionario
Ca 19.9	Antígeno Carbohidrato 19.9
HE 4	Proteína del Epidídimo Humano 4
WFDC2	WAP Four-Disulfide Core Domain 2
SG	Supervivencia global
IOTA	International Ovarian Tumor Analysis
Adnex Model	Assessment of Different Neoplasias in the Adnexa.
ACR	American College of Radiology
O – RADS	Ovarian - Adnexal Reporting Data System
TC	Tomografía computarizada
S	Sensibilidad
E	Especificidad
RMN	Resonancia magnética
PET TC	Tomografía por emisión de positrones
ICP	Índice de carcinomatosis peritoneal
EGFR	Receptor del factor de crecimiento epidérmico
GOG	Gynecologic Oncology Group
PDS	Cirugía de citorreducción primaria
NACT	Quimioterapia neoadyuvante
IDS	Cirugía de citorreducción intervalo
ASA	American Society of Anesthesiologists Physical Status Classification System
SCS	Cirugía de citorreducción secundaria
ECOG	Eastern Cooperative Oncology Group Performance Status
AGO score	Arbeitsgemeinschaft Gynäkologishe Onkologie score
ILE	Intervalo libre de enfermedad
HR	Hazard ratio
IC	Intervalo de confianza
iPARP	Inhibidores de la poli - ADP – ribosa polimerasa
HIPEC	Quimioterapia intraperitoneal hipertérmica
AUC	Área bajo la curva
IP	Quimioterapia intraperitoneal
BRCAwt	BRCA no mutado
BRCAmt	BRCA mutado

CAPÍTULO 1

Introducción y Objetivos

CAPÍTULO 1: INTRODUCCIÓN Y OBJETIVOS

1. INTRODUCCIÓN

El cáncer de ovario es una de las principales causas de mortalidad por cáncer ginecológico en mujeres a nivel mundial. Debido a su diagnóstico tardío y la falta de síntomas específicos en etapas iniciales, representa un desafío significativo para los sistemas de salud

El cáncer de ovario avanzado es el segundo cáncer ginecológico en frecuencia a nivel mundial. Es la primera causa de muerte por cáncer ginecológico con una supervivencia a 5 años menor al 30% debido a que el 75% se presenta en estadios avanzados (III/IV). (1)

La diseminación peritoneal de los tumores malignos era considerada una enfermedad incurable tributaria de tratamiento paliativo. En 1980 se empezaron a desarrollar diversas técnicas quirúrgicas para el abordaje de esta patología, en 1995 Paul Sugarbaker publicó diferentes procedimientos de peritonectomía para estandarizar la técnica de citorreducción con el objetivo de conseguir la resección radical del tumor diseminado en cavidad peritoneal.

Actualmente, la cirugía de citorreducción asociado a tratamiento quimioterápico intraquirúrgico o postquirúrgico se considera el tratamiento de elección para las pacientes con carcinomatosis peritoneal (CP) de origen ovárico.

1.1. EPIDEMIOLOGÍA:

Según las estimaciones de GLOBOCAN 2020, el cáncer de ovario representa una carga significativa a nivel mundial, con variaciones notables en incidencia y mortalidad entre diferentes regiones y países.(2,3)

Incidencia del cáncer de ovario:

A nivel mundial, se estimaron aproximadamente 313.959 nuevos casos de cáncer de ovario en 2020, lo que representa el 1.6% de todos los cánceres diagnosticados en ambos sexos. La incidencia varía considerablemente entre regiones:

- **Asia Oriental y Europa del Este** presentan las tasas más altas de incidencia, con 7.5 y 7.4 casos por 100.000 mujeres, respectivamente.
- **África Occidental y Asia Meridional** muestran las tasas más bajas, con 3.1 y 3.2 casos por 100.000 mujeres, respectivamente.

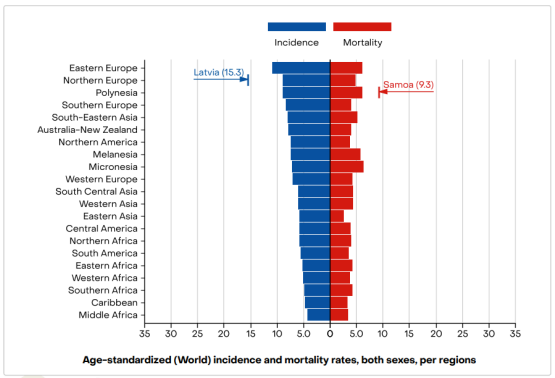
En España, la incidencia estimada para 2020 fue de 3.600 nuevos casos, con una tasa ajustada por edad de 7.1 por 100.000 mujeres, situándose en una posición intermedia en comparación con otros países europeos.

Mortalidad por cáncer de ovario:

En cuanto a la mortalidad, se registraron aproximadamente 207.252 muertes por cáncer de ovario en todo el mundo en 2020, representando el 2.1% de todas las muertes por cáncer en ambos sexos. Las tasas de mortalidad también varían según la región:

- **Europa del Este** tiene la tasa de mortalidad más alta, con 5.0 muertes por 100.000 mujeres.
- **África Occidental** presenta la tasa más baja, con 2.5 muertes por 100.000 mujeres.

En España, se estimaron 1.900 muertes por cáncer de ovario en 2020, con una tasa ajustada por edad de 3.8 por 100.000 mujeres, lo que refleja una mortalidad moderada en comparación con otros países europeos.



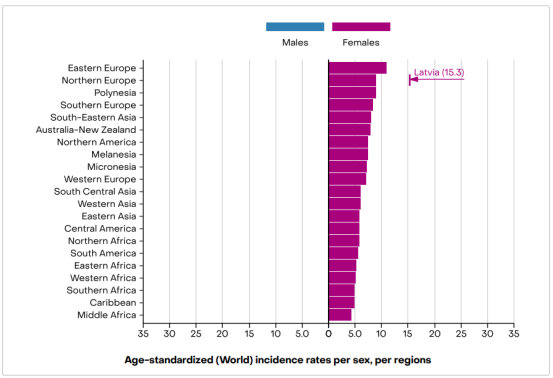


Figura 1a y 1b; Epidemiología del Cáncer de Ovario.

Ferlay J, Ervik M, Lam F, Laversanne M, Colombet M, Mery L, Piñeros M, Znaor A, Soerjomataram I, Bray F (2024). Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. Available from: https://gco.iarc.who.int/today.

El cáncer de ovario presenta una elevada heterogeneidad, entre los diferentes tipos histológicos de cáncer de ovario, e incluso intratumoral.

El cáncer de ovario se presenta a diferentes edades según el tipo histológico:

- **Carcinoma seroso de alto grado**: Es el subtipo más común de cáncer epitelial de ovario, representando aproximadamente el 75% de los casos. Suele diagnosticarse en mujeres posmenopáusicas, con una edad media de presentación alrededor de los 63 años.
- **Carcinoma de células claras**: Este subtipo es menos frecuente y se ha observado una mayor incidencia en mujeres jóvenes, especialmente de origen asiático. A menudo se asocia con endometriosis y puede presentarse en mujeres de entre 40 y 50 años.
- **Tumores de células germinales**: Representan entre el 5% y el 10% de los cánceres ováricos y afectan principalmente a mujeres jóvenes, con una edad media de diagnóstico de 19 años.
- **Tumores de los cordones sexuales-estromales**: Comprenden alrededor del 5% de los cánceres de ovario y pueden presentarse a cualquier edad. El tumor de células de la granulosa, un subtipo de este grupo tiene una edad media de presentación de 50 años.
- **Carcinoma de células pequeñas de tipo hipercalcémico**: Es una variante agresiva que afecta predominantemente a mujeres jóvenes, con una edad media de diagnóstico de 24 años.

1.2. FACTORES DE RIESGO:

El cáncer de ovario está influenciado por diversos factores de riesgo, entre los cuales se destacan:

- **Edad**: El riesgo de cáncer de ovario incrementa con la edad, siendo más común en mujeres mayores de 50 años, especialmente entre los 75 y 79 años, presentándose el 81% de los mismos en pacientes mayores de 50 años. (4)

- **Factores genéticos**:
  Aunque el 90% de los casos de cáncer de ovario se consideran esporádicos, cabe destacar los factores genéticos relacionados con el cáncer de ovario.

  a. Síndrome de cáncer de mama – ovario (BRCA 1 y BRCA2):

Mutaciones en los genes BRCA1 y BRCA2 incrementan significativamente el riesgo de cáncer de ovario. Las mujeres portadoras de mutaciones en BRCA1 tienen un riesgo de por vida de desarrollar cáncer de ovario del 39-46%, mientras que para mutaciones en BRCA2, el riesgo es del 10-27%.

Los genes BRCA 1 y BRCA 2 son genes supresores que participan en la reparación de ADN por la vía de la recombinación homóloga (HRD)
El 50% de los cánceres de ovario presentan alteraciones en los genes de la vía de recombinación homóloga resultante en alteraciones en la reparación del ADN.
Un 20% de los cánceres de ovario son secundarios a alteraciones germinales, de ellas la más frecuente son las mutaciones en los genes BRCA 1 y BRCA 2 (14% de las pacientes).(5)

Las mutaciones son más frecuentes en ciertas poblaciones, como los judíos asquenazíes, quienes tienen una prevalencia del 2.5% de mutaciones en BRCA.

Además, la alteración de estos genes se muestra en aproximadamente el 8 y el 6% de los cánceres de ovario avanzados.
En la siguiente tabla se muestran las alteraciones genéticas más frecuentes encontradas en los carcinomas serosos de ovario.
Para las pacientes portadoras de esta mutación en línea germinal, presentan un riesgo acumulativo total de 40% para cáncer de ovario y 60% para cáncer de mama para la mutación en BRCA 1 (gen oncosupresor situado en el cromosoma 17q21), y de 18% para cáncer de ovario y 55% para cáncer de mama en la mutación BRCA 2 (gen oncosupresor situado en el cromosoma 13q).
Este riesgo total se incrementa a partir de los 40 años. (6,7)

Alteración genética	%
Amplificación CCNE1	14
Metilación BRCA 1	11
Mutación germinal BRCA 1	8
Mutación germinal BRCA 2	6
Amplificación EMSY	6
Pérdida del PTEN	6
Otros HRD	5
Mutación somática BRCA1	4
Pérdida Rb1	4
Mutación somática BRCA 2	3
Mutación germinal MMR	2
Otros	31

Tabla 1: Alteraciones genéticas del Carcinoma Seroso de Ovario. (8)

b. Síndrome de Lynch tipo 2

El síndrome de Lynch es consecuencia de la presencia de mutaciones en genes de reparación de errores de apareamiento del ADN (MLH1, MSH2, MSH6, PMS2 y EPCAM)
Un 20 – 25% de las mutaciones ocurren en los genes; MLH1, MSH2, MSH6 y PMS2.
El riesgo de desarrollo de cáncer de ovario se sitúa entre el 9 – 12%. No obstante, aproximadamente el 40% de estos tumores se presentarán en pacientes menores de 40 años.

El tipo histológico con el que se asocia son los subtipos endometrioide y de células claras.

c. Síndrome familiar de cáncer de ovario
Se denomina con este término a aquellos casos en los que múltiples miembros de la familia presentan cáncer de mama/ovario a lo largo de diferentes generaciones.
Sin embargo, no se dispone de una herramienta de screening efectiva disponible para estas pacientes de alto riesgo.

d. Otros genes relacionados:
    a. RAD51C y RAD51D:
    Mutaciones en estos genes relacionados con la reparación del ADN se encuentran vinculadas a un riesgo moderado de cáncer de ovario.
    b. BRIP1:
    Las mutaciones en este gen se asocian con un riesgo intermedio, incrementando la probabilidad de desarrollar cáncer de ovario epitelial en aproximadamente 6%.
    c. TP53:
    El gen TP53 que regula el ciclo celular se encuentra frecuentemente mutado de forma isomática en el carcinoma seroso de alto grado.(9)

- **Endometriosis**:
La endometriosis está particularmente relacionada con dos subtipos de cáncer de ovario:
    - Cáncer de Ovario de Células Claras:
    Las pacientes con endometriosis tienen un riesgo 2-3 veces mayor de desarrollar cáncer de células claras. Este subtipo tiende a tener un peor pronóstico y, a menudo, es resistente a la quimioterapia.
    - Cáncer de Ovario Endometrioide:
    Estas pacientes presentan un riesgo 2 veces mayor de desarrollar este subtipo. Suele detectarse en etapas tempranas y tiene un mejor pronóstico en comparación con el carcinoma de células claras.(10)

Aunque los mecanismos precisos no están completamente claros, se han propuesto varias hipótesis:

1. **Inflamación Crónica:** La inflamación persistente en las lesiones endometriósicas puede conducir a la liberación de citocinas y factores de crecimiento, promoviendo daño al ADN y carcinogénesis.(11)
2. **Estrés Oxidativo:** La hemólisis de la sangre atrapada en los quistes endometriósicos genera especies reactivas de oxígeno (ROS), que pueden inducir mutaciones genéticas en las células epiteliales circundantes.
3. **Influencia Hormonal:** El estrógeno juega un papel en la patogénesis tanto de la endometriosis como del cáncer de ovario, promoviendo la proliferación celular en las lesiones endometriósicas.
4. **Alteraciones Genéticas y Epigenéticas:** Mutaciones en genes como ARID1A, PTEN, KRAS y PIK3CA se han identificado tanto en endometriosis como en los cánceres ováricos asociados, sugiriendo una vía molecular compartida.
5. **Transformación Metaplásica:** La transformación del epitelio endometriósico en células malignas ocurre debido a la exposición prolongada a factores inflamatorios y de estrés oxidativo.(11,12)

Un estudio de cohorte basado en una población encontró que las mujeres con endometriosis tienen un riesgo 1.5-2 veces mayor de desarrollar cáncer de ovario en comparación con las mujeres sin endometriosis. (13)Sin embargo, a pesar de este aumento relativo, el riesgo absoluto sigue siendo bajo, se sitúa en 5.2% (52 por 1000 mujeres). Por lo que la mayoría de las mujeres con endometriosis no desarrollarán cáncer de ovario. (14)

- **Obesidad**:
  Estudios han encontrado una asociación positiva entre un índice de masa corporal (IMC) elevado y un mayor riesgo de cáncer de ovario, particularmente en subtipos no serosos. (15). Un metaanálisis realizado por el Grupo Colaborativo de Estudios Epidemiológicos del Cáncer de Ovario informó un aumento del 6% en el riesgo de cáncer de ovario por cada incremento de 5 unidades en el IMC.(16)

  Mecanismos Que Vinculan la Obesidad y el Cáncer de Ovario
  - **Factores Hormonales:**
    Sobreproducción de Estrógenos:
    En mujeres posmenopáusicas, el tejido adiposo es la principal fuente de producción de estrógenos a través de la aromatización de andrógenos. Los niveles elevados de estrógenos promueven la proliferación de células epiteliales ováricas, aumentando el riesgo de cáncer.
    Resistencia a la Insulina e Hiperinsulinemia:
    La obesidad a menudo conduce a resistencia a la insulina y niveles elevados de esta hormona pueden fomentar el crecimiento de células cancerosas al activar las vías de señalización del factor de crecimiento.
  - **Inflamación Crónica:**
    El tejido adiposo es metabólicamente activo y secreta citocinas proinflamatorias (por ejemplo, IL-6, TNF-α) y adipocinas. La inflamación crónica de bajo grado crea un ambiente propicio para la carcinogénesis.
  - **Estrés Oxidativo:**
    El aumento del estrés oxidativo en personas obesas puede provocar daños en el ADN y, posteriormente, el desarrollo de cáncer.
  - **Disregulación Inmunitaria:**
    La obesidad afecta la vigilancia inmunitaria al alterar la función de células inmunes, como las células T y las células asesinas naturales (NK), lo que facilita la progresión tumoral.(17–19)

  Cabe destacar que el pronóstico en estas pacientes es peor, debido a que presentan mayores riesgos quirúrgicos, mayor tasa de complicaciones y dificultades para lograr una citorreducción óptima. Además, la dosificación de la quimioterapia puede ser subóptima en pacientes obesos debido a preocupaciones sobre la toxicidad.

- **Factores reproductivos**: La nuliparidad y la infertilidad se asocian con un aumento en el riesgo de cáncer de ovario. La nuliparidad incrementa dos veces más el riesgo de cáncer de ovario. La menarquia temprana y la menopausia tardía también son considerados factores de riesgo de cáncer de ovario, ya que el número de ciclos menstruales se encuentra relacionado con el cáncer de ovario.
  Como factores protectores encontramos la edad temprana para la primera gestación (menor a 35 años). La multiparidad se relaciona con una disminución del 50% de riesgo de cáncer de ovario.

El tratamiento con píldoras anticonceptivas presenta una disminución en la incidencia de cáncer de ovario de 30 – 50% con el uso de estas durante un mínimo de 5 años, manteniéndose hasta 10 – 15 años tras el cese de uso de estas.(20) No obstante, la utilización de terapia hormonal sustitutiva (THS) durante periodo largo de tiempo incrementa el riesgo de cáncer de mama, sin haberse demostrado su relación con el cáncer de ovario.
No obstante, un metaanálisis que incluyó 52 estudios epidemiológicos, tanto prospectivos como retrospectivos, encontró que el uso de THS en mujeres posmenopáusicas se asocia con un aumento significativo del riesgo de desarrollar cáncer de ovario. Este incremento es más pronunciado en los subtipos de carcinoma seroso y endometrioide. (21)
Además estudios observacionales han sugerido que el uso prolongado de THS con estrógenos solos en mujeres histerectomizadas podría elevar ligeramente el riesgo de cáncer de ovario. Sin embargo, la magnitud de este riesgo adicional es relativamente pequeña.(22)

Estos factores reproductivos no se han podido relacionar con el cáncer originado en trompa de Falopio.

Pese a que la infertilidad se considera un factor de riesgo, no se ha podido demostrar si la utilización de fármacos inductores de la ovulación en las técnicas de reproducción asistida se relaciona con el incremento del cáncer de ovario, siendo su asociación controvertida.

Un metaanálisis y revisión sistemática publicado en 2022 evaluó la incidencia de tumores ováricos borderline y cáncer de ovario en mujeres que se sometieron a inducción de la ovulación en comparación con grupos de control. El análisis no encontró diferencias significativas en la incidencia de carcinoma invasivo o borderline entre los grupos, lo que sugiere que la inducción de la ovulación podría no aumentar sustancialmente el riesgo de cáncer de ovario. (23)
Por otro lado, un estudio de 2008 investigó el riesgo de cáncer tras la exposición a tratamientos de inducción de la ovulación. Los resultados indicaron que las mujeres que usaron medicamentos inductores de la ovulación tenían un mayor riesgo de cáncer en cualquier sitio, con una razón de riesgo multivariada de 1.36 (intervalo de confianza del 95%: 1.06-1.74). (24)
Es importante señalar que la infertilidad en sí misma es un factor de riesgo conocido para el cáncer de ovario, lo que complica la evaluación de los efectos independientes de los medicamentos de fertilidad. Algunos estudios han propuesto que la causa subyacente de la infertilidad, más que los medicamentos utilizados en el tratamiento, podría contribuir al aumento del riesgo de cáncer. (24)
En resumen, si bien ciertos estudios sugieren una posible asociación entre los medicamentos inductores de ovulación y un mayor riesgo de cáncer de ovario, la evidencia no es definitiva. El riesgo potencial parece estar influenciado por factores como el tipo de medicamento de fertilidad utilizado, la duración del tratamiento y la causa subyacente de la infertilidad

Se han objetivado factores geográficos que influyen en la incidencia de cáncer de ovario, siendo más frecuente en Norte América y el norte de Europa con una incidencia de 13.3/100.000 mujeres, probablemente secundarios a alteraciones genéticas, dieta o exposición a determinados factores ambientales que potencialmente podrían influir en el desarrollo del cáncer de ovario. (25)

La salpinguectomía se ha asociado una disminución del riesgo de cáncer de ovario. Se ha reportado una disminución de más del 80% del riesgo tras este procedimiento. (26)
Aquellas pacientes sometidas a una histerectomía asociada a salpinguectomía, salpinguectomía aislada o anexectomía presentan una disminución de riesgo de cáncer epitelial de ovario que

podría reducir la incidencia de cáncer de ovario avanzado en un 20 – 40% en los próximos 20 años. (27,28)
La salpinguectomía es un procedimiento seguro y no se relaciona con un inicio temprano de la menopausia si se preserva la función ovárica. (26)
El Colegio Americano de Obstetricia y Ginecología (ACOG) sugieren la realización de salpinguectomía oportunista durante la cirugía pélvica por otras indicaciones como una estrategia para la prevención del cáncer de ovario. (29)

1.3. CLASIFICACIÓN HISTOLÓGICA

El cáncer de ovario es una enfermedad heterogénea que incluye varios subtipos histológicos. Es importante clasificar estas neoplasias según su biología, ya que de ello se desprenden los diferentes factores de riesgo epidemiológicos y genéticos, las lesiones precursoras, los patrones de diseminación la biología molecular y la respuesta de la enfermedad al tratamiento y al pronóstico.
Cada uno tiene características moleculares, clínicas e histopatológicas únicas. La histología del cáncer de ovario se clasifica principalmente en tumores epiteliales, tumores de células germinales y tumores de los cordones sexuales-estromales. A continuación, se presenta un resumen de estas categorías:

1. **Tumores Epiteliales del Ovario**
   Comprenden aproximadamente el 90% de los casos de cáncer de ovario. Probablemente derivados del epitelio de las trompas de Falopio, la superficie ovárica o quistes de inclusión peritoneal.
   Subtipos:
   1. **Tumores Serosos**
      - **Carcinoma Seroso de Alto Grado (HGSC) (70 – 80%):**
        Es el subtipo más común y agresivo. Caracterizado por mutaciones en TP53 e inestabilidad genómica.
        Características Histológicas: Estructuras papilares, alta actividad mitótica y láminas sólidas de células malignas.
      - **Carcinoma Seroso de Bajo Grado (LGSC) (< 5%):**
        Menos agresivo, asociado a mutaciones en KRAS, BRAF y ERBB2.
        Características Histológicas: Células pequeñas y uniformes con mínima atipia nuclear.
   2. **Carcinoma Endometrioide (10%):**
      Asociado a endometriosis y mutaciones en PTEN, ARID1A y PIK3CA.
      Características Histológicas: Estructuras glandulares que se asemejan al carcinoma endometrial.
   3. **Carcinoma de Células Claras (10%):**
      Asociado a la endometriosis.
      Características Histológicas: Células con citoplasma claro y apariencia de "clavo de tachuela" (hobnail).
   4. **Carcinoma Mucinoso (3%):**
      Poco frecuente. Descartar origen metastásico, principalmente del tracto gastrointestinal.
      Características Histológicas: Células columnares altas con mucina intracelular.
   5. **Tumores de Células Transicionales (Brenner):**
      Subtipo raro con nidos de células epiteliales transicionales. Frecuentemente benigno.

2. Tumores de Células Germinales

Comprenden el 5-10% de los casos de cáncer de ovario.

Derivados de las células germinales del ovario, típicamente afectan a mujeres jóvenes.

Subtipos:

1. **Disgerminoma:**
   Análogo al seminoma en hombres.
   Características Histológicas: Células grandes y redondas con citoplasma claro y núcleos centrales.
2. **Tumor del Saco Vitelino (Tumor del Seno Endodérmico):**
   Patognomónico la elevación de los niveles de alfa-fetoproteína (AFP).
   Características Histológicas: Cuerpos de Schiller-Duval (estructuras glomeruloides).
6. **Teratoma:**
   Compuesto por tejidos de las tres capas germinales (ectodermo, mesodermo y endodermo).
   - **Teratoma Inmaduro:** Contiene tejidos embrionarios o fetales.
   - **Teratoma Maduro (Quiste Dermoide):** Benigno y contiene tejidos maduros como pelo, piel o dientes.
7. **Carcinoma Embrionario:**
   Raro, agresivo y a menudo produce hCG y AFP.
   Características Histológicas: Láminas de células grandes y no diferenciadas.

3. Tumores de los Cordones Sexuales-Estromales

Comprenden el 5-10% de los casos de cáncer de ovario. Derivados del estroma ovárico o los cordones sexuales.

Subtipos:

1. **Tumores de Células de la Granulosa:**
   Tipo Adulto:
   Asociado a la producción de estrógenos e hiperplasia endometrial.
   Características Histológicas: Cuerpos de Call-Exner (estructuras foliculares pequeñas).
2. **Tumores Tecoma-Fibroma:**
   Benignos, a menudo hormonales (productores de estrógenos).
   Características Histológicas: Células fusiformes con citoplasma rico en lípidos.
3. **Tumores de Células de Sertoli-Leydig:**
   Tumores poco frecuentes que pueden producir virilización debido a la producción de andrógenos.
   Características Histológicas: Estructuras tubulares similares a las células de Sertoli y células de Leydig con citoplasma eosinofílico.

4. Tumores Metastásicos al Ovario

- **Tumor de Krukenberg:**
  Metástasis de cánceres primarios del tracto gastrointestinal, especialmente adenocarcinoma gástrico.
  Características Histológicas: Células en anillo de sello con mucina.

El subtipo histológico influye en las decisiones terapéuticas y el pronóstico. (30–33)

En la siguiente tabla se muestran las principales características inmunohistoquímicas y la biología molecular de los diferentes tipos histológicos. (33)

TIPOS HISTOLÓGICOS	INMUNOHISTOQUIMICA	ALTERACIONES GENÉTICAS
Seroso alto grado	P53+, WT1 +, PAX8 +. Ki67 elevado	TP53 BRCA 1, 2
Seroso bajo grado	WT1 +, PAX8 +, P53wt Ki67 bajo	BRAF KRAS
Endometroide	RE +, PAX 8+, Vimentina +, WT1 -, P53wt	PTEN CTNNB - 1
Células claras	HNF beta +, WT1 -, RE -	KRAS PTEN PIK3CA
Mucinoso	CK20+, cdx2+, CK7+, RE -, WT1 -	KRAS

Tabla 2: Perfil inmunohistoquímico y mutaciones genéticas en los subtipos histológicos de cáncer de ovario

1.4. TEORIAS CARCINOGÉNESIS

- Teoría de la ovulación constante:

  Durante la ovulación se produce un trauma en la superficie ovárica que se repara inmediatamente. Esto se produce de forma repetida durante la vida fértil de la mujer, hecho que puede incurrir en un daño en el ADN celular.

  Este daño celular se deriva de la invaginación estromal, formando los llamados quistes de inclusión cortical. Estos quistes al estar en contacto con el microambiente estromaly la estimulación hormonal se produce la proliferación celular. (4,34)

  Los tumores ováricos suelen presentarse en forma de masa ovárica con afectación de la superficie peritoneal. No obstante, el carcinoma epitelial ovárico muestra un aspecto morfológico diferente a las células que encontramos en el tejido ovárico compuesto principalmente por células germinales y estromales no encontrándose células epiteliales.

  Esta teoría de la "constante ovulación" fue propuesta por Fathalla. Según ella, la ovulación genera un trauma repetido en la superficie ovárica, y es el proceso de reparación continuado el que ocasiona un daño en el ADN con la consiguiente transformación de las células del epitelio de superficie ovárica.

  Esta teoría es concordante con los datos epidemiológicos disponibles, en los que el número de ovulaciones incrementa el riesgo de cáncer de ovario. (35,36)

  No obstante, esta teoría presenta una serie de inconsistencias:

  a. La metaplasia mülleriana debería presentarse, al menos de forma temporal, en fenotipos intermediarios híbrido con expresión de marcadores müllerianos y de células de la superficie ovárica, pero este hallazgo es extraordinario.(37)
  b. Las células de la superficie ovárica son indistinguibles del mesotelio, y su transformación tumoral no es similar a la de los mesoteliomas como cabría esperar.
  c. Los testículos se encuentran recubiertos por mesotelio modificado denominado la túnica albugínea, que presenta escaso desarrollo de enfermedad tumoral.

d. No hay prácticamente descritas lesiones preinvasivas afectando las células de la superficie ovárica o los quistes de inclusión. (38)
e. Los escasos estudios moleculares existentes no han demostrado diferencias en la expresión de genes disreguladores comúnmente encontrados en el carcinoma epitelial de ovario, como la sobre – expresión de p53 o la mutación TP53(39)
f. Las pacientes con síndrome de ovario poliquístico presentan un mayor riesgo de cáncer de ovario, pese a que experimentan un menor número de ovulaciones. (33,34)

- Teoría del origen tubárico de los carcinomas serosos:

En 2001, se describe la presencia de lesiones displásicas y lesiones de carcinoma seroso de alto grado en el epitelio de las trompas de Falopio de pacientes sometidas a salpingooforectomía por presentar la mutación germinal en los genes BRCA1 y BRCA2. (40,41)
Estudios posteriores han confirmado la presencia de estas lesiones denominadas como "carcinoma intraepitelial seroso en trompa" (STIC). (42,43)
En aquellos estudios en los que las trompas eran cuidadosamente evaluadas siguiendo el protocolo de estudio mediante sección y examen exhaustivo de la parte final de las fimbrias, se evidenció que estos hallazgos no sólo estaban presentes en las pacientes portadoras de esta mutación, sino también en el 50 – 60% de las pacientes con cáncer seroso de ovario de alto grado esporádico.
Además de la concordancia histológica, se ha objetivado la presencia de las mismas alteraciones moleculares, expresión de TP 53, así como p16, FAS, Rsf – 1 y CCNE - 1.
La expresión de TP53 es una respuesta que muestra daños en el ADN de las células epiteliales tubáricas debido a la exposición a citoquinas y oxidantes. No obstante, aproximadamente el 50% de las mutaciones de TP53 acaban convirtiéndose en cancerosas. (34,44)
Debido a estos hallazgos, se propone que la implantación de células malignas desde STIC al ovario desarrolla las masas tumorales en el ovario. Es decir, durante la ovulación se adhieren al epitelio de la superficie ovárica clusters de células desde la mucosa tubárica. Del mismo modo, células procedentes de la superficie ovárica se desprenden y ocasionan lesiones en la superficie peritoneal. (45–47)
No obstante, esta teoría también presenta incongruencias, ya que hasta en un 30% de las pacientes con cáncer de ovario no se encuentran las lesiones descritas en la superficie tubárica, sobre todo en aquellos tumores seroso de alto grado con patrón sólido, pseudoendometroide o patrón de crecimiento transicional. (48)
Este 30% en el que no se identifica el STIC, podría estar constituido por una lesión tan pequeña que no se identificara incluso aplicando el protocolo exhaustivo de evaluación de las fimbrias, o que el origen tumoral fuera el peritoneo (carcinoma peritoneal primario) o procediera de los quistes de inclusión y del daño continuado de la superficie ovárica debido a la ovulación, lo que nos impide descartar totalmente la teoría propuesta por Fathalla, que además es consistente con la epidemiología de la enfermedad, y con que aquellas intervenciones que disminuyen el número de ovulaciones, como la anticoncepción hormonal o los embarazos, disminuyen la incidencia de cáncer de ovario.
El 70 – 80% de los STIC se originan en la región de la fimbria, la zona de la trompa más cercana al ovario, y, por tanto, expuesta a los mismos factores estresantes del

ovario. Esta zona, además, se encuentra altamente vascularizada, por lo que se facilitan las metástasis desde el ovario hacia el torrente sanguíneo.(49)
Este hecho se encuentra respaldado por la expresión de genes concordante entre el carcinoma seroso de alto grado ovárico y las estructuras con un origen Mülleriano como la trompa, y no con las estructuras con un origen mesotelial/urogenital u ovárico. De acuerdo con ello, expresando marcadores inmunohistoquímicos como el PAX8, pero no marcadores mesoteliales como la calretinina. (50,51)

- Teoría de las dos vías:

En 2004, Kurman y Shih dividen el cáncer de ovario en dos tipos:
Tipo 1: seroso de bajo grado, mucinoso, endometroide, células claras y tipos histológicos transicionales.
Tipo 2: seroso de alto grado, indiferenciados y carcinosarcomas.
En el tipo 1, las lesiones precancerosas se originan en el ovario, presentan un crecimiento lento, normalmente se diagnostican limitadas al ovario y son genéticamente estables. (52)
La patogénesis es mediante la vía clásica, en la que los quistes de inclusión de la superficie epitelial ovárica reciben un estímulo para la proliferación que en ocasiones pueden desarrollar células cancerosas. Las mutaciones en este tipo de cáncer corresponden a KRAS y BRAF. Ambos activan la vía oncogénica MAPK. (34,49)
El tipo 2 se origina fuera del ovario, en la trompa de Falopio. Los tipos histológicos englobados en este grupo son cánceres más agresivos, de crecimiento rápido, que se diagnostican en estadios avanzados y genéticamente más inestables.
La mutación más frecuentemente encontrada en este grupo es en TP53 (50 – 80%), Her2/neu (10 – 20%) y AKT (12 – 18%). Aproximadamente un 50% de estos cánceres se relacionan con la mutación en el gen BRCA1/2. (4,49,52)

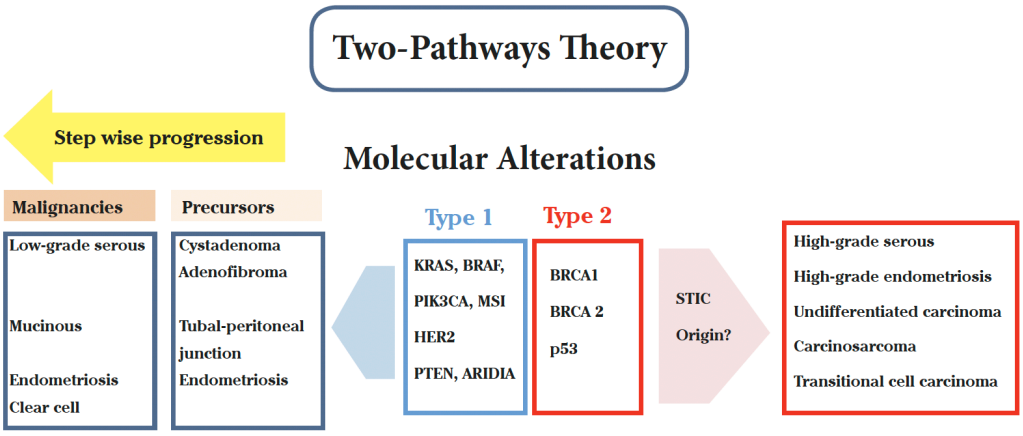


Figura 2: La teoría de las dos vías del cáncer de ovario. Imagen obtenida de: Budiana ING, Angelina M, Pemayun TGA. Ovarian cancer: Pathogenesis and current recommendations for prophylactic surgery. J Turk Ger Gynecol Assoc. 2019 Feb 26;20(1):47-54. doi: 10.4274/jtgga.galenos.2018.2018.0119. Epub 2018 Oct 26. PMID: 30362670; PMCID: PMC6501866.

1.5. ESTADIFICACIÓN.

El sistema de estadificación de la Federación Internacional de Ginecología y Obstetricia (FIGO) combina la clasificación del carcinoma de ovario, trompa de Falopio y peritoneo, y se basa principalmente en los hallazgos obtenidos en la exploración quirúrgica.
La tabla 2 muestra la estadificación FIGO presentada en 2014 con su equivalencia en el sistema TNM (Tumor, Node, Metastasis Classification System), dentro de la "Union for International Cancer Control" (UICC).

El sistema TNM describe la extensión de la enfermedad desde la localización primaria basado en el tamaño y la extensión del tumor primario (T), afectación de ganglios linfáticos (N) y la presencia de metástasis a distancia (M).

Stage I: Tumor confined to ovaries or fallopian tube(s)	**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:	
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**
Stage IVA: Pleural effusion with positive cytology	
Stage IVB: Parenchymal metastases and metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)	

Tabla 3: Estadificación FIGO cáncer de ovario, trompa de Falopio y primario peritoneal con su correlación en el TNM.
Berek JS, Renz M, Kehoe S, Kumar L, Friedlander M. Cancer of the ovary, fallopian tube, and peritoneum: 2021 update. Int J Gynaecol Obstet. 2021 Oct;155 Suppl 1(Suppl 1):61-85. doi: 10.1002/ijgo.13878. PMID: 34669199; PMCID: PMC9298325

1.6. FISIOPATOLOGÍA CARCINOMATOSIS PERITONEAL

Las vías de diseminación del cáncer de ovario son las siguientes:

- Extensión directa a órganos vecinos.
- Vía linfática: a través del drenaje linfático ovárico pudiendo desarrollar metástasis linfáticas en los siguientes territorios; para – aórticos, inguinales e iliacos internos y externos.
- Por exfoliación y diseminación de clonas de células hacia la cavidad peritoneal.
- Vía hematógena que condiciona la metástasis en órganos sólidos.

Por estas diferentes vías de diseminación se desarrolla la carcinomatosis peritoneal, en un proceso que se encuentra mediado por diferentes procesos moleculares y celulares.

La fisiopatología de la carcinomatosis peritoneal es compleja. Los mecanismos de diseminación peritoneal fueron descritos por Y. Yonemura. (53)

1. Desprendimiento de las células tumorales

El desprendimiento inicial de las células tumorales de la superficie serosa del tumor primario implica la supresión de la molécula E-cadherina, un importante mediador de la adhesión celular. Esta supresión está asociada a alteraciones genéticas en el gen que codifica esta molécula, así como a la sobreexpresión de S100-A4, una proteína implicada en la motilidad celular por su capacidad de activar la miosina no muscular. La combinación de una baja expresión de E-

cadherina y una alta expresión de S100-A4 se asocia a adenocarcinomas pobremente diferenciados y puede ser un predictor de carcinomatosis peritoneal.
No obstante, las células tumorales expresan numerosas integrinas y cadherinas, ICAM – 1 y VCAM – 1 que favorecen la adhesión a la superficie peritoneal.
Tras desprenderse, las células tumorales deben sobrevivir en el fluido peritoneal y colonizar nuevas áreas. Existen dos principales mecanismos que facilitan esta diseminación:

2. Mecanismos de Diseminación

a) Vía Transmesotelial

- Barreras Mesoteliales: Las células mesoteliales forman una "barrera plasmático-peritoneal" que regula el intercambio de nutrientes y oxígeno entre el espacio submesotelial y la cavidad peritoneal, además de prevenir la invasión tumoral.
- Adhesión Tumoral: Las células tumorales logran atravesar esta barrera mediante moléculas adhesivas como CD44, facilitadas por citoquinas tumorales que inducen contracción de las células mesoteliales.
- Invasión Submesotelial: Una vez alcanzado el espacio submesotelial, las células tumorales se adhieren a la membrana basal mediante integrinas, moléculas clave cuya sobreexpresión está estrechamente relacionada con la capacidad de diseminación peritoneal.
- Proliferación y Angiogénesis: En este entorno, las células liberan factores como el VEGF (vascular endothelial growth factor), que promueven la neoangiogénesis, debilitan la barrera plasmático-peritoneal y fomentan la proliferación celular.

b) Vía Translinfática

- Acceso Linfático: Las células tumorales alcanzan el espacio submesotelial a través de orificios linfáticos, conocidos como stomata, presentes en la serosa peritoneal, particularmente en el epiplón mayor, apéndices epiploicos, peritoneo pélvico, peritoneo diafragmático, ligamento falciforme y el mesenterio del intestino delgado.
- Manchas Lechosas ("Milky Spots"): Estas estructuras submesoteliales, ricas en macrófagos y linfocitos T y B, juegan un rol inmunológico crítico. Sin embargo, también proporcionan una vía para que las células tumorales accedan a los vasos linfáticos y proliferen mediante la neoangiogénesis.

c) Transición mesotelial a mesenquimal (MMT).

Es un proceso clave en la progresión de la carcinomatosis peritoneal, en el cual las células mesoteliales pierden sus características epiteliales y adquieren propiedades mesenquimales. Este cambio es impulsado por señales provenientes de células tumorales, como el factor de crecimiento transformante beta (TGF-β) y diversas citoquinas inflamatorias.
Esto favorece los siguientes cambios:

- Pérdida de Adhesión Epitelial: Las células mesoteliales pierden moléculas de adhesión intercelular como la E-cadherina, lo que reduce su cohesión.
- Ganancia de Características Mesenquimales: Expresan marcadores como la vimentina y la α-actina de músculo liso, aumentando su capacidad de migración e invasión.
- Reorganización del Citoesqueleto: Adquieren una morfología más alargada, característica de las células mesenquimales.

Estos cambios facilitan el desarrollo de la carcinomatosis peritoneal:

- **Remodelación de la Matriz Extracelular (ECM)**:
  Las células mesoteliales transformadas remodelan la ECM al liberar enzimas como las metaloproteinasas de matriz (MMPs), facilitando la invasión de las células tumorales.

Esta remodelación genera un entorno que favorece la adhesión y la proliferación tumoral.

- **Promoción de la Angiogénesis**:
  Las células mesoteliales en transición secretan factores angiogénicos, como el VEGF, que estimulan la formación de nuevos vasos sanguíneos. Esto asegura el suministro de nutrientes y oxígeno a las células tumorales en expansión.
- **Invasión Tumoral**:
  La pérdida de la barrera protectora epitelial en el peritoneo facilita el acceso de las células tumorales al espacio submesotelial.
  La interacción entre integrinas en las células tumorales y los componentes remodelados de la ECM amplifica la diseminación.(54,55)

El desarrollo de la ascitis en estas pacientes viene producido por la secreción por parte de las células tumorales de VEGF y IL – 6, lo que conlleva un incremento en la permeabilidad vascular y la ruptura de la homeostasis.
La acumulación de fluidos en la cavidad peritoneal (ascitis) crea un nicho favorable para la supervivencia de las células tumorales y la extensión de estas en la superficie peritoneal.

Estos mecanismos contribuyen a la diseminación progresiva de las células tumorales en el peritoneo, permitiendo el desarrollo de múltiples lesiones metastásicas. Estas interacciones complejas subrayan la importancia de las moléculas de adhesión, factores de crecimiento y la inmunomodulación del peritoneo en la patogenia de la CP.

La explicación de ambos mecanismos se encuentra resumido en la Figura 3.

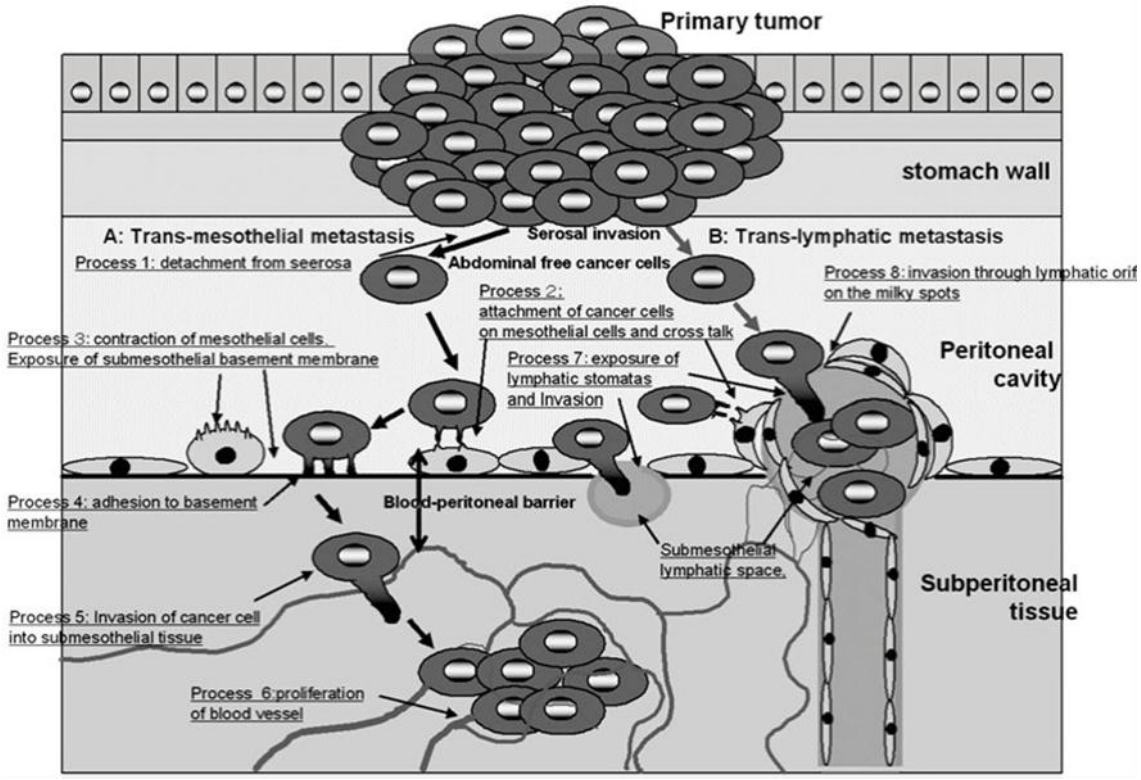


Figura 3: Esquema de los mecanismos supuestos para el desarrollo de metástasis peritoneal. Tomado de Yonemura. (53)

1.7. PRESENTACIÓN CLÍNICA

La presentación clínica de la carcinomatosis peritoneal es variable, depende de la extensión de la enfermedad.

La sintomatología es insidiosa. La duración de la presencia de estos síntomas no difiere entre aquellas con estadios iniciales y aquellas que se presentan estadios avanzados.

Frecuentemente, los tumores serosos de bajo grado, mucinosos, endometroides o células claras suelen presentarse en estadios iniciales, mientras que los serosos de alto grado se encuentran en estadios avanzados, debido a su facilidad para diseminarse por ser tumores más agresivos. El 80% de los tumores serosos de alto grado de ovario se presentan en estadio III o IV al diagnóstico.

Los síntomas que presentan son inespecíficos; dolor abdominal, alteraciones menstruales, dispepsia, síntomas digestivos leves - moderados.

Durante las etapas iniciales cursa de forma asintomática. Posteriormente inicia una clínica inespecífica:

- Síntomas abdominales: distensión abdominal y plenitud gástrica temprana, secundarios a la presencia de ascitis y al crecimiento de los nódulos peritoneales. Dolor abdominal generalizado secundario a irritación peritoneal o compresión de la masa.
- Síntomas digestivos:
  Las pacientes con carcinomatosis peritoneal pueden presentar náuseas y vómitos como resultado de pseudo-obstrucción u obstrucción intestinal o secundaria al enlentecimiento del tránsito intestinal. Cambios en el hábito intestinal como diarrea o estreñimiento por compresión abdominal consecuencia de la enfermedad peritoneal o de la ascitis.
  Estas pacientes presentan una disminución de la ingesta por la sensación de plenitud gástrica, así como la caquexia producida por la enfermedad avanzada.
- Síntomas constitucionales:
  Cualquier enfermedad oncológica avanzada genera pérdida de peso, anemia o desnutrición debido a la disminución de la ingesta, así como el estado hipercatabólico asociado a las enfermedades oncológicas.
- Síntomas respiratorios:
  El incremento en la ascitis puede ocasionar síntomas respiratorios secundarios al incremento de presión intra - abdominal, o producir derrame pleural por el trasudado a cavidad pleural.
- Síntomas pélvicos:
  Síntomas urinarios debido a la compresión de las masas anexiales incrementando la frecuencia miccional. En aquellos casos con afectación de estructuras pélvicas puede producirse imposibilidad para la micción.
  Sensación de presión pélvica debido a la presencia de masas o líquido en la parte baja del abdomen.

Finalmente, el crecimiento de estos nódulos sobre la superficie intestinal, la infiltración tumoral intestinal o la producción de adherencias secundarias a los tratamientos recibidos pueden condicionar la invasión y la obstrucción, siendo la oclusión intestinal la complicación más frecuente en el cáncer de ovario avanzado (16 - 52%). (56,57)

1.8. DIAGNÓSTICO

La cirugía de citorreducción es el tratamiento de elección para las pacientes con carcinomatosis peritoneal de origen ovárico. Por ello, es fundamental realizar un correcto diagnóstico y evaluar la extensión de la enfermedad para realizar una correcta selección de las pacientes tributarias al tratamiento quirúrgico de la enfermedad.
La exploración física con una correcta anamnesis que identifique los factores de riesgo, la presencia de antecedentes familiares, y una exploración física general asociada a una exploración mamaria, pélvica y rectal.
Los factores en la exploración que orientan hacia malignidad son los siguientes:

- Edad de la paciente
- Status menopáusico
- Bilateralidad
- Fijación clínica del tumor en la exploración.
- Ascitis

Tras realizar la exploración física es conveniente realizar una analítica sanguínea que permita establecer la situación basal y el estado nutricional de la paciente. Así como la determinación de biomarcadores:

a. Marcadores tumorales:
   - Ca 125 (Antígeno del Cáncer 125):
     Es el marcador tumoral utilizado en el diagnóstico y el seguimiento de las pacientes con cáncer de ovario, ya que se encuentra elevado en cerca del 90% de las pacientes en estadios avanzados, y en el 40 – 50% de los estadios iniciales.
     Ha demostrado su validez en la valoración de la respuesta al tratamiento y en la detección de la recurrencia. (58)

   - CEA (Antígeno carcinoembrionario):
     Ratio Ca 125/CEA mayor de 25:1 indica que probablemente sea de origen ginecológico, aunque no permite descartar completamente un origen gastrointestinal.
     Esta ratio se utiliza como un elemento de apoyo en el diagnóstico diferencial de la CP. (59)

   - Ca 19.9 (Antígeno Carbohidrato 19.9)
     La realización de CEA y Ca 19.9 indican la posibilidad de un tumor metastásico de origen digestivo a nivel ovárico que puede imitar un cáncer de ovario avanzado.
     Sin embargo, los tumores mucinosos de ovario se encuentra elevado, probablemente porque este subtipo histológico comparte características con los tumores de origen digestivo.
     En este subgrupo de tumores un valor elevado de este marcador presenta valor pronóstico ya que se relaciona con la extensión de la enfermedad. (59)

   - HE 4 (Proteína del Epidídimo Humano 4):
     El HE 4 se encuentra codificado por el gen WFDC2, el cual se encuentra sobrexpresado en el cáncer de ovario, pero no en tejido sano. Se encuentra elevado en pacientes con cáncer de ovario comparado con controles sanos y con pacientes con enfermedades benignas de ovario, mostrándose con mayor especificidad que el Ca 125 para el diagnóstico diferencial con enfermedades benignas. (60)

Posteriormente se procede a evaluar la extensión extra e intra - abdominal que pueden condicionar la imposibilidad de realizar citorreducción completa (ausencia de residuo tumoral), objetivo que ha demostrado impacto en la supervivencia global (SG) en estas pacientes.
Para la evaluación de la extensión de la enfermedad es necesario conocer las técnicas diagnósticas disponibles:

b. Ultrasonografía: es el primer escalón en el diagnóstico de las pacientes con carcinomatosis peritoneal, permitiendo la evaluación de ascitis, las masas anexiales y los implantes peritoneales a partir de 2 cm.
   Esta técnica presenta una elevada reproducibilidad, inocuidad y bajo coste.
   Con el objetivo de clasificar correctamente las masas anexiales, en el año 2000 el grupo de "Análisis Internacional de Tumores Ováricos" (IOTA, International Ovarian Tumor Analysis) definió las características ecográficas que deben ser evaluadas con la intención de catalogarlas como benignas o malignas.

Característica	Descripción	
Localización	Anexo derecho/izquierdo Douglas (peritoneo) Abdomen/Pelvis	
Aspecto	Sólido Quístico	
Número de lóculos	Uni o multilocular	
Tabiques	Banda de tejido que cruza una masa quística desde su superficie interna hasta el el lado contralateral	Finos Gruesos/regulares
Porción sólida	Tejido ecogénico en el interior de la lesión	
Proyección papilar	Proyección sólida en una cavidad quística de al menos 3 mm de altura	
Sombra acústica	Bandas hipoecoicas detrás de una estructura	Sí/No
Ascitis	Líquido en fondo de saco de Douglas que sobrepasa el fondo uterino	Sí/No

Tabla 4: Características ecográficas evaluadas en una masa anexial.

Pese a los scores ecográficos que permiten una evaluación de las masas anexiales más objetivas, la mayor validez diagnóstica en la evaluación y caracterización de las tumoraciones anexiales es la evaluación subjetiva de un ecografista experto.
En 2008, el grupo IOTA publicó 10 reglas (IOTA Simples Rules) con el propósito de clasificar las masas como benignas o malignas. El estudio de malignidad o benignidad según las "Simples Rules" se considera si cumple tres reglas:

- Regla 1: 1 ó más características de malignidad y ninguna de benignidad, la masa se cataloga como maligna.
- Regla 2: 1 ó más características de benignidad y ninguna de malignidad, la masa se cataloga como benigna.
- Regla 3: si la masa presenta características de benignidad y malignidad, o no aparece ninguna característica de benignidad o malignidad, la masa es inclasificable.

BENIGNIDAD (B)	MALIGNIDAD (M)
B1: Unilocular	M1: Tumor sólido irregular
B2: Presencia de componente sólido < 7 mm de diámetro máximo	M2: Ascitis
B3: Sombra acústica	M3: ≥ 4 papilas
B4: Tumor multilocular regular con diámetro máximo < 100 mm	M4: Tumor sólido irregular multilocular con diámetro máximo > 100 mm.
B5: Mapa color negativo (score color 1)	M5: Mapa color abundante (score color 4)

Tabla 5: Simple Rules IOTA

En 2016, el grupo IOTA añadió a las Simples Rules, la evaluación de la masa en un centro oncológico, estableciendo una probabilidad de masa maligna o benigna dependiendo de si la paciente es estudiada en un centro oncológico o no.(61,62)

El Adnex Model (Assessment of Different Neoplasias in the Adnexa), score publicado en 2014; en este caso se valoran tres predictores clínicos; edad, Ca 125 sérico (UI/mL), tipo de centro de referencia oncológico y seis valores ecográficos; diámetro máximo de la lesión (mm), diámetro máximo de la parte sólida mayor (mm), más de 10 lóculos, número de proyecciones papilares (0, 1, 2, 3, >3), presencia de sombras acústicas, presencia de ascitis.
El Adnex Model además de proporcionar el riesgo de malignidad, benignidad o borderline de una lesión, también nos establece en el caso de malignidad la probabilidad de que se presente en los diferentes estadios. (63)

En 2020, el American College of Radiology (ACR) publicó el Ovarian - Adnexal Reporting Data System (O - RADS), éste clasifica las masas anexiales según 6 categorías desarrollada por el grupo IOTA, e incluye probabilidades o riesgo de malignidad y pautas de manejo según la categoría de riesgo. (64)

O-RADS Score	Risk Category [IOTA Model]	Lexicon Descriptors		Management	
				Pre-menopausal	Post-menopausal
0	Incomplete Evaluation [N/A]	N/A		Repeat study or alternate study	
1	Normal Ovary [N/A]	Follicle defined as a simple cyst ≤ 3 cm		None	N/A
		Corpus Luteum ≤ 3cm			
2	Almost Certainly Benign [< 1%]	Simple cyst	≤ 3 cm	N/A	None
			> 3 cm to 5 cm	None	Follow up in 1 year. *
			> 5 cm but < 10 cm	Follow up in 8 - 12 weeks	
		Classic Benign Lesions	See **Figure 3** for separate descriptors	See **Figure 3** for management strategies	
		Non-simple unilocular cyst, smooth inner margin	≤ 3 cm	None	Follow up in 1 year * If concerning, US specialist or MRI
			> 3 cm but < 10 cm	Follow-up in 8 - 12 weeks If concerning, US specialist	US specialist or MRI
3	Low Risk Malignancy [1-<10%]	Unilocular cyst ≥ 10 cm (simple or non-simple)		US specialist or MRI Management by gynecologist	
		Typical dermoid cysts, endometriomas, hemorrhagic cysts ≥ 10 cm			
		Unilocular cyst, any size with irregular inner wall <3 mm height			
		Multilocular cyst < 10 cm, smooth inner wall, CS = 1-3			
		Solid smooth, any size, CS = 1			
4	Intermediate Risk [10- < 50%]	Multilocular cyst, no solid component	≥ 10 cm, smooth inner wall, CS = 1-3	US specialist or MRI Management by gynecologist with GYN-oncologist consultation or solely by GYN-oncologist	
			Any size, smooth inner wall, CS = 4		
			Any size, irregular inner wall and/or irregular septation, any color score		
		Unilocular cyst with solid component	Any size, 0-3 papillary projections, CS = any		
		Multilocular cyst with solid component	Any size, CS = 1-2		
		Solid	Smooth, any size, CS = 2-3		
5	High Risk [≥ 50%]	Unilocular cyst, any size, ≥ 4 papillary projections, CS = any		GYN-oncologist	
		Multilocular cyst with solid component, any size, CS = 3-4			
		Solid smooth, any size, CS = 4			
		Solid irregular, any size, CS = any			
		Ascites and/or peritoneal nodules**			

Figura 4: Ovarian-Adnexal Reporting and Data System (O-RADS) y el Sistema de manejo. (64)

c. Tomografía computarizada (TC):

Es el método más utilizado en la valoración de la carcinomatosis peritoneal. La utilización de contraste endovenoso permite mejorar el rendimiento diagnóstico de la prueba.

La sensibilidad (S) del TC varía entre los diferentes estudios entre 64 – 93%, y la especificidad (E) se encuentra entre el 92 – 100%. (65)

Esta variación en la sensibilidad es consecuencia de la limitación que presenta la técnica dependiendo del tamaño y de la localización de las lesiones:

- Lesiones mayores de 5 mm, las de menor tamaño difícilmente van a ser visualizadas mediante esta técnica.
- Determinadas zonas presentan una limitación de evaluación, como son las cúpulas diafragmáticas, el mesenterio, los espacios paracólicos y la superficie intestinal debido a la superposición de diferentes estructuras.
- Tumores con densidad similar al peritoneo pueden dificultar la identificación de las lesiones peritoneales.
- Una ascitis abundante o poco líquido también influye negativamente en la identificación de las lesiones.
- En las pacientes sometidas a tratamiento quirúrgico u oncológico la diferencia de las lesiones fibróticas o residuales de aquellas con tumor viable es un reto para los radiólogos. (65)

En determinados centros se combina con la utilización de contaste oral para delimitar la superficie intestinal y valorar con mayor exactitud la superficie visceral, uno de los factores limitantes de esta técnica, ya que la precisión del TC es menor en la zona media del abdomen.

En un estudio comparativo en el que se comparó enterografía y el TC con contraste en el diagnóstico de la carcinomatosis de origen ovárico para cuantificar la carga de enfermedad, se evidenció una mayor sensibilidad de la enterografía respecto al TC con contraste; S de 64 – 71% respecto al 32 – 39% y una E del 82 – 89% vs 96 – 97% respectivamente.
Al comparar la exactitud diagnóstica de enfermedad a nivel de la superficie intestinal se muestra una mayor sensibilidad de la enterografía con una S de 39% (IC al 95% 28 – 51%) y una E 97% (IC al 95% 93 – 100%), evidenciando que el TC con contraste no realiza una correcta evaluación de la superficie intestinal y el mesenterio, mostrándose la enterografía como una técnica superior en la evaluación de la carcinomatosis peritoneal. (66)
En resumen, la sensibilidad del TC con contraste se encuentra íntimamente relacionada con el tamaño del implante peritoneal; siendo del 25% para implantes menores de 0.5 cm, alcanzando el 90% para implantes de 5 cm o mayor. Es por este motivo que el TC puede infraestimar la extensión de la enfermedad hasta en el 70% de los casos. (67–69)

d. Resonancia magnética (RMN): la sensibilidad de la RMN para la detección de implantes peritoneales tras administración de gadolinio en secuencias obtenidas en supresión grasa es mayor que para la RMN convencional o el TC.
Debido a la mayor capacidad de contraste del tejido graso permite mejorar la distinción de los implantes tumorales del tejido adyacente, facilitando la identificación de implantes de menor tamaño.
La utilización de las diferentes modalidades permite mejorar el rendimiento diagnóstico de la técnica:
    - Difusión: las áreas hiperrefringentes se corresponden con los implantes tumorales, lo que mejora la detección a nivel de la superficie intestinal y del mesenterio, áreas con exploración limitada mediante el TC.
    - Realce dinámico por contraste: evalúa la vascularización de las lesiones gracias a los diferentes patrones de realce.
    - Espectroscopia y secuencias avanzadas: podrían proporcionar datos moleculares y del metabolismo de las lesiones mejorando la caracterización en el futuro.

    La sensibilidad y la especificidad presentan valores del 90% y del 96.5% respectivamente. (70–72)
    Otra ventaja para tener en cuenta de la técnica es la no utilización de radiación ionizante, dato para tener en cuenta en pacientes jóvenes o que precisen de la realización de múltiples pruebas de imagen.
    En determinados tumores, la realización de la RMN presenta ventajas en la detección de las lesiones, como ocurre en los tumores mucinosos, en los que el TC presenta menor sensibilidad, y en cambio en la RMN pueden ser mejor definidos. (73–75)
    No obstante, la utilización de esta técnica se encuentra actualmente limitada debido a que su coste y tiempo en la realización de esta es superior al TC. Del mismo modo que la complejidad es mayor al necesitar periodos de apnea para la correcta evaluación y la imposibilidad de realización en pacientes con claustrofobia.
    Por todo ello, su uso en la práctica clínica se encuentra limitado a casos en los que el TC no sea concluyente o en escenarios clínicos que precisen de mayor precisión diagnóstica.

e. Tomografía por emisión de positrones (PET TC): mediante el uso del radiotrazador de 10 - fluorodesoxiglucosa (FDG) administrado de forma intravenosa permite medir la actividad metabólica de las diferentes células, en concreto de las células tumorales.
Esta técnica presenta la ventaja de detectar lesiones de menor tamaño y diferenciar entre lesiones benignas y malignas en casos de cambios postratamiento.
Del mismo modo es capaz de identificar anormalidades metabólicas no asociadas a alteraciones anatómicas como la afectación ganglionar. (76)
No obstante, esta evaluación metabólica presenta falsos positivos en aquellas pacientes con procesos inflamatorios, infecciosos o con cualquier patología que incremente la actividad metabólica de los tejidos. (77)
Estas imágenes funcionales se fusionan con las imágenes obtenidas mediante TC alcanzando una exactitud diagnóstica similar a la RMN con difusión.
Su principal limitación se encuentra en tumores de bajo grado debido a la menor actividad metabólica de estas células.
El PET TC se muestra como una técnica útil en la valoración de enfermedad extra - abdominal.
La sensibilidad del PET TC para las lesiones peritoneales alcanza el 76.19% con una especificidad del 95.65%, alcanzando el 100% en ambas para la detección de enfermedad pélvica. (78,79)
Actualmente se están evaluando la utilización de diferentes radiotrazadores que pueden mejorar la sensibilidad y la especificidad de esta técnica. (80,81)

f. Otras pruebas de imagen:
    - La mamografía debe realizarse en aquellas pacientes en las que la prevalencia de cáncer de mama sea elevada y no hayan realizado un correcto cribado.
    - La colonoscopia está indicada en aquellas pacientes con sintomatología compatible con afectación intestinal como puede ser hematoquecia, cambios en el hábito intestinal o sintomatología obstructiva como distensión abdominal, estreñimiento o vómitos.
      Se recomienda realizar esta técnica en pacientes con sospecha de afectación intestinal en las pruebas de imagen o en aquellas pacientes en las que sea previsible la resección intestinal durante el procedimiento quirúrgico. (82,83)
      No obstante, cabe destacar la posibilidad de la presencia de un tumor sincrónico gastro – intestinal o la posibilidad de que la masa anexial sea metastásica. (84,85)

Las regiones limitantes que debemos evaluar previamente para la correcta decisión terapéutica es la superficie intestinal del intestino delgado, mesenterio y región epigástrica. (86)
Otro método de evaluación de la extensión de la enfermedad peritoneal es la laparoscopia.

g. Laparoscopia diagnóstica:
   La laparoscopia se utiliza en el proceso diagnóstico del cáncer de ovario avanzado con el objetivo de determinar la carga de enfermedad por su impacto pronóstico y determinar la posibilidad de realizar una citorreducción completa.(87,88)
   La realización de esta técnica permite la visualización directa de la cavidad abdominal, facilitando la visualización de áreas que se consideran limitantes en la citorreducción, evitando laparotomías innecesarias en pacientes con enfermedad irresecable. (86,88)
   Para ello, se utilizan dos scores:
   - Score de Fagotti:

En 2008 se presenta un estudio de Fagotti et al., en el que se incluyen 150 pacientes con cáncer de ovario avanzado (estadio FIGO III/IV) y pacientes con respuesta parcial tras tratamiento con quimioterapia neoadyuvante.
Este estudio incluye 6 parámetros y cada parámetro se puntúa con 0 ó 2

- Omental cake:
  - 0: no afectación
  - 2: masa omental.
- Carcinomatosis peritoneal:
  - 0: no afectación o afectación limitada.
  - 2: afectación difusa
- Carcinomatosis diafragmática:
  - 0: no afectación.
  - 2: afectación.
- Retracción mesentérica:
  - 0: mesenterio normal.
  - 2: nódulos o retracción mesentérica.
- Infiltración estómago:
  - 0: no afectación
  - 2: tumor en la superficie gástrica.
- Afectación intestinal:
  - 0: no afectación.
  - 2: tumor en la superficie intestinal
- Metástasis hepática;
  - 0: no afectación
  - 2: presencia de tumor en superficie hepática.

Se muestra que el 100% de las pacientes con un score de 8 presenta una cirugía incompleta, con un valor predictivo positivo (VPP) de 100%, valor predictivo negativo de 50.8% con una tasa de cirugías incompletas del 40.5%.(89,90)

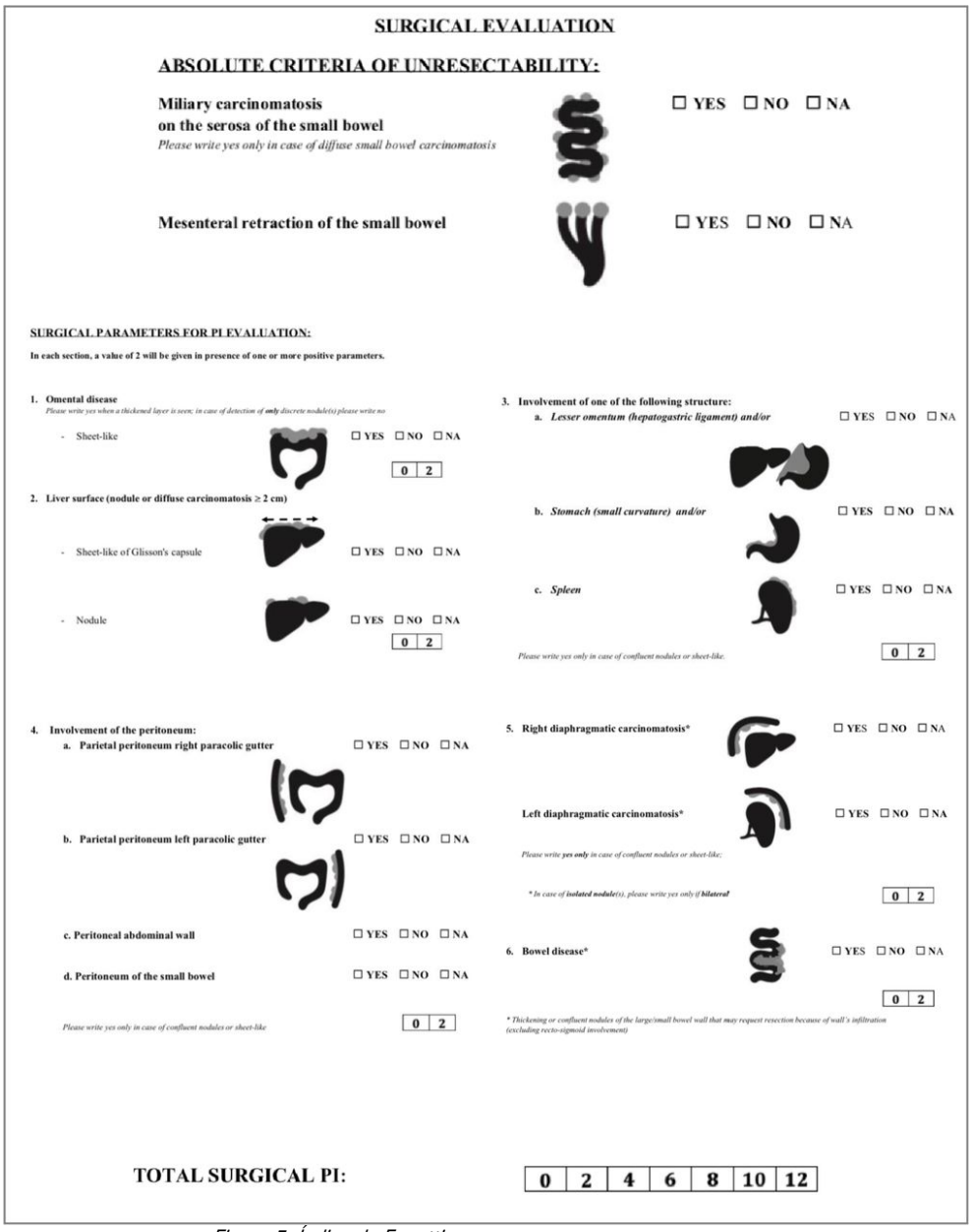


Figura 5: Índice de Fagotti.

- Índice de Carcinomatosis Peritoneal de Sugarbaker (ICP):
  Índice descrito por Sugarbaker para carcinomatosis peritoneal de origen colorrectal. Este índice evalúa de forma cuantitativa la distribución del tumor y el tamaño de los implantes en 13 regiones abdominopélvicos; 9 corresponden a regiones abdomino – pélvicas y 4 a la superficie del intestino delgado.
  A las lesiones localizadas en cada región se le proporciona una puntuación:
  - 0: ausencia de tumor visible
  - 1: tumor ≤ 0.5 cm.
  - 2: tumor de 0.5 cm a 5 cm
  - 3: tumor > 5 cm o confluente.

  Este score proporciona un valor entre 0 – 39.
  Esto permite realizar un índice reproducible entre diferentes centros, además de que tiene relación con el pronóstico. (69)

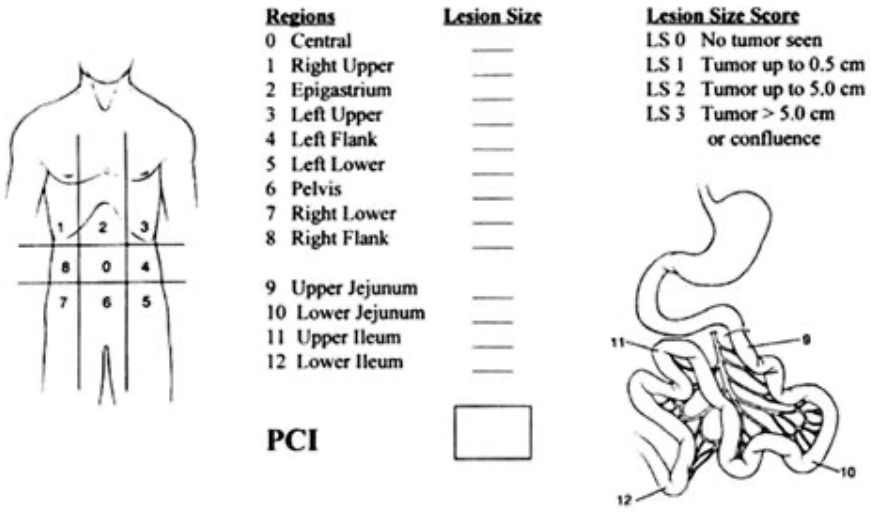


Figura 6: Índice de Carcinomatosis Peritoneal de Sugarbaker.

1.9. TRATAMIENTO.

El pronóstico del cáncer de ovario avanzado depende de:

- Estadio tumoral al diagnóstico.
- Subtipo histológico y grado tumoral
- Volumen de enfermedad tumoral al diagnóstico.
- Performance status del paciente
- Tumor residual tras el tratamiento quirúrgico
- Ca125 elevado en el período postquirúrgico y que no se consigue normalizar tras tres ciclos de tratamiento quimioterápico.
- Factores genéticos; sobre – expresión de TP53 (proteína tumoral 53) y EGFR (receptor del factor de crecimiento epidérmico)(91,92)

El tratamiento del cáncer de ovario avanzado es multifactorial, dependiendo de la situación basal de la enferma, de las características propias de la enfermedad, tales como la extensión de esta y el perfil molecular, y de la realización del tratamiento indicado en un centro de referencia con un equipo especializado.(93)

En la Unidad Multidisciplinar de Carcinomatosis Peritoneal del Hospital General Universitario de Castellón se establecen una serie de criterios de irresecabilidad, determinados mediante prueba de imagen y en el procedimiento quirúrgico. Se muestran en la siguiente tabla. (94)

Radiologic-laparoscopic criteria for unresectability

CT scan	Lung metastasis
	Hepatic metastasis in three or more hepatic segments
	Severe hepatic pedicle involvement
	Progression after NACT
Diagnostic laparoscopy	Diffuse serous small bowel disease

CT computed tomography, *NACT* neoadjuvant chemotherapy

Tabla 6: Criterios de irresecabilidad en carcinomatosis peritoneal. (86)

Aquellas pacientes que presentan alguno de los criterios mencionados son remitidas a quimioterapia neoadyuvante. (95,96)

La presencia de enfermedad residual tras la cirugía es uno de los principales factores pronósticos que influyen en el intervalo libre de enfermedad y en la supervivencia global, demostrando que la ausencia de enfermedad tumoral tras la cirugía de citorreducción primaria es un factor pronóstico independiente en los estadios avanzados del cáncer de ovario. (97,98)

En dos estudios realizados por el Gynecologic Oncology Group (GOG) se evidencia una relación entre el tamaño del residuo tumoral y la supervivencia global a 4 años, siendo del 60% para aquellas con residuo tumoral microscópico, 40% con tamaño menor a 2 cm, disminuyendo por debajo del 20% para tamaño superior a 2 cm. Además, Eisenhauer et al., establecieron que la respuesta al tratamiento quimioterápico es del 84% en pacientes con cirugía óptima, disminuyendo al 44% para pacientes con residuo tumoral mayor a 1 cm. (99–102)

Es por ello por lo que el pilar fundamental del tratamiento del cáncer de ovario avanzado es la cirugía de citorreducción (PDS) completa seguida por tratamiento quimioterápico.(98)

Por tanto, el principio fundamental del procedimiento quirúrgico en cáncer de ovario avanzado es la exéresis de toda la enfermedad macroscópica. Es por ello que además de los procedimientos quirúrgicos estándar como son la histerectomía, la anexectomía, apendicectomía, linfadenectomía pélvica y para – aórtica, omentectomía y resección intestinal, se añaden otros procedimientos como el stripping diafragmático o la resección de mismo, la esplenectomía, la pancreatectomía distal, la resección hepática, la exploración del hilio hepático, y en algunas ocasiones, la vídeo – toracoscopia. Con todos estos procedimientos, las tasas de citorreducción completa y óptima (residuo menor a 1 cm) varían entre el 50 – 80% de las pacientes según la experiencia del equipo quirúrgico. (68,86,97,103)

Debido a la agresividad de la cirugía, debemos tener presente la morbimortalidad generada sobre todo en el subgrupo de aquellas pacientes añosas con escasa resiliencia para la correcta selección de las pacientes. (104,105)

Con el objeto de cuantificar el esfuerzo quirúrgico, la complejidad quirúrgica y el número de procedimientos realizados, se ha descrito por parte de Aletti, un score de complejidad quirúrgica.
Este score cataloga a las pacientes en 3 categorías: alta complejidad con un score por encima de 8, complejidad intermedia de 4 – 8 y baja complejidad igual o menor a 3. (105)

Procedimiento	Puntos
Histerectomía total + Anexectomía bilateral	1
Omentectomía	1
Linfadenectomía pélvica	1
Linfadenectomía para – aórtica	1
Stripping peritoneal pélvico	1
Stripping peritoneal abdominal	1
Anastomosis recto – sigmoidea termino – terminal	3
Resección intestino grueso	2
Stripping diafragmático/resección	2
Esplenectomía	2
Resección hepática	2
Resección intestino delgado	2
Grupos de complejidad quirúrgica	Puntos
1 (bajo)	</= 3
2 (intermedio)	4 – 8
3 (alto)	>/= 8

Tabla 7: Score de complejidad quirúrgica. (104)

Con el uso de este score se evidencia que, a mayor agresividad quirúrgica, mayores tasas de citorreducción completa. Se recomienda el uso de esta clasificación con el objetivo de comparar los diferentes procedimientos quirúrgicos entre los diferentes centros, debido a la elevada heterogeneidad entre los diferentes estudios.

Esta agresividad quirúrgica con el objeto de conseguir la ausencia de residuo tumoral implica la necesidad de evaluar la morbilidad y mortalidad derivada de este tipo de cirugía.
Varios estudios han evaluado los factores de riesgo relacionados con la morbimortalidad postquirúrgica. En el artículo publicado por Aletti et al., se muestra que la edad, un nivel bajo prequirúgico de albúmina, un bajo performance status y una cirugía de alto nivel de complejidad se relaciona con un incremento en la morbilidad y la mortalidad. (104,105)
La correcta selección de las pacientes permite identificar un pequeño grupo de pacientes, aproximadamente el 6.6% de las pacientes con cáncer de ovario avanzado que presentan las siguientes características:

- Edad avanzada (≥ 75 años)
- Elevado volumen tumoral / Estadio FIGO IV
- Performance status bajo (ASA ≥ 3) o un pobre estado nutricional (Albúmina prequirúrgica < 3.0 g/dL)

En este subgrupo de pacientes la obtención de un residuo tumoral bajo o una citorreducción completa no se asocia con un incremento en la supervivencia global, ya que estas pacientes presentan un elevado riesgo de morbilidad perioperatoria. Ésta Alcanza al 63.6% para pacientes con una complejidad quirúrgica elevada, 44.4% en intermedia y al 33.3% para las pacientes con complejidad quirúrgica baja.
Es por ello por lo que en este subgrupo de pacientes es posible que el tratamiento con quimioterapia neoadyuvante sea una opción de tratamiento. (104)

La morbimortalidad derivada de este procedimiento influye en la capacidad de la paciente de recibir el tratamiento quimioterápico. Kumar et al., en 2016 describe un nomograma compuesto por 6 variables: edad, ASA, IMC, estadio FIGO, complejidad quirúrgica y el nivel de albúmina con el objetivo de predecir las complicaciones postquirúrgicas a los 30 días postquirúrgico y la mortalidad a 90 días postquirúrgicos. (106)

La morbimortalidad a los 90 días postquirúrgicos no se relaciona únicamente con las complicaciones secundarias al tratamiento quirúrgico, sino que presenta implicaciones pronósticas al relacionarse con la progresión tumoral, cambios en el objetivo terapéutico y con la tolerancia del paciente a los diferentes tratamientos. (106,107)

Este tipo de nomogramas son útiles para poder seleccionar correctamente a las pacientes que se podrían beneficiar de una cirugía de citorreducción, evitando incrementar la morbilidad y la mortalidad a corto plazo. Esta correcta selección de pacientes es, actualmente, un reto en el tratamiento del cáncer de ovario avanzado. (108)

QUIMIOTERAPIA NEOADYUVANTE:
La otra opción de tratamiento en aquellas pacientes en las que la cirugía citorreductora primaria no es posible por la extensión de la enfermedad o por el estado basal de la paciente, es la administración de quimioterapia neoadyuvante (NACT) seguida de una cirugía de intervalo (IDS). La NAC_T se realiza tras la administración de 3 ciclos de quimioterapia.(109)

La selección de las pacientes depende del performance status de la paciente, de la morbilidad y de la extensión y resecabilidad de la enfermedad.

- Factores relacionados con la enfermedad:
    - Afectación de la arteria mesentérica superior.
    - Infiltración del mesenterio.
    - Carcinomatosis miliar/amplia en intestino delgado.
    - Afectación ganglionar extensa torácica
    - Múltiples metástasis hepáticas y pulmonares
    - Infiltración tumoral de los vasos hepatoduodenales o del tronco celíaco.
    - Metástasis cerebrales.
- Factores relacionados con el paciente:
    - Estado basal deficiente y elevada comorbilidad.
    - No aceptación del paciente de estomas temporales o definitivos.
- Factores relacionados con el equipo quirúrgico:
    - Tasas de citorreducción del equipo quirúrgico.
    - Hospital terciario

Vergote et al., realizó un estudio randomizado comparando la supervivencia entre pacientes sometidas a cirugía primaria y pacientes con cirugía de intervalo. Se incluyeron 718 pacientes en estadio IIIC/IV. La tasa de cirugía completa fue del 19% para cirugía primaria y del 51% para cirugía de intervalo. El resultado obtenido no mostró diferencias estadísticamente significativas entre estos dos grupos.(109)
Posteriormente se ha publicado una revisión de la Cochrane que no muestra diferencias estadísticamente significativas entre las pacientes sometidas a PDS respecto a las pacientes tratadas con NACT en términos de supervivencia global e intervalo libre de enfermedad. No obstante, hay diferencias estadísticamente significativas a favor del tratamiento neoadyuvante:

- Mortalidad postquirúrgica
- Complicaciones quirúrgicas graves
- Necesidad de utilización de estomas
- Resección intestinal.

La conclusión obtenida es que la cirugía de intervalo presenta beneficio en aquellas pacientes en las que no sea posible la cirugía primaria por el elevado riesgo de morbimortalidad. (110)

En el estudio CHORUS publicado en 2015, se comparan los resultados entre estos dos procedimientos en pacientes con un peor performance status (aproximadamente el 50% presentan un ECOG 1) que en otros estudios previos evaluando impacto en supervivencia global, siendo similar entre ambos grupos y con menor morbimortalidad en el grupo de la cirugía de intervalo. (111)

En resumen, el tratamiento óptimo en pacientes diagnosticadas de cáncer de ovario avanzado debe considerarse en base a las características de la paciente, la factibilidad quirúrgica y la biología tumoral.

CITORREDUCCIÓN SECUNDARIA

La probabilidad de recurrencia en el cáncer de ovario avanzado es elevada a pesar del tratamiento óptimo, con una incidencia del 70 – 90% en los primeros dos años. (112,113)
La tasa de recurrencia depende de factores como:

- Estadio al diagnóstico.
- Enfermedad residual tras cirugía.
- Biología y perfil molecular tumoral.
- Respuesta al tratamiento quimioterápico:
    - Platino – sensible; recurrencia ≥ 6 meses tras finalizar el tratamiento quimioterápico.
    - Platino – resistente; recurrencia ≤ 6 meses tras finalizar el tratamiento quimioterápico
    - Platino refractario: progresión de la enfermedad durante el tratamiento quimioterápico. (114–116)

La citorreducción secundaria (SCS) se refiere al tratamiento de la recidiva del cáncer de ovario.

La cirugía de SCS en el tratamiento del cáncer de ovario, según diferentes estudios retrospectivos, muestra un incremento en la supervivencia global en aquellas pacientes en las que se consigue una citorreducción completa, sin residuo tumoral.

Por tanto, sigue siendo un reto en este grupo de pacientes la selección adecuada de las mismas para no incurrir en laparotomías innecesarias en pacientes con una esperanza de vida limitada; siendo de 2 – 3 años en pacientes con recidiva platino – sensible y de 12 – 18 meses en recidiva platino – resistentes sometidas a SCS.(117,118)

El objetivo de esta citorreducción secundaria sigue siendo la ausencia de residuo tumoral. En aquellos casos en los que esta situación no sea posible, se recomienda no realizar el procedimiento quirúrgico con el objetivo de minimizar la morbilidad postquirúrgica e iniciar el tratamiento quimioterápico lo antes posible. (112)

El DESKTOP I, ensayo dirigido por la Arbeitsgemeinschaft Gynäkologishe Onkologie identifica unos parámetros predictivos para la citorreducción completa: buen performance status (ECOG 0), ausencia de residuo tumoral tras la intervención de citorreducción y ausencia de ascitis. En las pacientes en las que se cumplen estos factores la tasa de citorreducción completa alcanza el 79%, por el contrario, si se objetiva carcinomatosis la tasa de citorreducción completa disminuye a 26%.(119)

Posteriormente se valida este score (AGO score), en el DESKTOP II, estudio prospectivo multicéntrico. Se incluyen 516 pacientes, de ellas 261 (51%) cumple los criterios establecidos por el AGO score. En129 (49.4%), se realiza una cirugía de citorreducción secundaria. La tasa de citorreducción completa en aquellas pacientes que cumplen el score propuesto es del 76%.(120)

En una revisión sistemática se muestra un incremento en la tasa de citorreducción del 10%, que se traduce en un incremento de 3 meses en la supervivencia global. (121,122)

De los factores pronósticos relacionados con la citorreducción secundaria, la ausencia de residuo tumoral se muestra como un factor pronóstico independiente para la supervivencia global.
El intervalo libre de enfermedad (ILE) es un factor controvertido, ya que en los estudios realizados se incluyen pocas pacientes con un intervalo libre menor a 6 meses.
Eisenkop et al., (123)aporta un beneficio de tratamiento mayor, a mayor intervalo libre de enfermedad, del mismo modo que Chi et al. (124)
Scarabelli et al., únicamente muestra un beneficio en la supervivencia en el subgrupo de pacientes con intervalo libre de 13 – 24 meses, sin encontrar este beneficio en pacientes con intervalos mayores o menores. (125)

TRATAMIENTO QUIMIOTERÁPICO:
El pilar de tratamiento del cáncer de ovario avanzado se basa en la cirugía de citorreducción completa asociada al tratamiento quimioterápico intravenoso con platino – paclitaxel. Con esto se consigue una respuesta completa en el 50% de las pacientes, una respuesta anatomo – patológica del 25 – 30%, un intervalo libre de enfermedad de 14 – 21 meses y una supervivencia global de 26 – 57 meses.
El protocolo de tratamiento quimioterápico estándar consiste en carboplatino con una dosis de concentración en área debajo de la curva (AUC) de 5 – 7.5 en combinación con paclitaxel con una dosis de 175 mg/m^2 cada 3 semanas hasta completar 6 ciclos. (126,127)
Un ensayo japonés muestra una superioridad de la dosis densa semanal con paclitaxel (80 mg/m^2 en los días 1, 8 y 15) asociado a carboplatino AUC 6 (día 1) vs el tratamiento quimioterápico estándar intravenoso (128). Sin embargo, esta superioridad no ha sido confirmado en dos estudios randomizados europeos (129,130)

- QUIMIOTERAPIA INTRAPERITONEAL
  La quimioterapia intraperitoneal consiste en la administración del tratamiento directamente sobre la superficie peritoneal a través de un catéter que permite la administración de varios ciclos.
  La base fisiopatológica que apoya la utilización de los fármacos quimioterápicos por esta vía de administración es la posibilidad de utilizar dosis mayores, la reducción de efectos secundarios al disminuir la exposición sistémica y la destrucción de enfermedad peritoneal microscópica.

El estudio GOG – 172 muestra un incremento en la supervivencia global alcanzando los 65.6 meses, en el grupo de quimioterapia intraperitonal asociado a quimioterapia intravenosa vs. 49.7 meses en el grupo de quimioterapia intravenosa. Mostrando también beneficio en el intervalo libre de enfermedad. (131)
Algunos estudios randomizados fase III muestran que la quimioterapia intraperitoneal mejora los resultados en pacientes con ausencia de residuo tumoral, o con residuo pequeño cuando se compara con el uso de la quimioterapia intravenosa sola.
Un meta – análisis publicado en 2006 por parte de Jaaback et al., que incluye 1819 pacientes muestra que las pacientes tratadas con quimioterapia intraperitoneal asociado al tratamiento quimioterápico intravenoso presentan una mejora en el intervalo libre de enfermedad (HR = 0.79 IC al 95% = 0.60 – 0.90), y en la supervivencia global (HR = 0.79 IC al 95% = 0.60 – 0.90). Sin embargo, hay un incremento en los efectos gastrointestinales, fiebre y dolor en este subgrupo de pacientes.
Los efectos secundarios descritos, además de la heterogeneidad de los regímenes de tratamiento, han llevado a que esta modalidad de tratamiento no se considere un estándar de tratamiento. (132)

- TERAPIAS DIRIGIDAS:
  El uso de inhibidores angiogénicos, como el bevacizumab, un anticuerpo monoclonal dirigido contra e factor de crecimiento endotelial (VEGF), ha sido investigado.
  La adición del bevacizumab al tratamiento quimioterápico estándar ha mostrado un incremento en el intervalo libre de enfermedad en el tratamiento primario de cáncer de ovario. Sin embargo, análisis post hoc evidencian un incremento en la supervivencia global de aquellas pacientes con peor pronóstico por presentar resistencia al tratamiento con quimioterapia. (133)
  La combinación del bevacizumab con la quimioterapia intravenosa o con el uso de dosis – densas iv de quimioterapia ha contribuido a reducir la aplicación clínica de la quimioterapia intraperitoneal. (134)
  Dos estudios randomizados fase III, el GOG 218 y el ICON 7 muestran una mejora en el intervalo libre de enfermedad con el uso del bevacizumab como tratamiento de mantenimiento tras la finalización de la quimioterapia. En el ICON 7 muestra un mayor beneficio en pacientes en estadio III – IV con factores de mal pronóstico. Como efectos secundarios, en el GOG 218 se evidencia hipertensión grado 3 – 4, perforación gastro – intestinal grado 3, hemorragia en un 10% y un 2.3% de fístula en pacientes con bevacizumab concurrente con la quimioterapia y o con terapia de mantenimiento. (135,136)

  El bevacizumab también es utilizado en el tratamiento de la recidiva del cáncer de ovario en pacientes platino – sensible, combinado con la quimioterapia y, posteriormente como tratamiento de mantenimiento mostrando mejoría en el intervalo libre de enfermedad. (137,138)

  En aquellas pacientes con recidiva de cáncer de ovario platino – resistente el estudio AURELIA evidencia que la combinación del bevacizumab con el régimen quimioterápico mejora la respuesta al tratamiento oncológico e incrementa el intervalo libre de enfermedad. (134)

En todos los estudios el bevacizumab presenta mayor beneficio en aquellas pacientes con mayor extensión tumoral o factores de mal pronóstico.

No obstante, en ninguno de los estudios ha mostrado impacto en la supervivencia global.

- TRATAMIENTO DE MANTENIMIENTO:
  Actualmente, en pacientes con mutación BRCA o deficiencia en la vía de la recombinación homóloga (HRD) se ha objetiva que la utilización de terapia dirigida mediante el uso de inhibidores de la poli - ADP – ribosa polimerasa (iPARP) ha demostrado un incremento en el intervalo libre de enfermedad a pesar de la presencia de efectos adversos. (139)
  Estos fármacos inhiben la función de la enzima poli – ADP – ribosa polimerasa provocando la acumulación de errores genéticos en la célula causando la muerte celular.
    - Olaparib: muestra un incremento en la supervivencia en aquellas pacientes con diagnóstico de cáncer de ovario que presentan alteración en la HRD. (140)
    - Niraparib: en un estudio randomizado fase III muestra un incremento en el intervalo libre de enfermedad en las pacientes con cáncer de ovario avanzado independientemente del status molecular. (141,142)
    - Rucaparib: en el estudio ARIEL3 muestra un beneficio en el intervalo libre de enfermedad en aquellas pacientes con recaída por cáncer de ovario tras el tratamiento quimioterápico. (143,144)

- TRATAMIENTO QUIMIOTERAPIA INTRAPERITONEAL HIPERTÉRMICA.
  El tratamiento quimioterápico intraperitoneal hipertérmico (HIPEC) es una variante del tratamiento intraperitoneal en el que se administra el fármaco quimioterápico durante el procedimiento quirúrgico a una temperatura de 40ºC, lo que incrementa el efecto citotóxico del fármaco.
  En el estudio publicado en 2018, OVHIPEC – 1 se evidencia un beneficio en términos de supervivencia global en aquellas pacientes sometidas a tratamiento neoadyuvante y cirugía de intervalo, con una supervivencia de 10.8 meses más que las pacientes que no recibieron HIPEC. (145,146)
  Se ha realizado un estudio retrospectivo multicéntrico en el que se objetiva que el uso de HIPEC en la cirugía de intervalo del cáncer de ovario y en el que se evidencia un incremento en el intervalo libre de enfermedad, aunque no en la supervivencia global. No obstante, cabe destacar que en este estudio no se evidencia un incremento en la morbilidad postquirúrgica a los 30 días en las pacientes tratadas con HIPEC. (147)
  Actualmente se está llevando a cabo el estudio OVHIPEC – 2 en el que se está evaluando el posible beneficio en supervivencia del uso de HIPEC en pacientes sometidas a cirugía primaria en cáncer de ovario avanzado. (148)
  Recientemente se han publicado los resultados del estudio CHIPOR que muestra beneficio en la supervivencia global en pacientes con recidiva por cáncer de ovario en las que se aplica HIPEC en la cirugía de la recurrencia. (149)

CAPÍTULO 1

Objetivos

2. OBJETIVOS:

Por lo expuesto en el apartado anterior, los objetivos de la presente tesis son los siguientes:

- Establecer el mejor score laparoscópico para determinar la carga de enfermedad y optimizar el tratamiento primario de las pacientes con cáncer de ovario avanzado.
- Valorar el beneficio de la quimioterapia intraperitoneal en las pacientes intervenidas mediante cirugía primaria.
- Establecer la evidencia disponible para el tratamiento óptimo de las pacientes con recidiva de cáncer de ovario.

Todo ello nos permite desarrollar herramientas para conseguir realizar un tratamiento individualizado en las pacientes con cáncer de ovario.

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CAPITULO 2

Comparison of Peritoneal Carcinomatosis Scoring Methods in Predicting Resectability and Prognosis in Gynecologic Malignancies

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Capitulo 2: Carcinomatosis Scoring Methods in Predicting Resecability and Prognosis in Gynecologic Malignancies

1. Abstract

Objective:

Peritoneal carcinomatosis is a disease's presentation in the advanced stage of many gynecologic tumours. The distribution and volume of the disease are the main factors in achieving complete debulking. Diagnostic laparoscopy is a technique to allow evaluation of the disease.

This study's objective is to compare two laparoscopic scores (Fagotti's index and Sugarbaker's peritoneal cancer index (PCI)) and assess the diagnostic accuracy to select patients for neoadjuvant treatment and reduce unnecessary laparotomies.

Methods:

A non-randomised retrospective cohort study was conducted in patients with peritoneal carcinomatosis (ovarian and endometrial origin) who underwent laparoscopy and subsequent laparotomy. We evaluated the scores' ability to predict incomplete surgery and whether they were related to the patients' prognosis.

Results:

We included 34 patients, of which 23.5% received neoadjuvant chemotherapy. The rate of complete cytoreductive surgery was 79.4% (n = 27 patients). The highest sensitivity was obtained with a PCI value greater than 20. It was the best parameter to determine incomplete debulking. Survival curves were analysed according to the "cut off" established for each score, and statically significant differences were found using PCI with respect to Fagotti's Index. However, these differences were not found with Fagotti's score.

Conclusion:

The best diagnostic method to classify patients with peritoneal cancer is the PCI. It could be adapted to each surgical team because it allows identifying the "cut off point", which depends on incomplete surgery rate.

1. Introduction

Ovarian cancer is a significant cause of death from gynaecologic cancer, with 70–80% of cases diagnosed in advanced stages [1,2]. Complete primary debulking surgery is an independent survival factor [1,2] because the tumour residue's size is inversely related to overall survival [3,4].

The distribution and volume of the disease are the main factors in achieving complete debulking. The FIGO classification is not a useful tool to determine the disease's extent due to patients' disparity with the same stage.

Among the diagnostic methods, laparotomy continues to be the most accurate one to determine the burden of disease in patients. It is an invasive method of diagnosis with associated complications [1].

Diagnostic laparoscopy is a less-invasive evaluation alternative that reduces suboptimal surgery from 39% to 10% [2,5]. This technique can improve optimal surgery rates, limiting unnecessary morbidity and reducing costs derived from unnecessary laparotomy [6,7].

The application of an evaluation method that allows quantifying the disease in patients with peritoneal carcinomatosis would improve the test's accuracy.

The use of scores is a method to compare results and determine in an objective way the treatment indicated for each patient; however, it is currently a challenge.

The use of laparoscopic scores could reduce unnecessary laparotomies for those patients to whom the possibility of complete cytoreduction is scarce or non-existent. Neoadjuvant therapy and interval surgery are presented as valid alternatives for these patients [2].

The most widely used laparoscopic predictive models evaluating ovarian cancer's extension are the peritoneal carcinomatosis index, described by Sugarbaker, and the Fagotti score [8]. Traditionally, gynecologist oncologists in Europe have used Fagotti's index to predict cytorreductive surgery in laparotomy for gynecologic malignancies [9–11].
This study aims to compare these scores, assessing the diagnostic accuracy to select patients for neoadjuvant treatment and reduce unnecessary laparotomies, morbidity and mortality derived from them, and correlation with the prognosis of these patients.

2. Material and Methods

3.1. Patients

115 patients with diagnosis of peritoneal carcinomatosis.

Patients were required to meet all the following eligibility criteria:

- Aged 18 years old or older.
- Diagnosis of peritoneal carcinomatosis.
- Written consent of surgery.

We excluded patients who did not have diagnosis of peritoneal carcinomatosis or did not give consent for data collection.
71 patients (61.7%) had not undergone laparoscopy at diagnosis, so they were excluded from the study.
Of 54 patients on whom laparoscopy was performed to evaluate primary debulking, 10 (18.5%) were referred for neoadjuvant treatment without subsequent laparotomy.
A total of 81 patients were referred for neoadjuvant treatment for reasons attributable to the patient (e.g., comorbidity, anaesthetic risk), to the disease (e.g., metastasis, number of intestinal resections) or, criteria of unresectability established by the Multidisciplinary Unit of Abdominal Pelvic Surgery (MUAPOS) (Radiologic criteria; lung metastasis, hepatic metastasis in three or more hepatic segments, severe hepatic pedicle involvement and progression after neoadjuvant chemotherapy) [1,3,6]. The comparison was made among patients where the laparoscopy score suggested the possibility of performing a successful debulking surgery, and subsequent laparotomy was performed within a maximum period of 10 days (34 patients) (Figure 1).
The absence of tumour disease was defined as complete surgery, not distinguishing between optimal (tumour residue less than 1 cm) and suboptimal surgery (tumour residue greater than 1 cm). We included these two types of surgery under the term 'incomplete cytoreductive surgery' [4].
The patients' preoperative evaluation consisted of a complete gynaecological examination, transvaginal ultrasound, tumour markers (Ca 125, CEA, Ca 19.9 and HE4), complete analysis, and thoracic-abdominopelvic computed tomography. Informed consent was obtained from all patients, and the ethics committee approved the study.

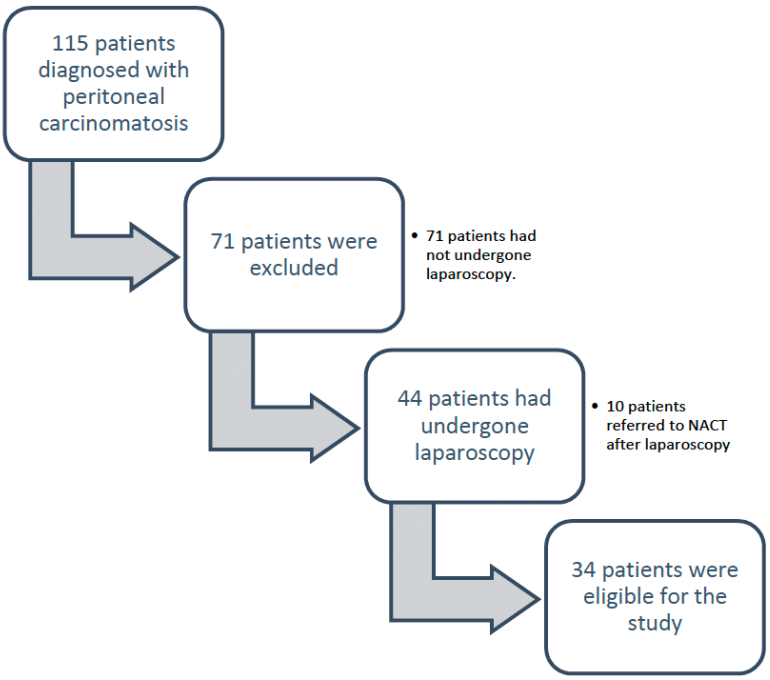


Figure 1: Patient selection

3.2. Surgical Technique

A 15 mm supraumbilical longitudinal incision was made, and a 12 mm Hasson's trocar was introduced in the abdomen. A suprapubic 5 mm accessory trocar was placed, adding another trocar 5 mm in the iliac fossa if required, both under direct vision.

The entire abdominal cavity was examined, and a biopsy of the ovaries, metastatic nodules, or peritoneal surface was performed to confirm the diagnosis.

In our unit, it is considered that PCIs greater than 20 are associated with high morbidity with a decrease in the possibility of complete debulking. The value considered as unresectable in the case of the Fagotti index is higher than 8 [12,13]. However, the subjective evaluation of the oncologist surgeon, the histology of the disease, and the performance status of the patient are evaluated prior to the decision to perform surgery for posterior debulking.

If the patient is considered to be subject to debulking surgery, it was performed in the second stage, after histological diagnosis, with a xifo – pubic midline incision.

3.3 Scores

3.3.1. Fagotti Score

The Fagotti Score is based on the evaluation of seven parameters: omental cake, peritoneal carcinomatosis, diaphragmatic carcinomatosis, mesenteric retraction, stomach infiltration, bowel infiltration, and liver metastases. Each parameter is valued with a 0 if absent or 2 if present. The total value is between 0 and 14. A value above or equal to 8 is related to suboptimal surgery. [7,12].

3.3.2. Sugarbaker Score (PCI)

The abdomen is divided into nine regions: central (0), right hypochondrium (1), left hypochondrium (3), epigastrium (2), left flank (4), left iliac fossa (5), pelvis (6), right iliac fossa (7), and right flank (8). Four regions corresponding to the digestive tract are added: upper

jejunum (9), lower jejunum (10), upper ileum (11), and lower ileum (12). Each area scores 0 if there is no evidence of a tumour; 1 with a tumour smaller than 0.5 cm, 2 with a tumour up to 5 cm, and 3 with a tumour larger than 5 cm or confluent.
The value obtained is between 0 and 39.
The "cut off" established in the bibliography is between 10 and 20 [5,6].
The description of the scores is described in Appendix A.

3.5. Statical Analysis

The objective of this retrospective descriptive non-randomised study is to compare the two laparoscopic scores to determine sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy to predict suboptimal cytoreduction in patients with gynaecological peritoneal carcinomatosis.
The demographic characteristics of each patient, the tumour, and the surgical results obtained were analysed.
Parameters such as FIGO stage, PCI, and Fagotti score were determined for each patient who underwent laparoscopy and laparotomy.
The main objective was to determine if the models correlated with the incomplete debulking rate (optimal or suboptimal) and overall survival, using ROC (receiver operating characteristic) curves and the Kaplan–Meier method for survival.
Significance was assumed with a p-value less than 0.05.
The statistical program used was IBM SPSS Statistics version 19 (IBM Corp, released in 2010. IBM SPSS Statistics for Windows, Version 19.0. Armonk, NY, USA).

3. Results:

Between 2013 and 2017, 115 patients were diagnosed with peritoneal carcinomatosis at the University General Hospital of Castellón. The data were extracted from the database of the Multidisciplinary Unit of Abdominal Pelvic Surgery (MUAPOS). During the study period, 34 patients who underwent laparoscopy surgery and posterior cytoreductive surgery were included in the data analysis.
The mean age of the patients was 62 years.
According to the FIGO classification [1,2], 79.4% (n = 27 patients) were classified as FIGO III, 20.6% (n = 7 patients) presented stage IV.
58.8% were high-grade serous tumours.
The origin of the peritoneal carcinomatosis was ovarian in 85.3%; in 14.7% of the patients, it was endometrial.
The mean tumour marker (Ca 125) was 1020.94 IU/mL.
23.5% of the patients received neoadjuvant chemotherapy.
Maneuvers were performed in the upper abdomen in 61.8% of the patients.
The complete cytoreduction rate was 79.4% (n = 27 patients) with 52.9% postoperative complications, of which 5.8% were severe.
The suboptimal cytoreduction rate was 20.6%, leaving a macroscopic tumour residue equal or more than 1 cm.
The clinicopathological features shown in the table (Table 1).
Overall survival at 5 years was 46.31 months (95% CI 33.06–69.57) (Figure 2).
The mean of Fagotti's score with laparoscopic approach was 4.79 (se 0.406), and Sugarbaker's score was 13.03 (se 1.06).
A comparison of means between the two scores and their capacity to predict complete debulking applied by laparoscopy or laparotomy was conducted.
Statistically significant differences were found in the means of the Sugarbaker index

in complete cytoreductive surgery (R0) about incomplete cytoreductive surgery (No R0) and not at all in the Fagotti's score (Tables 2 and 3).

Table 1. Clinicopathological features

	n = 34	%
Median age at surgery (years)	61.97	
Neoadjuvant chemotherapy	8	23.5
Surgical procedures upper abdomen	20	58.8
Exitus	17	50
Mean follow-up time (months)	25.79	
Mean pre-surgical Ca 125	1020.94	
Complete cytoreductive surgery	27	79.4
Complete/optimal cytoreductive surgery	29	85.3
Suboptimal cytoreductive surgery	7	20.6
FIGO stage		
III	27	79.4
IV	7	20.6
Histology		
Serous	20	58.8
Endometroid	7	20.6
Others	7	20.6
Tumour origin		
Ovarian	29	85.3
Endometrial	5	14.7
Tumour		
Primary	31	91.2
Relapse	3	8.8

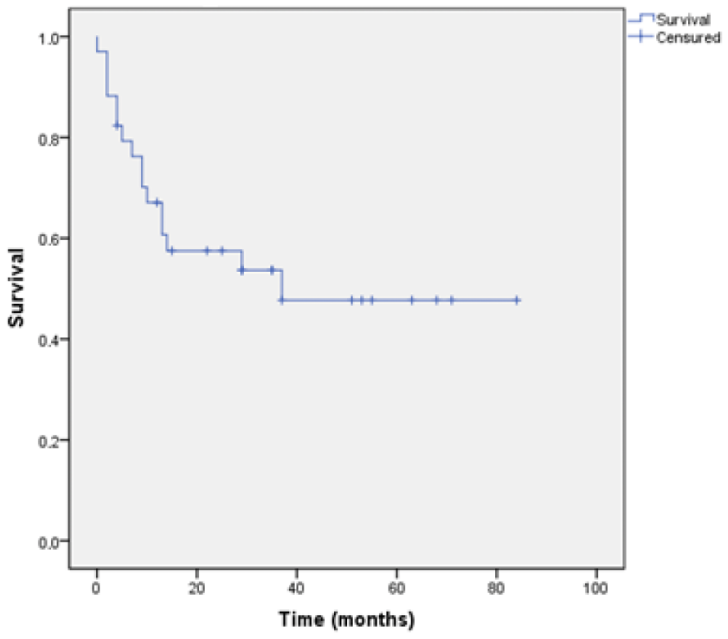


Figure 2: Overall Survival

Table 2. Laparoscopic index and complete cytoreductive surgery.

Laparoscopy	R0	No R0	*p*
PCI	11.44 (se 1.13)	19.14 (se 1.16)	0.002
Fagotti	4.78 (0.46)	5.71 (se 0.808)	0.338

R0: complete cytoreductive surgery. No R0: incomplete cytoreductive surgery. SE: standard error.

Table 3. Laparotomic index and complete cytoreductive surgery.

Laparotomy	R0	No R0	*p*
PCI	10.30 (se 1.16)	23.86 (se 1.43)	0.000
Fagotti	5.56 (se 0.59)	7 (se 1.09)	0.273

R0: complete cytoreductive surgery. No R0: incomplete cytoreductive surgery.

The predictive capacity of the different indices applied laparoscopically to predict incomplete debulking surgery was evaluated.
The highest sensitivity was obtained with PCI value greater than 20, resulting in 43%, with a specificity of 88%, a PPV of 50% and an NPV of 86%.
Based on the data provided, the Sugarbaker score was the best parameter to determine the possibility of incomplete debulking (Table 4).

Table 4. Diagnostic Parameters.

Laparoscopic Score	Sensibility	Specificity	PPV	NPV	Accuracy
PCI $\geq$ 10	30%	88%	30%	100%	53%
PCI $\geq$ 20	43%	88%	50%	86%	79%
Fagotti $\geq$ 8	14%	81%	16%	78%	68%

PPV: positive predictive value. NPV: negative predictive value.

The most significant discriminative capacity test was the peritoneal cancer index described by Sugarbaker, regardless of whether it was applied via laparoscopy or laparotomy (Figure 3).

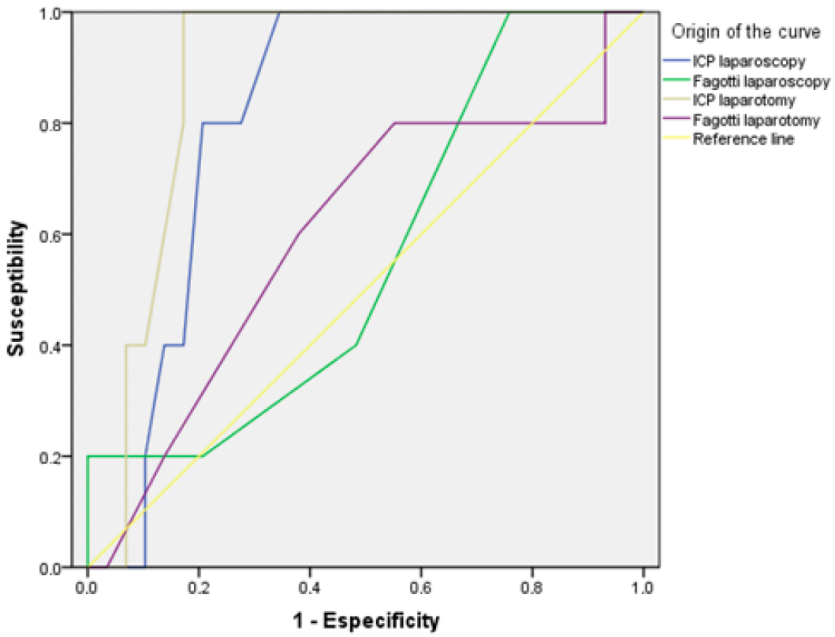


Figure 3. Roc curves shows the accuracy of these tests applied for laparotomy or laparoscopy.

This data was evaluated using the ROC curves.
Survival curves were analysed according to the "cut off" established for each score evaluated and determined if they had a prognostic impact when this score was applied via laparoscopy.
These tables show the overall survival, depending on whether the value of the index applied via laparoscopy is greater than the established values 10 and 20 for the Sugarbaker PCI, and 8 for the Fagotti index.
These differences in overall survival were found with statistically significant differences when using the PCI (Figures 4 and 5 and Tables 5 and 6); however, these differences were not found with the Fagotti's score (Figure 6 and Table 7).

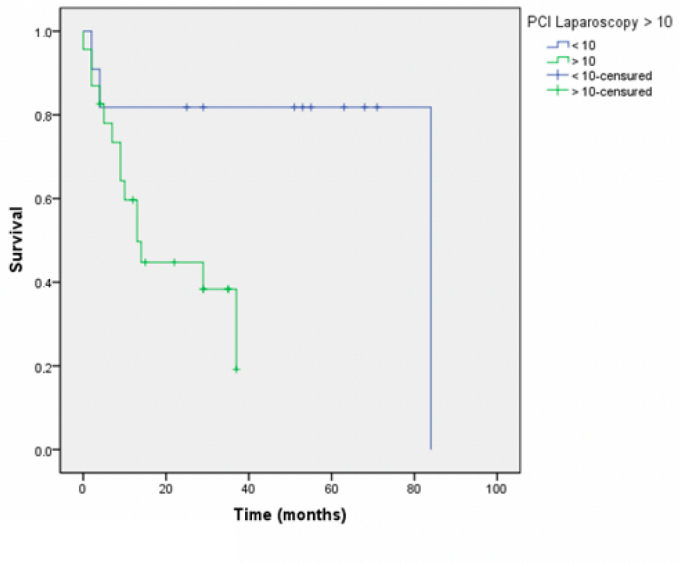


Figure 4: Survival PCI > 10

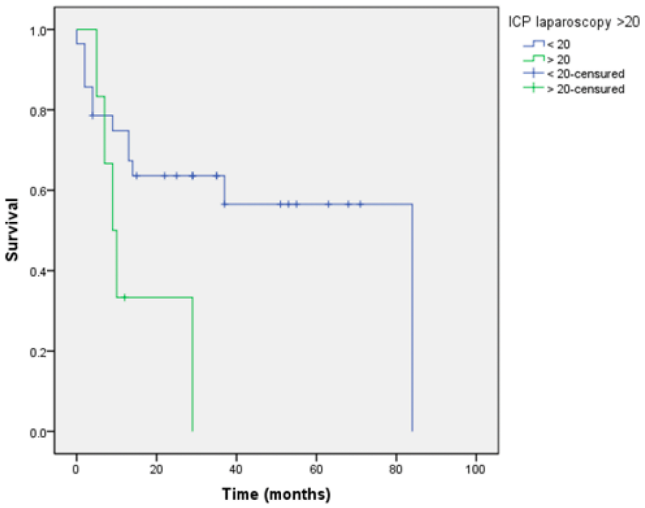


Figure 5: Survival PCI > 20

Table 5. Survival PCI "cut off" 10

	Mean Overall Survival (Months)	95% CI
PCI LPS < 10	69.27	46.66–91.89
PCI LPS ≥ 10	20.22	13.82–26.61

PCI LPS: Laparoscopic Peritoneal Carcinomatosis Index.

Table 6. Survival PCI "cut off" 20

	Mean Overall Survival (Months)	95% CI
PCI LPS < 20	52.44	37.35–67.54
PCI LPS ≥ 20	14.38	5.76–23.90

PCI LPS: Laparoscopic Peritoneal Carcinomatosis Index.

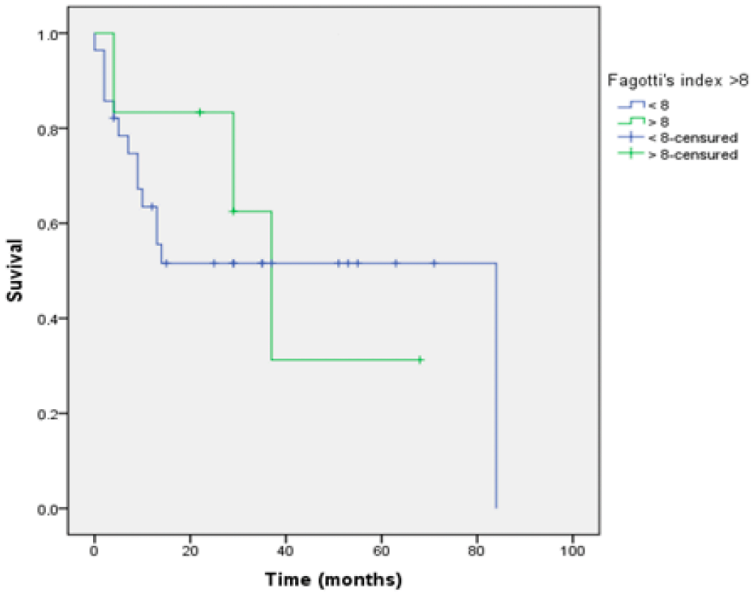


Figure 6. Survival Fagotti's Index

Table 7. Survival Fagotti "cut off" 8.

	Mean Overall Survival (Months)	95% CI
Fagotti < 8	47.76	31.54–61.97
Fagotti ≥ 8	39.52	19.25–59.71

To determine the risk of incomplete debulking, the relative risk was calculated for the scores described by the "cut off."
A laparoscopic-PCI >20 was a risk factor for incomplete debulking and unnecessary laparotomy RR 3.5 95% CI (10.44–11.734).
This association was not evidenced with PCI cut-off of 10, nor with the Fagotti score.

4. Discussion

The present study shows that the peritoneal carcinomatosis index described by Sugarbaker for colorectal cancer is a valid diagnostic test that provides prognostic value in evaluating peritoneal carcinomatosis of gynaecological origin.
Patients with a PCI greater than 20 showed a decrease of 37.61 months in overall survival [6,14].
The results obtained in our sample for Fagotti's index in specificity and positive predictive value present values below those described in their study, showing an AUC of 0.66, also lower than that obtained in the external validation of Brun et al. and Chéreau, which was 0.74 and 0.69, respectively [6,8,10–12] These findings are probably a consequence of the suboptimal cytoreduction rate since in Fagotti's validation study, it was 32.8%, while in this sample, the rate is 20.6% [10]
The best diagnostic test to determine the eligible patients for neoadjuvant treatment is the Sugarbaker's peritoneal cancer index, increasing diagnostic accuracy with the increase in the cut-off point.
This cut-off point should be established according to the complete debulking rate obtained in each working group [13].
One of the factors that influence overall survival is the volume of the disease.
The article by Llueca et al. [5,6,13] shows that the subgroup of patients with PCI less than or equal to 10 presents better survival than a value above 20. These findings are confirmed in our study with a decrease in survival as the peritoneal cancer index value increases. This prognostic impact is not observed in Fagotti's model because it is not a model that quantifies disease.
The gold standard for evaluating the burden of peritoneal carcinomatosis is laparotomy.
In an article by Llueca et al. [5], two predictive models were compared; the accuracy of this evaluation increases with the laparotomic exploration [9,15,16]. However, due to the morbidity associated with this technique, it is not considered a diagnostic technique. [17].
However, the potential discrepancy between the PCI assessment by laparoscopy and laparotomy could interfere with the main objective of the study [5,15,18].
Nevertheless, the objective of the study is to establish a better index to apply the laparoscopic method to identify with the least error the patients who would benefit from neoadjuvant therapy because complete debulking surgery is unlikely [19,20].
One of the strengths of this study is the homogeneity of the sample. According to the same criteria for unresectability, all patients were evaluated and treated by the same surgical team with an established suboptimal cytoreduction rate (tumour residue greater than 1 cm) of approximately 16%.
Another noteworthy point of this study is to include patients with peritoneal carcinomatosis

of endometrial origin. This subgroup has a worse prognosis as it is a tumour with less chemosensitivity than the ovary, and neoadjuvant treatment in this group is not standard clinical practice [9,21].

The study's main limitation is a retrospective evaluation of the data. A selection bias was achieved when choosing the patients who underwent laparoscopy and later laparotomy. This fact implies that the surgical team has already selected the patients as probably resectable. This is the reason why there are few patients with PCI values greater than 20 and few patients with suboptimal surgery. Another limitation is the inclusion of patients undergoing neoadjuvant therapy (23.5%). This patient usually has a lower burden of disease; however, when subjected to laparoscopy before surgery, they probably have a greater volume of disease greater than expected in the pre-surgical study [3,22].

One of the weakness of the study is the small sample size, but there is a lack of information in this field, and we could contribute to closing the gap.

It is necessary to carry out prospective studies with a greater number of patients to verify the results obtained in our evaluation.

5. Conclusion

Based on the data obtained in our study, it is possible to suggest that the best diagnostic method to classify patients with peritoneal cancer to indicate primary treatment is the peritoneal carcinomatosis index. It presents a better correlation of the extension of the disease and provides prognostic information.

We consider this score could be adapted to the suboptimal cytoreduction rate of each surgical team, allowing the cut-off point to be established at a particular moment and evolving according to the results obtained by the surgical team.

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7. ANNEXO: Original Publication "Carcinomatosis Scoring Methods in Predicting Resecability and Prognosis in Gynecologic Malignancies"

Journal of *Clinical Medicine*

MDPI

Article

Comparison of Peritoneal Carcinomatosis Scoring Methods in Predicting Resectability and Prognosis in Gynecologic Malignancies

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Abstract: Objective: Peritoneal carcinomatosis is a disease's presentation in the advanced stages of many gynecologic tumours. The distribution and volume of the disease are the main factors in achieving complete debulking. Diagnostic laparoscopy is a technique to allow evaluation of the disease. This study's objective is to compare two laparoscopic scores (Fagotti's index and Sugarbaker's peritoneal cancer index (PCI)) and assess the diagnostic accuracy to select patients for neoadjuvant treatment and reduce unnecessary laparotomies. Methods: A non-randomised retrospective cohort study was conducted in patients with peritoneal carcinomatosis (ovarian and endometrial origin) who underwent laparoscopy and subsequent laparotomy. We evaluated the scores' ability to predict incomplete surgery and whether they were related to the patients' prognosis. Results: We included 34 patients, of which 23.5% received neoadjuvant chemotherapy. The rate of complete cytoreductive surgery was 79.4% (n = 27 patients). The highest sensitivity was obtained with a PCI value greater than 20. It was the best parameter to determine incomplete debulking. Survival curves were analysed according to the "cut off" established for each score, and statically significant differences were found using PCI with respect to Fagotti's Index. However, these differences were not found with Fagotti's score. Conclusion: The best diagnostic method to classify patients with peritoneal cancer is the PCI. It could be adapted to each surgical team because it allows identifying the "cut off point", which depends on incomplete surgery rate.

Keywords: laparoscopy; peritoneal carcinomatosis; PCI; Fagotti index; resecability

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1. Introduction

Ovarian cancer is a significant cause of death from gynaecologic cancer, with 70–80% of cases diagnosed in advanced stages [1,2]. Complete primary debulking surgery is an independent survival factor [1,2] because the tumour residue's size is inversely related to overall survival [3,4].

The distribution and volume of the disease are the main factors in achieving complete debulking. The FIGO classification is not a useful tool to determine the disease's extent due to patients' disparity with the same stage.

Among the diagnostic methods, laparotomy continues to be the most accurate one to determine the burden of disease in patients. It is an invasive method of diagnosis with associated complications [1].

Diagnostic laparoscopy is a less-invasive evaluation alternative that reduces suboptimal surgery from 39% to 10% [2,5]. This technique can improve optimal surgery rates, limiting unnecessary morbidity and reducing costs derived from unnecessary laparotomy [6,7].

The application of an evaluation method that allows quantifying the disease in patients with peritoneal carcinomatosis would improve the test's accuracy.

The use of scores is a method to compare results and determine in an objective way the treatment indicated for each patient; however, it is currently a challenge.

The use of laparoscopic scores could reduce unnecessary laparotomies for those patients to whom the possibility of complete cytoreduction is scarce or non-existent. Neoadjuvant therapy and interval surgery are presented as valid alternatives for these patients [2].

The most widely used laparoscopic predictive models evaluating ovarian cancer's extension are the peritoneal carcinomatosis index, described by Sugarbaker, and the Fagotti score [8].

Traditionally, gynecologist oncologists in Europe have used Fagotti's index to predict cytorreductive surgery in laparotomy for gynecologic malignancies [9–11].

This study aims to compare these scores, assessing the diagnostic accuracy to select patients for neoadjuvant treatment and reduce unnecessary laparotomies, morbidity and mortality derived from them, and correlation with the prognosis of these patients.

2. Material and Methods

2.1. Patients

115 patients with diagnosis of peritoneal carcinomatosis.

Patients were required to meet all the following eligibility criteria:

- Aged 18 years old or older.
- Diagnosis of peritoneal carcinomatosis.
- Written consent of surgery.

We excluded patients who did not have diagnosis of peritoneal carcinomatosis or did not give consent for data collection.

71 patients (61.7%) had not undergone laparoscopy at diagnosis, so they were excluded from the study.

Of 54 patients on whom laparoscopy was performed to evaluate primary debulking, 10 (18.5%) were referred for neoadjuvant treatment without subsequent laparotomy.

A total of 81 patients were referred for neoadjuvant treatment for reasons attributable to the patient (e.g., comorbidity, anaesthetic risk), to the disease (e.g., metastasis, number of intestinal resections) or, criteria of unresectability established by the Multidisciplinary Unit of Abdominal Pelvic Surgery (MUAPOS) (Radiologic criteria; lung metastasis, hepatic metastasis in three or more hepatic segments, severe hepatic pedicle involvement and progression after neoadjuvant chemotherapy) [1,3,6].The comparison was made among patients where the laparoscopy score suggested the possibility of performing a successful debulking surgery, and subsequent laparotomy was performed within a maximum period of 10 days (34 patients) (Figure 1).

The absence of tumour disease was defined as complete surgery, not distinguishing between optimal (tumour residue less than 1 cm) and suboptimal surgery (tumour residue greater than 1 cm). We included these two types of surgery under the term 'incomplete cytoreductive surgery' [4].

The patients' preoperative evaluation consisted of a complete gynaecological examination, transvaginal ultrasound, tumour markers (Ca 125, CEA, Ca 19.9 and HE4), complete analysis, and thoracic-abdominopelvic computed tomography. Informed consent was obtained from all patients, and the ethics committee approved the study.

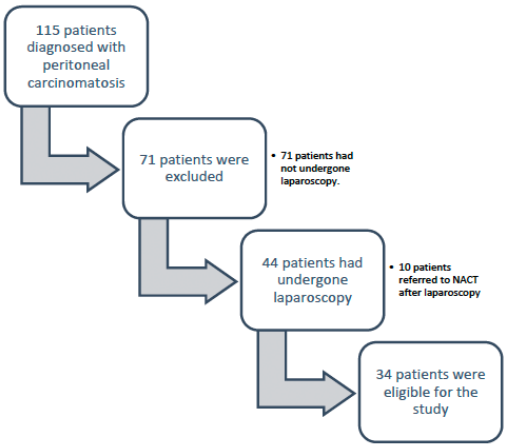


Figure 1. Patient selection.

2.2. Surgical Technique

A 15 mm supraumbilical longitudinal incision was made, and a 12 mm Hasson's trocar was introduced in the abdomen. A suprapubic 5 mm accessory trocar was placed, adding another trocar 5 mm in the iliac fossa if required, both under direct vision.

The entire abdominal cavity was examined, and a biopsy of the ovaries, metastatic nodules, or peritoneal surface was performed to confirm the diagnosis.

In our unit, it is considered that PCIs greater than 20 are associated with high morbidity with a decrease in the possibility of complete debulking. The value considered as unresectable in the case of the Fagotti index is higher than 8 [12,13]. However, the subjective evaluation of the oncologist surgeon, the histology of the disease, and the performance status of the patient are evaluated prior to the decision to perform surgery for posterior debulking.

If the patient is considered to be subject to debulking surgery, it was performed in the second stage, after histological diagnosis, with a xipho-pubic midline incision.

2.3. Scores

2.3.1. Fagotti Score

The Fagotti Score is based on the evaluation of seven parameters: omental cake, peritoneal carcinomatosis, diaphragmatic carcinomatosis, mesenteric retraction, stomach infiltration, bowel infiltration, and liver metastases. Each parameter is valued with a 0 if absent or 2 if present. The total value is between 0 and 14. A value above or equal to 8 is related to suboptimal surgery [7,12].

2.3.2. Sugarbaker Score (PCI)

The abdomen is divided into nine regions: central (0), right hypochondrium (1), left hypochondrium (3), epigastrium (2), left flank (4), left iliac fossa (5), pelvis (6), right iliac fossa (7), and right flank (8). Four regions corresponding to the digestive tract are added: upper jejunum (9), lower jejunum (10), upper ileum (11), and lower ileum (12). Each area scores 0 if there is no evidence of a tumour; 1 with a tumour smaller than 0.5 cm, 2 with a tumour up to 5 cm, and 3 with a tumour larger than 5 cm or confluent.

The value obtained is between 0 and 39.

The "cut off" established in the bibliography is between 10 and 20 [5,6].

The description of the scores is described in Appendix A.

2.4. Statical Analysis

The objective of this retrospective descriptive non-randomised study is to compare the two laparoscopic scores to determine sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy to predict suboptimal cytoreduction in patients with gynaecological peritoneal carcinomatosis.

The demographic characteristics of each patient, the tumour, and the surgical results obtained were analysed.

Parameters such as FIGO stage, PCI, and Fagotti score were determined for each patient who underwent laparoscopy and laparotomy.

The main objective was to determine if the models correlated with the incomplete debulking rate (optimal or suboptimal) and overall survival, using ROC (receiver operating characteristic) curves and the Kaplan–Meier method for survival.

Significance was assumed with a p-value less than 0.05.

The statistical program used was IBM SPSS Statistics version 19 (IBM Corp, released in 2010. IBM SPSS Statistics for Windows, Version 19.0. Armonk, NY, USA).

3. Results

Between 2013 and 2017, 115 patients were diagnosed with peritoneal carcinomatosis at the University General Hospital of Castellón. The data were extracted from the database of the Multidisciplinary Unit of Abdominal Pelvic Surgery (MUAPOS). During the study period, 34 patients who underwent laparoscopy surgery and posterior cytoreductive surgery were included in the data analysis.

The mean age of the patients was 62 years.

According to the FIGO classification [1,2], 79.4% (n = 27 patients) were classified as FIGO III, 20.6% (n = 7 patients) presented stage IV.

58.8% were high-grade serous tumours.

The origin of the peritoneal carcinomatosis was ovarian in 85.3%; in 14.7% of the patients, it was endometrial.

The mean tumour marker (Ca 125) was 1020.94 IU/mL.

23.5% of the patients received neoadjuvant chemotherapy.

Maneuvers were performed in the upper abdomen in 61.8% of the patients.

The complete cytoreduction rate was 79.4% (n = 27 patients) with 52.9% postoperative complications, of which 5.8% were severe.

The suboptimal cytoreduction rate was 20.6%, leaving a macroscopic tumour residue equal or more than 1 cm.

The clinicopathological features shown in the table (Table 1).

Overall survival at 5 years was 46.31 months (95% CI 33.06–69.57) (Figure 2).

The mean of Fagotti's score with laparoscopic approach was 4.79 (se 0.406), and Sugarbaker's score was 13.03 (se 1.06).

A comparison of means between the two scores and their capacity to predict complete debulking applied by laparoscopy or laparotomy was conducted.

Statistically significant differences were found in the means of the Sugarbaker index in complete cytoreductive surgery (R0) about incomplete cytoreductive surgery (No R0) and not at all in the Fagotti's score (Tables 2 and 3).

Table 1. Clinicopathological features.

	n = 34	%
Median age at surgery (years)	61.97	
Neoadjuvant chemotherapy	8	23.5
Surgical procedures upper abdomen	20	58.8
Exitus	17	50
Mean follow-up time (months)	25.79	
Mean pre-surgical Ca 125	1020.94	
Complete cytoreductive surgery	27	79.4
Complete/optimal cytoreductive surgery	29	85.3
Suboptimal cytoreductive surgery	7	20.6
FIGO stage		
III	27	79.4
IV	7	20.6
Histology		
Serous	20	58.8
Endometroid	7	20.6
Others	7	20.6
Tumour origin		
Ovarian	29	85.3
Endometrial	5	14.7
Tumour		
Primary	31	91.2
Relapse	3	8.8

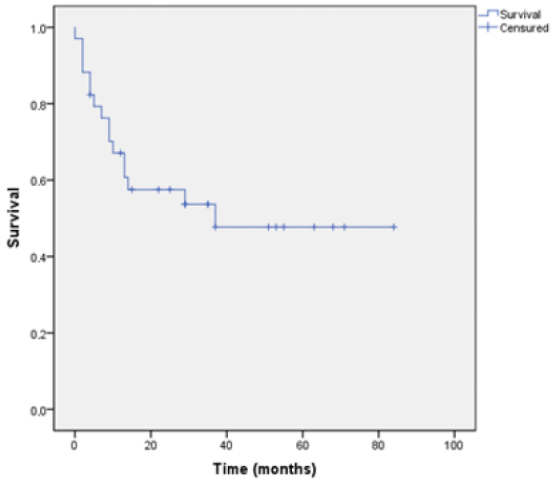


Figure 2. Overall Survival.

Table 2. Laparoscopic index and complete cytoreductive surgery.

Laparoscopy	R0	No R0	*p*
PCI	11.44 (se 1.13)	19.14 (se 1.16)	0.002
Fagotti	4.78 (0.46)	5.71 (se 0.808)	0.338

R0: complete cytoreductive surgery. No R0: incomplete cytoreductive surgery. SE: standard error.

Table 3. Laparotomic index and complete cytoreductive surgery.

Laparotomy	R0	No R0	*p*
PCI	10.30 (se 1.16)	23.86 (se 1.43)	0.000
Fagotti	5.56 (se 0.59)	7 (se 1.09)	0.273

R0: complete cytoreductive surgery. No R0: incomplete cytoreductive surgery.

The predictive capacity of the different indices applied laparoscopically to predict incomplete debulking surgery was evaluated.

The highest sensitivity was obtained with PCI value greater than 20, resulting in 43%, with a specificity of 88%, a PPV of 50% and an NPV of 86%.

Based on the data provided, the Sugarbaker score was the best parameter to determine the possibility of incomplete debulking (Table 4).

Table 4. Diagnostic Parameters.

Laparoscopic Score	Sensibility	Specificity	PPV	NPV	Accuracy
PCI ≥ 10	30%	88%	30%	100%	53%
PCI ≥ 20	43%	88%	50%	86%	79%
Fagotti ≥ 8	14%	81%	16%	78%	68%

PPV: positive predictive value. NPV: negative predictive value.

The most significant discriminative capacity test was the peritoneal cancer index described by Sugarbaker, regardless of whether it was applied via laparoscopy or laparotomy (Figure 3).

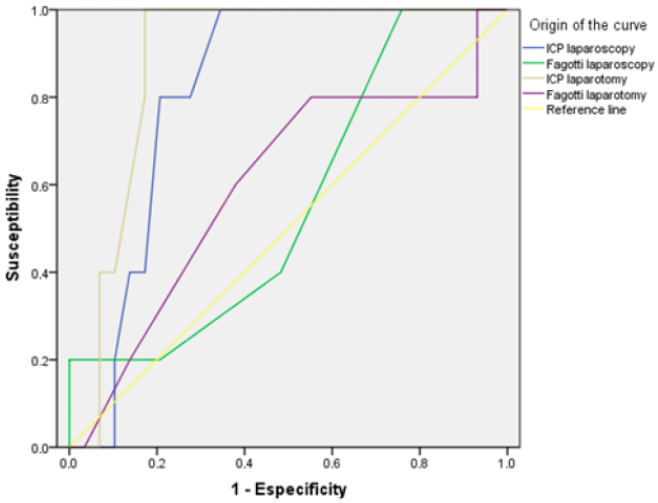


Figure 3. Roc curves shows the accuracy of these tests applied for laparotomy or laparoscopy.

This data was evaluated using the ROC curves.

Survival curves were analysed according to the "cut off" established for each score evaluated and determined if they had a prognostic impact when this score was applied via laparoscopy.

These tables show the overall survival, depending on whether the value of the index applied via laparoscopy is greater than the established values 10 and 20 for the Sugarbaker PCI, and 8 for the Fagotti index.

These differences in overall survival were found with statistically significant differences when using the PCI (Figures 4 and 5 and Tables 5 and 6); however, these differences were not found with the Fagotti's score (Figure 6 and Table 7).

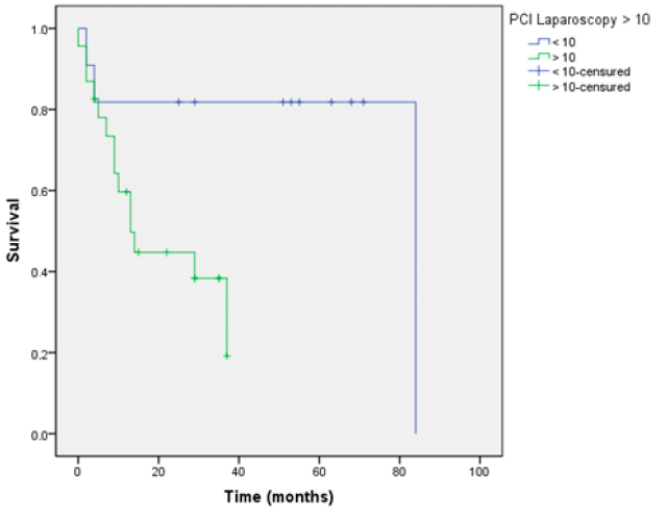


Figure 4. Survival PCI > 10.

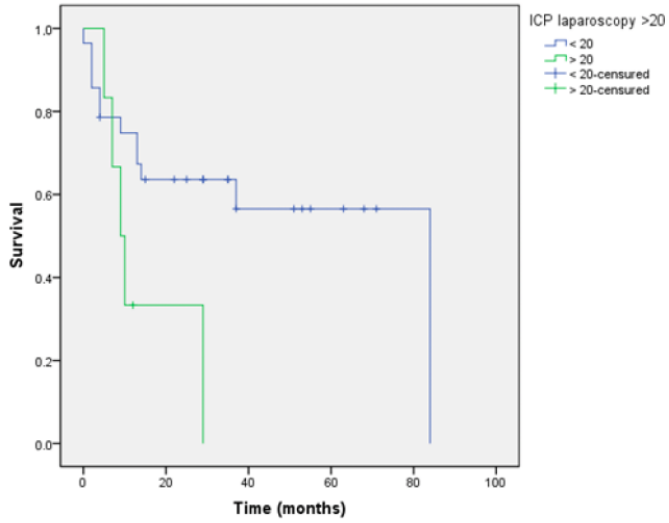


Figure 5. Survival PCI > 20.

Table 5. Survival PCI "cut off" 10.

	Mean Overall Survival (Months)	95% CI
PCI LPS < 10	69.27	46.66–91.89
PCI LPS ≥ 10	20.22	13.82–26.61

PCI LPS: Laparoscopic Peritoneal Carcinomatosis Index.

Table 6. Survival PCI "cut off" 20.

	Mean Overall Survival (Months)	95% CI
PCI LPS < 20	52.44	37.35–67.54
PCI LPS ≥ 20	14.38	5.76–23.90

PCI LPS: Laparoscopic Peritoneal Carcinomatosis Index.

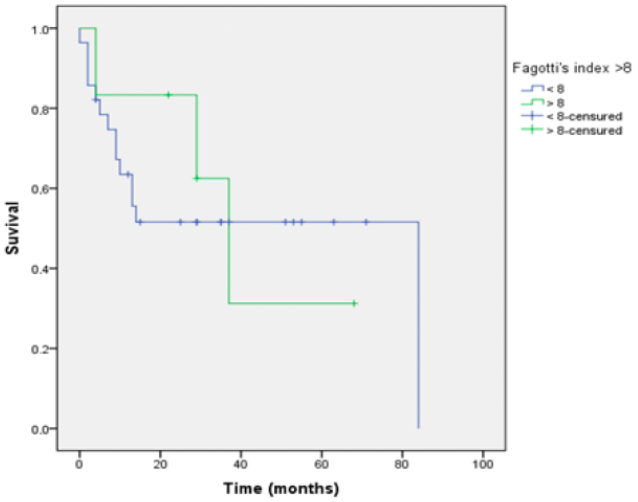


Figure 6. Survival Fagotti's Index.

Table 7. Survival Fagotti "cut off" 8.

	Mean Overall Survival (Months)	95% CI
Fagotti < 8	47.76	31.54–61.97
Fagotti ≥ 8	39.52	19.25–59.71

To determine the risk of incomplete debulking, the relative risk was calculated for the scores described by the "cut off."

A laparoscopic-PCI >20 was a risk factor for incomplete debulking and unnecessary laparotomy RR 3.5 95% CI (10.44–11.734).

This association was not evidenced with PCI cut-off of 10, nor with the Fagotti score.

4. Discussion

The present study shows that the peritoneal carcinomatosis index described by Sugarbaker for colorectal cancer is a valid diagnostic test that provides prognostic value in evaluating peritoneal carcinomatosis of gynaecological origin.

Patients with a PCI greater than 20 showed a decrease of 37.61 months in overall survival [6,14].

We consider this score could be adapted to the suboptimal cytoreduction rate of each surgical team, allowing the cut-off point to be established at a particular moment and evolving according to the results obtained by the surgical team.

Author Contributions: Conceptualization, M.T.C., A.S., J.G.-E., J.G.-A. and A.L.; data curation, M.T.C. and J.G.-E.; formal analysis, M.T.C., J.G.-E. and J.G.-A.; investigation, M.T.C. and A.L.; methodology, M.T.C. and A.L.; software, A.S.; supervision, J.G.-E., J.G.-A. and A.L.; visualization, J.G.-A.; writing—original draft, M.T.C.; writing—review and editing, M.T.C., A.S. and A.L. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee of University General Hospital of Castellon (HIP/CI version (3 June 2021)).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to privacity of the patients included in this article.

Acknowledgments: The authors would like to thank Begoña Bellés-Fortuño for editing and proofreading the manuscript. *MUAPOS working group (Multidisciplinary Unit of Abdominal Pelvic Oncology Surgery): Gomez-Quiles L., Játiva R., Cebrian G., Bosso, V., Villarin, A., Maiocchi, K., Delgado-Barriga K., Rodrigo-Aliaga M., Ruiz N., Herrero C., Frances, A., Beato I., Ferrer C., Aracil J.P., Boldo E., Boldo A. and Adell R.

Conflicts of Interest: The authors declare no conflict of interest.

Appendix A

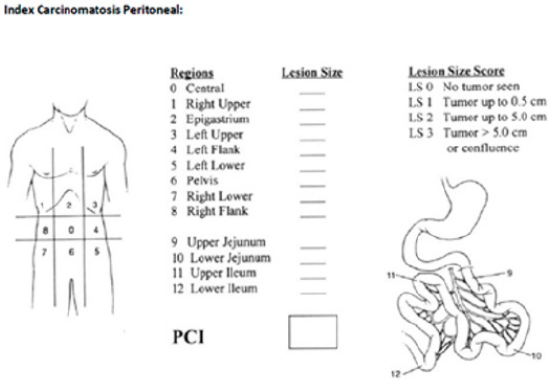


Figure A1. Sugarbaker Index Carcinomatosis Peritoneal.

Table A1. Fagotti's Index.

Fagotti's Index	0	2
Omental cake		
Peritoneal carcinosis		
Diaphragmatic carcinosis		
Mesenteric retraction		
Bowel infiltration		
Stomach infiltration		
Liver metastases		

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CAPITULO 3

Surgery in Recurrent Ovarian Cancer: a Meta – analysis.

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Capitulo 3: Surgery in Recurrent Ovarian Cancer: A Meta - Analysis

Simple Summary:

Ovarian cancer has the highest mortality rate of any type of gynecological cancer because it is diagnosed in advanced stages and its recurrence rate is about 80%. The standard treatment for recurrences of ovarian cancer is systemic chemotherapy. Secondary cytoreductive surgery may be a treatment option for selected patients. We evaluated three randomized studies to determine the effect on overall survival and disease-free survival. This analysis shows better results in this group than in the patients who were treated with chemotherapy alone, with statistically significant differences. This benefit is maintained when analyzing patients in whom complete cytoreduction is achieved. The main limitation of the selected studies is the different criteria for selecting patients for secondary cytoreduction, which is why prospective studies are needed to determine which patients will benefit from this treatment.

1. Abstract:

Background:

The second cytoreductive surgery performed for a patient who has recurrent ovarian cancer remains controversial. Our study analyzes overall survival (OS) and disease-free survival (DFS) for cytoreductive surgery in addition to chemotherapy in recurrent ovarian cancer instead of chemotherapy alone.

Methods: A meta-analysis was conducted using PubMed and the Cochrane database of systematic reviews to select randomized controlled studies. In total, three randomized studies were used, employing a total of 1249 patients.

Results: The results of our meta-analysis of these randomized controlled trials identified significant differences in OS (HR = 0.83, IC 95% 0.70–0.99, $p < 0.04$) and DFS (HR = 0.63, IC 95% 0.55–0.72, $p < 0.000001$). A subgroup analysis comparing complete cytoreductive surgery and surgery with residual tumor achieved better results for both OS (HR = 0.65, IC 95% 0.49–0.86, $p = 0.002$) and DFS (HR = 0.67, IC 95% 0.53–0.82, $p = 0.0008$), with statistical significance.

Conclusions: A complete secondary cytoreductive surgery (SCS) in recurrent ovarian cancer (ROC) demonstrates an improvement in the OS and DFS, and this benefit is most evident in cases where complete cytoreductive surgery is achieved. The challenge is the correct patient selection for secondary cytoreductive surgery to improve the results of this approach.

Keywords: secondary cytoreductive surgery; recurrent epithelial ovarian cancer; overall survival; disease-free survival; systematic revision; meta-analysis

2. Introduction

Almost 75% of new high-grade epithelial ovarian cancer diagnoses debut at an advanced stage. In this scenario, complete cytoreduction surgery is the cornerstone of management in primary treatment [1]. About 80% of patients will relapse despite chemotherapy treatment (CHT) and targeted maintenance therapy [2]. The treatment of recurrent ovarian cancer (ROC) is thus a significant clinical challenge [3]. However, the use of proteomics and the presence of mutation detection are currently being developed in advanced ovarian cancer in order to outline and establish molecular subgroups that, in the future, will allow the use of therapeutic targets, improving the prognosis of our patients [4,5].

The standard treatment for ROC patients includes intravenous CHT, chosen based on platinum sensitivity [4]. It is important to clarify the role of secondary cytoreductive surgery (SCS) in these patients and the choice of a surgical approach [1,2,5–12]. Numerous retrospective studies have shown that SCS improves overall survival (OS) in platinum-sensitive recurrent patients compared to chemotherapy alone [2] and that complete resection is the most important prognostic factor, as in the primary treatment of ovarian cancer [6–8]. Due to the fact that these studies are retrospective and too heterogeneous, they do not allow reliable conclusions [1,2,5,9,10,13,14].

Therefore, the results obtained in reference to disease-free survival (DFS) and OS associated with SCS + CHT compared to CHT present little scientific evidence [2].

Bizarri et al. demonstrated that in patients with neoadjuvant chemotherapy and interval surgery, there was no difference in progression-free survival [1], data that were extrapolated to patients with relapse [2,15].

The theoretical benefit of SCS in recurrence ovarian cancer is based on enhancement of the chemotherapeutic effect by removing large tumor volumes with a poor blood supply, equal to that of primary surgery in advanced ovarian cancer [5]. This is the reason why complete resection is the main prognostic factor in primary cytoreductive surgery in ovarian cancer, and it is possible to extrapolate this benefit to the SCS. It is a challenge to select the patients who will benefit from the procedure in primary and recurrent surgery [10].

A Cochrane meta-analysis shows a better survival outcome in ROC patients when the absence of tumor residue is achieved, particularly in platinum-sensitive patients [16]. To achieve this complete cytoreduction, predictive models must be used to allow the correct patient selection [16,17].

In DESKTOP II, a selection model for SCS is proposed based on the absence of ascites at recurrence, an Eastern cooperative oncology group (ECOG) performance status of 0, and no tumor residue at primary surgery [6]. In the study of Tian et al., the proposed selection model is based on the previous criteria in addition to FIGO stage and Ca 125 value [1].

Due to the lack of scientific evidence with sufficient statistical power during the 2010s, three randomized articles were designed to assess whether SCS + CHT has better prognostic outcomes than CHT alone in patients with recurrent ovarian cancer. It should be noted that some retrospective studies do not consider the use of maintenance therapy with iPARPs or anti-VEGF, which is why the information obtained from randomized studies in this field with a 5-year follow-up allows for highly reliable results compared to those previously published.

The purpose of this systematic review and meta-analysis is to evaluate the prognostic impact of SCS and CHT on patients with ROC (OS and DFS). Additionally, we perform a subgroup analysis to assess the impact of complete cytoreduction in these patients.

3. Methods

3.1. Search Strategy

This analysis was reported in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines (PRISMA 2020, http://www.prismastatement.org).

From 2017 to April 2022, the PubMed and Cochrane central register of controlled trials databases were systematically searched to compare the results of secondary cytoreduction surgery plus chemotherapy with the use of chemotherapy alone in recurrent ovarian cancer.

The search terms used for all databases were ('Relapse ovarian cancer' OR 'recurrent ovarian cancer') AND ('surgery'), and randomized controlled clinical trials were included. The information extracted from each article chosen according to the inclusion criteria was the following: study design, study population, median or average age, intervention method, median OS, and median DFS. The hazard ratio of the intervention measure and the 95% confidence interval (CI) for OS and DFS were obtained for each article. Currently, following the recommendations of the Vancouver consensus, optimal surgery is defined as surgery without macroscopic evidence of disease after surgery (R0) and suboptimal with evidence of a residual tumor (R1-2) [16]. In the included articles, the term incomplete surgery is used for any amount of tumor residue, and complete surgery is used to indicate no macroscopic residual disease.

3.2. Inclusion and Exclusion Criteria

According to the PICOS criteria (population, intervention, comparison, outcome, and study design), randomized clinical studies in patients with relapsed ovarian cancer comparing two treatment groups—chemotherapy alone vs. surgery plus chemotherapy—and assessing DFS and OS outcomes were selected. We included studies published in the last 5 years in the Spanish and English languages and excluded articles lacking complete cytoreduction data and with the presence of extra-abdominal disease.

3.3. Selection Process

Two review authors independently evaluated the eligibility of the papers and resolved their disagreements by discussion or by appeal to a third review author.

The search was performed using the following filters:

- Languages: English and Spanish
- Date: the last 5 years
- Type of study: randomized controlled trial

3.4. Statistical Analysis

The objective of the study is the assessment of OS and DFS using the association measure hazard ratio through the model fixed effect regardless of the heterogeneity due to the small number of articles included in the statistical analysis. The results obtained are represented using the forest plot graph. The results are considered statistically significant when the $p > 0.05$.

The heterogeneity of the articles included is assessed using the I2 tool, with a value of less than 25% being considered low heterogeneity, 50% intermediate, and greater than or equal to 75% being considered high heterogeneity.

All the results were evaluated using RevMan 5 software (Review Manager [RevMan] Version 5.4, The Cochrane Collaboration, 2020).

4. Results

4.1. Selected Studies

The search strategy uncovered a total of 6212 results in PubMed Research and 68 in Cochrane Research. After filtering articles with electronic tools and eliminating duplicates, 3 articles in PubMed and 1 article in Cochrane were selected. Finally, three articles were included in the review. Figure 1 shows the selection process carried out and the reasons for the exclusion of the articles.

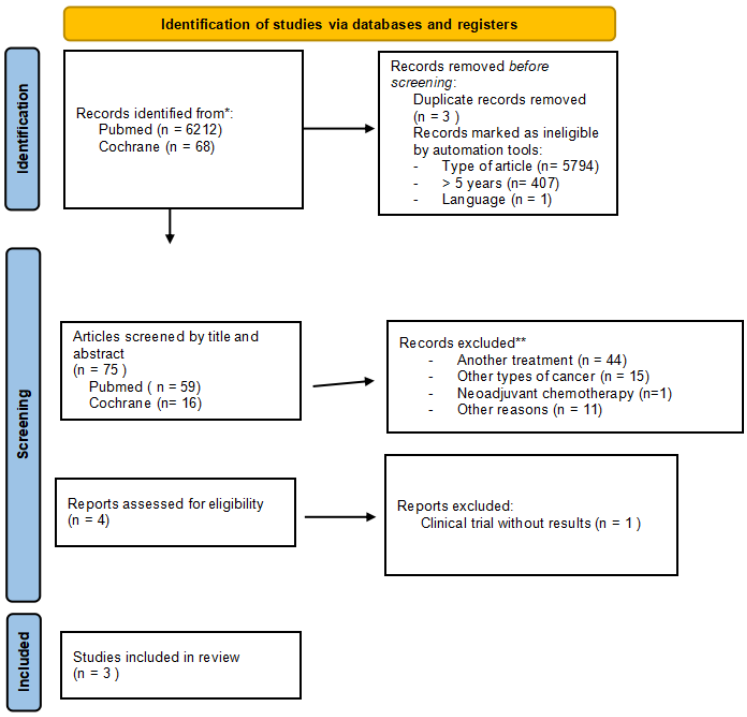


Figure 1. PRISMA diagram showing the selection process of the articles included in the study.

The three randomized clinical trials (RCTs) selected included a study population of 1249 patients. Tables 1 and 2 show highlights of the included studies. Bias analyses are detailed in Figures 2 and 3.

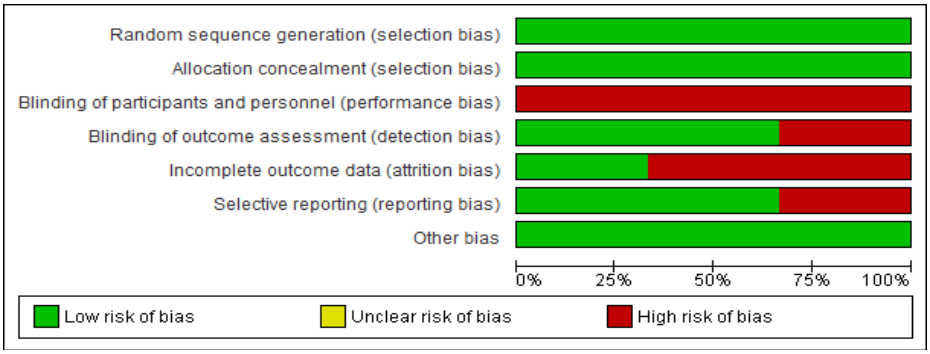


Figure 2. *Risk of bias summary.*



Figure 3. *Risk of bias graph.*

Table 1. Principal results of included randomized clinical trials.

	Groups	*N Of Patients*	*Selection Criteria*	*CTC %*	*Survival In Scs*	*Survival In No Scs*
DESKTOP III	*SCS* *No SCS*	*206* *201*	*AGO score*	*76%*	*53.7 m (OS)*	*46 m (OS)*
GOG 0213	*SCS* *No SCS*	*240* *245*	*None*	*67%*	*50.6 m (OS)*	*64.7 m (OS)*
SOC-1	*SCS* *No SCS*	*182* *175*	*IModel + PET TC*	*77%*	*58.1 m (OS)*	*53.9 m (OS)*

CTC, complete tumor cytoreduction; PFS, progression-free survival; OS, overall survival; SCS, secondary cytoreductive surgery; No SCS, q chemotherapy alone; PET TC, positron emission tomography—computed tomography.

Table 2. Characteristics of patients in randomized clinical trials.

	Age	FIGO	Platinum-Free Interval	Previous Bevacizumab	Histology
DESKTOP III	SCS 60.8 (54.2–67.3)	III 145 (70.4%) IV 16 (7.8%)	6–12 m 48 (23.6%) >12 m 155 (76.4%)	33 (16%)	Serous 177 (85.9%) Other 23 (14.1%)
	No SCS 62.2 (54.2–69.9)	III 143 (71.1%) IV 13 (6.5%)	6–12 m 47 (23.7%) >12 m 151 (76.3%)	31 (15.4%)	Serous 161 (80.1%) Other 40 (19.9%)
GOG 0213	SCS <60 years 135 (56.2%) >60 years 105 (43.8%)	NE	NE	25 (10.4%)	Serous 211 (87%) Other 29 (12.3%)

	No SCS <60 years 145 (59.1%) >60 years 100 (40.8%)				30 (12.2%)	Serous 207 (84.5%) Other 38 (15.5%)
SOC-1	SCS <54 years 80 >54 years 102 No SCS <54 years 90 >54 years 85	III 128 IV 20 III 121 IV 25	NE		NE	Serous 158 Another 24 Serous 145 Another 30

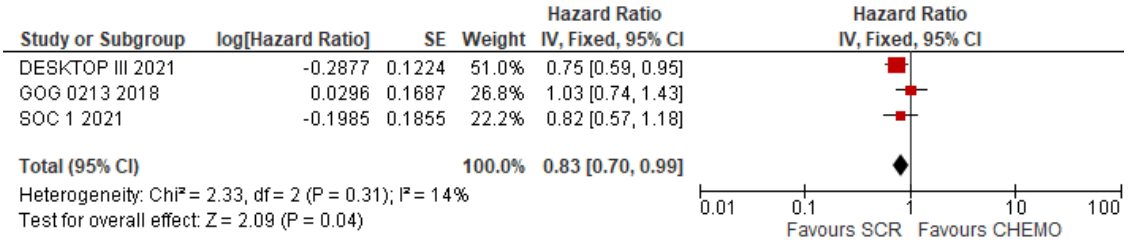
4.2. Overall meta-analyses of OS and DFS

The three articles showed OS and DFS. The results obtained from each study are represented in Table 3.

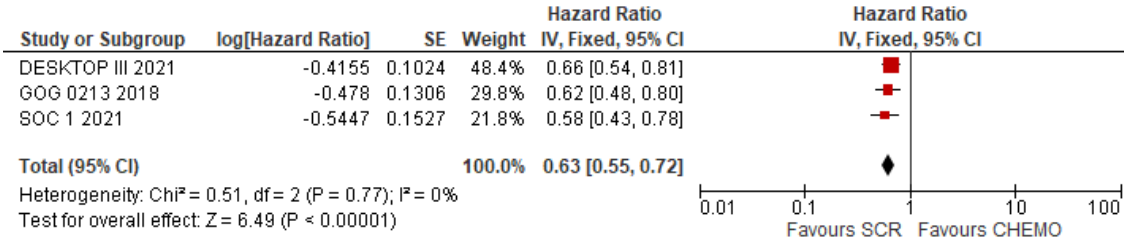
Table 3. Main results of the included articles.

	Groups	DFS (Median Months)	HR	IC 95%	P	OS (Median Months)	HR	IC 95%	P
DESKTOP III	SCS	18.4	0.66	12.7–20.8	NE	53.7	0.75	0.59–0.96	0.02
	No SCS	14				46			
GOG 0213	SCS	18.9	0.62	0.48–0.80	NE	50.6	1.03	0.74–1.43	0.08
	No SCS	16.2				64.7			
SOC-1	SCS	17.4	0.58	0.45–0.74	<0.0001	58.1	0.82	0.57–1.19	NE
	No SCS	11.9				53.9			

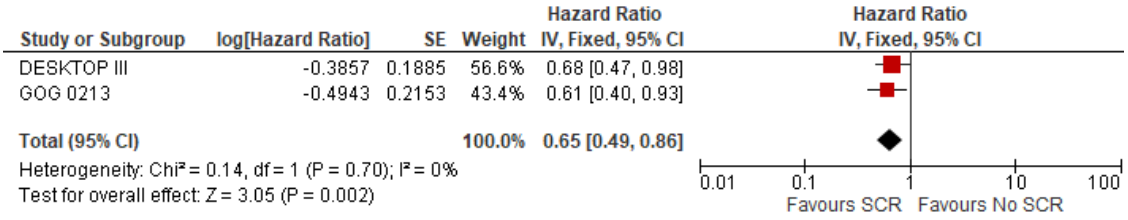
Analysis of the data obtained exhibited an improvement in OS in the secondary cytoreductive surgery group of patients compared to standard chemotherapy treatment. (HR 0.83, IC 95% 0.70–0.99, $p = 0.04$) (Figure 4a).



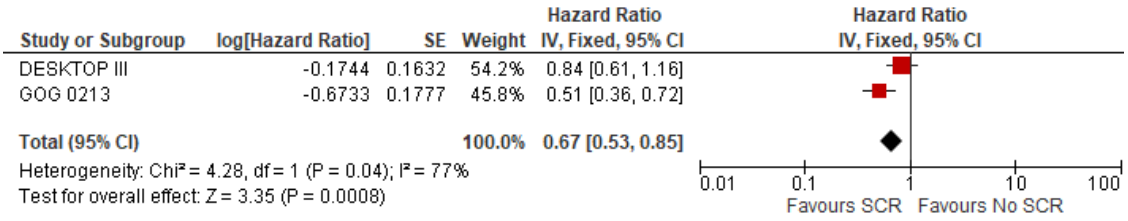
(**a**)



(**b**)



(**c**)



(**d**)

Figure 4*. (**a**): Statistical study OS: Results obtained from all studies included in the review. (**b**): Statistical study DFS: Results obtained from all studies included in the review. (**c**): Subgroup analysis of overall survival with complete cytoreductive surgery vs. residual tumor. (**d**): Subgroup analysis of disease-free survival with complete cytoreductive surgery vs. residual tumor.*

Additionally, the DFS analysis showed statistically significant differences between two groups, with an improvement in the group of patients who underwent CRS. (Figure 4b) (HR 0.63, IC 95% 0.55–0.72, $p <$ 0.000001).

3.3. Subgroup Analysis

OS and DFS results were collected and analysed according to whether complete resection was achieved. Only two studies showed relevant results. These studies suggested a statistically significant improvement in both OS (HR = 0.65, IC 95% 0.49–0.86, $p = 0.002$) and DFS (HR = 0.67, IC 95% 0.36–0.72, $p =$ 0.0008) when complete resection was achieved (Figure 4 c,d).

5. Discussion

The principal findings of our meta-analysis suggest that in patients with ROC, SCS plus chemotherapy could improve OS and DFS, and this benefit is greater in those patients without tumor residue.

The results of DESKTOP III and SOC-1 showed an improvement in overall survival and disease-free interval in the first two studies, while GOG 0213 only shows a benefit in disease-free interval in the complete resection surgery population. It is necessary to determine whether this benefit is intrinsic to the surgery or whether it derives from the selection of patients with a better prognosis [18,19]. In addition to determining the benefit derived from surgery that offsets those secondary to the economic cost of these highly complex surgeries, hospital stays, complications, and possible delays in the initiation of chemotherapy treatment.

Moreover, it is necessary to determine the patient groups most likely to benefit from this treatment. [16,18,20]

The ability to select ideal candidates for secondary surgery represents a clinical challenge, as has already been seen in primary cytoreductive surgery [1,3,4,9,13*].*

Two of the articles analyzed used methods for selecting patients for secondary cytoreduction.

Coincidentally, the same two articles showed the best results for OS and DFS in the SCS group (DESKTOP III and SOC-1) [19,21]. In the GOG 0213 study, the selection criterion was the surgeon's decision; these differences in OS between the two groups were not evident, but a better prognosis was observed in the

chemotherapy group [7]. However, better results for DFS were evidenced in the SCS group. These are the data used in the statistical analysis because the complete debulking rate in this article was the lowest of the three, there was an unspecified percentage of cross-over between the non-surgical and surgical groups that could benefit the chemotherapy group alone, and patient selection was based on surgeon judgment. Therefore, to minimize heterogeneity, it was decided to use this hazard ratio value.
The method of patient selection was an important difference between the studies.
The DESKTOP-III trial used the selection method described in DESKTOP-I (AGO score) [6].
This method is based on presenting a performance status of 0 according to the Eastern cooperative oncology group (ECOG) scale, the presence of ascites at recurrence, and complete resection at primary surgery. This algorithm has a predicted rate of complete cytoreduction in patients with recurrence of more than 66% [4,9,19].
By contrast, in the SOC-1 article, the algorithm is based on the following clinical data: FIGO stage at diagnosis, presence of residual tumor at primary surgery, platinum sensitivity interval, performance status (ECOG), Ca 125 level at relapse, and the presence of ascites at recurrence, with the addition of PET CT findings [1,21].
The selection criteria in the models used in DESKTOP III and SOC-1 are different, so the selected population differs between them. The iMODEL in SOC-1 selected more candidates; moreover, these patients are younger compared with those enrolled in DESKTOP III and GOG 0213 [22–24]. That fact could explain the improvement in results and the higher selection of patients for the experimental group in SOC-1. However, the platinum-free interval in the SOC-1 study is the shortest of all, being 16 months, compared to 20.4 months in GOG 0213 and 21.1 in DESKTOP III, which could translate into a worse prognosis profile.
The DESKTOP-III and SOC-1 trials led to complete resection in 74.5% and 77% of the patients, respectively, higher percentages than obtained in the GOG-0213 trial (67%) [1,5,19,24]. Due to the aforementioned, it seems that an objective model for selecting patients who are candidates for SCS could be the reason for the higher rates of complete cytoreduction and evidence of impact on OS and DFS in the SCS group in both trials (DESKTOP-III and SOC-1), in contrast to the GOG-0213 trial.
Another factor to consider in the selection of patients for SCS is that it is based on patient selection models that do not include laparoscopic assessment. Llueca et al. show that for proper selection of patients for primary surgery, the addition of diagnostic laparoscopy increases the accuracy of patient selection [18,22–24]. Similarly, Gallota et al. show that the use of laparoscopy in selected patients with ROC allows cytoreduction to be performed in addition to assessment of the extent of disease [14,25]. It is possible that the addition of diagnostic laparoscopy in the previous selection model increased the number of patients with complete resection.
Another difference is the use of adjuvant therapy in three articles, specifically the use of bevacizumab. The activity of bevacizumab is not comparable to the beneficial effect of surgery in patients with recurrence [5,26,27]. Bevacizumab was used in 84% of patients in the GOG-0213 trial, while it was only used in 23% and 1% of patients in DESKTOP III and SOC-1, respectively, in the non-surgical chemotherapy group. It should be noted that the latter two trials were mainly surgical, while GOG-0213 performed a mixture of chemotherapy and surgery in patients with ROC.
To assess the effect of bevacizumab, GOG 0213 conducted an analysis in the group of patients who had not received maintenance bevacizumab. This subgroup showed persistent improvement in the benefit of chemotherapy over SCR regardless of bevacizumab use, with an OS of 67 months in the first group compared to 32.4 months in the SCR group [2,9,24].
However, it should be noted that these results were obtained in a subgroup of patients that corresponds to less than 20% of the total number of patients included, this subgroup not having been defined prospectively and before the article was written [7,9].
Moreover, only 6% of patients enrolled had not received bevacizumab at the time of randomization. A detriment in OS was observed in the surgery group that did not receive bevacizumab (HR: 2.29, 95% IC: 1.31–3.88); meanwhile, this difference was not that evident in the surgery and no surgery groups plus

bevacizumab: 61.7 months vs. 58.5 months, respectively. It is possible that the non-use of bevacizumab makes subsequent lines of therapy less likely to affect long-term outcomes [26,27].
Although the subgroup of patients who did not receive bevacizumab in the DESKTOP III and in the SOC-1 trials (77% and 99% of the trial population, respectively) was larger than that in the GOG-0213 trial, the analysis of this subgroup was neither blind nor placebocontrolled, and the analysis of this subgroup was not established in the initial study design, which created a substantial bias, and the results are of low confidence [5,19,24].
Chemotherapy treatment after CRS is not standardized and was different in the included studies.
It is possible that the choice of one treatment or another is influenced by different factors, such as postoperative complications, randomization outcome, residual tumor, or the preferences of patients or investigators.
Therefore, it is not possible to draw conclusions about the benefit of bevacizumab in patients with incomplete surgery or whether the effect of bevacizumab is comparable to the benefit of surgery in relapsed ovarian cancer [23].
Another key point is that the overall survival of patients in the chemotherapy group in GOG 0213 is longer than expected in that population group, at 64.7 months, based on the results of published retrospective studies [7].
The OS obtained in GOG 0213 in the SCR group is 56 months, with no statistically significant differences compared to the chemotherapy group [7,9]. This decrease in survival could be a consequence of the delay in starting chemotherapy after surgery. In SOC-1, the period from surgery to the start of chemotherapy was 16 days, while in GOG 0213 it was 40 days. In this same study, a post hoc study was performed showing an increased risk of death after 25 days with a delay in chemotherapy [7]. This worsening in survival due to the delay of chemotherapy had already been demonstrated in retrospective studies.
Another limitation of the included studies is the cross-over of patients from the standard treatment group to the SCR group, which in SOC-1 reaches up to 37% of patients.
This fact is a selection bias, decreasing the statistical power of the study to detect a negative result in OS in the control group [24].
All three studies are multicenter studies, and it is convenient to highlight the need to perform complete cytoreduction surgeries in reference centers to ensure excellence in the procedure [28–30]. In DESKTOP-III and SOC-1, it is specified in the material and methods that the centers chosen to be included in the study were selected according to the number of procedures they had performed on patients with advanced ovarian cancer and previous experience in studies in ovarian cancer, which possibly also influenced the rates of complete cytoreduction. GOG 0213 does not specify the method of selection used by the centers included in the study.
In the present meta-analysis, there are a few limitations, as we have observed during the discussion. First, several criteria were used to select patients for randomization, which could lead to selective bias. Second is the absence of standardization of complementary treatment after surgery (addition of bevacizumab or iPARP to conventional chemotherapy). There are other factors to consider in the ROC, such as tumor histology, somatic or germline mutation, homologous recombination deficiency (HRD) or BRCA status, previous use or relapse during use of antiangiogenic drug (bevacizumab) or PARP inhibitor (PARPi) treatment, and the pattern of relapse presentation [13,26,27,31–33], which could change the management of the ROC [33–36]. Some of these treatments have shown a DFS benefit among patients with ROC.
Moreover, it has been shown that in a certain group of patients with BRCA1/BRCA2 wild type, they present an immune profile of the tumor showing the expression of PD-1/PDL-1 that would benefit from the treatment of iPARP associated with immunotherapy directed at these two biomarkers. That is why, currently, the genomic analysis of the tumor is a fundamental step in the treatment of patients with ovarian cancer [35,37,38].

A weakness of the included studies is that none of them specify the pattern of relapse or the mutational status of BRCA. This could imply a selection bias because the somatic or germline mutation in BRCA 1/2 confers chemosensitivity. In addition, BRCA status plays a role in the treatment of patients with relapse [38,39]. BRCA mutational status appears to determine the possibility of secondary cytoreduction in patients with liver metastases showing better PFS, which is relevant information to know in patients with ovarian cancer [38].

The principal strength of this meta-analysis is that it is the only study that includes the results of three RCTs, which gives the results of this study the highest level of evidence to date in the surgical treatment of ROC. Another strength of this study is that the low percentage of heterogeneity obtained when comparing the RCTs offers a high level of evidence for the results of the meta-analysis.

The results of this review show an improvement in OS and DFS in those patients who underwent SCR. This benefit is increased in those in which complete cytoreduction is achieved.

These findings are consistent with the benefit of chemotherapy in patients with complete debulking in primary surgery due to the hypothesized potential effect of chemotherapy in patients without residual tumors.

6. Conclusion

In conclusion, SCR might result in improved DFS and OS in patients with ROC. Complete cytoreductive surgery could bring survival benefits. The achievement of complete surgery highlights the need for the development of a selection model for secondary cytoreductive surgery. These findings redefine a new standard of care for patients with recurrent, platinum-sensitive ovarian cancer. However, it is worth considering the possibility of a change in the recurrence type in patients on targeted maintenance therapy, as platinum sensitivity classification may not be sufficient to determine whether a patient is amenable to surgery for ovarian cancer relapse.

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Conflicts of interest: The authors declare that they have no competing interests.

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Review

Surgery in Recurrent Ovarian Cancer: A Meta-Analysis

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Simple Summary: Ovarian cancer has the highest mortality rate of any type of gynecological cancer because it is diagnosed in advanced stages and its recurrence rate is about 80%. The standard treatment for recurrences of ovarian cancer is systemic chemotherapy. Secondary cytoreductive surgery may be a treatment option for selected patients. We evaluated three randomized studies to determine the effect on overall survival and disease-free survival. This analysis shows better results in this group than in the patients who were treated with chemotherapy alone, with statistically significant differences. This benefit is maintained when analyzing patients in whom complete cytoreduction is achieved. The main limitation of the selected studies is the different criteria for selecting patients for secondary cytoreduction, which is why prospective studies are needed to determine which patients will benefit from this treatment.

Abstract: Background: The second cytoreductive surgery performed for a patient who has recurrent ovarian cancer remains controversial. Our study analyzes overall survival (OS) and disease-free survival (DFS) for cytoreductive surgery in addition to chemotherapy in recurrent ovarian cancer instead of chemotherapy alone. **Methods**: A meta-analysis was conducted using PubMed and the Cochrane database of systematic reviews to select randomized controlled studies. In total, three randomized studies were used, employing a total of 1249 patients. **Results**: The results of our meta-analysis of these randomized controlled trials identified significant differences in OS (HR = 0.83, IC 95% 0.70–0.99, $p < 0.04$) and DFS (HR = 0.63, IC 95% 0.55–0.72, $p < 0.000001$). A subgroup analysis comparing complete cytoreductive surgery and surgery with residual tumor achieved better results for both OS (HR = 0.65, IC 95% 0.49–0.86, $p = 0.002$) and DFS (HR = 0.67, IC 95% 0.53–0.82, $p = 0.0008$), with statistical significance. **Conclusions**: A complete secondary cytoreductive surgery (SCS) in recurrent ovarian cancer (ROC) demonstrates an improvement in the OS and DFS, and this benefit is most evident in cases where complete cytoreductive surgery is achieved. The challenge is the correct patient selection for secondary cytoreductive surgery to improve the results of this approach.

Keywords: secondary cytoreductive surgery; recurrent epithelial ovarian cancer; overall survival; disease-free survival; systematic revision; meta-analysis

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1. Introduction

Almost 75% of new high-grade epithelial ovarian cancer diagnoses debut at an advanced stage. In this scenario, complete cytoreduction surgery is the cornerstone of management in primary treatment [1].

About 80% of patients will relapse despite chemotherapy treatment (CHT) and targeted maintenance therapy [2]. The treatment of recurrent ovarian cancer (ROC) is thus a significant clinical challenge [3].

However, the use of proteomics and the presence of mutation detection are currently being developed in advanced ovarian cancer in order to outline and establish molecular subgroups that, in the future, will allow the use of therapeutic targets, improving the prognosis of our patients [4,5].

The standard treatment for ROC patients includes intravenous CHT, chosen based on platinum sensitivity [4]. It is important to clarify the role of secondary cytoreductive surgery (SCS) in these patients and the choice of a surgical approach [1,2,5–12].

Numerous retrospective studies have shown that SCS improves overall survival (OS) in platinum-sensitive recurrent patients compared to chemotherapy alone [2] and that complete resection is the most important prognostic factor, as in the primary treatment of ovarian cancer [6–8].

Due to the fact that these studies are retrospective and too heterogeneous, they do not allow reliable conclusions [1,2,5,9,10,13,14].

Therefore, the results obtained in reference to disease-free survival (DFS) and OS associated with SCS + CHT compared to CHT present little scientific evidence [2].

Bizarri et al. demonstrated that in patients with neoadjuvant chemotherapy and interval surgery, there was no difference in progression-free survival [1], data that were extrapolated to patients with relapse [2,15].

The theoretical benefit of SCS in recurrence ovarian cancer is based on enhancement of the chemotherapeutic effect by removing large tumor volumes with a poor blood supply, equal to that of primary surgery in advanced ovarian cancer [5]. This is the reason why complete resection is the main prognostic factor in primary cytoreductive surgery in ovarian cancer, and it is possible to extrapolate this benefit to the SCS. It is a challenge to select the patients who will benefit from the procedure in primary and recurrent surgery [10].

A Cochrane meta-analysis shows a better survival outcome in ROC patients when the absence of tumor residue is achieved, particularly in platinum-sensitive patients [16]. To achieve this complete cytoreduction, predictive models must be used to allow the correct patient selection [16,17].

In DESKTOP II, a selection model for SCS is proposed based on the absence of ascites at recurrence, an Eastern cooperative oncology group (ECOG) performance status of 0, and no tumor residue at primary surgery [6]. In the study of Tian et al., the proposed selection model is based on the previous criteria in addition to FIGO stage and Ca 125 value [1].

Due to the lack of scientific evidence with sufficient statistical power during the 2010s, three randomized articles were designed to assess whether SCS + CHT has better prognostic outcomes than CHT alone in patients with recurrent ovarian cancer.

It should be noted that some retrospective studies do not consider the use of maintenance therapy with iPARPs or anti-VEGF, which is why the information obtained from randomized studies in this field with a 5-year follow-up allows for highly reliable results compared to those previously published.

The purpose of this systematic review and meta-analysis is to evaluate the prognostic impact of SCS and CHT on patients with ROC (OS and DFS). Additionally, we perform a subgroup analysis to assess the impact of complete cytoreduction in these patients.

2. Methods

2.1. Search Strategy

This analysis was reported in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines (PRISMA 2020, http://www.prismastatement.org).

From 2017 to April 2022, the PubMed and Cochrane central register of controlled trials databases were systematically searched to compare the results of secondary cytoreduction surgery plus chemotherapy with the use of chemotherapy alone in recurrent ovarian cancer.

The search terms used for all databases were ('Relapse ovarian cancer' OR 'recurrent ovarian cancer') AND ('surgery'), and randomized controlled clinical trials were included. The information extracted from each article chosen according to the inclusion criteria was

the following: study design, study population, median or average age, intervention method, median OS, and median DFS. The hazard ratio of the intervention measure and the 95% confidence interval (CI) for OS and DFS were obtained for each article.

Currently, following the recommendations of the Vancouver consensus, optimal surgery is defined as surgery without macroscopic evidence of disease after surgery (R0) and suboptimal with evidence of a residual tumor (R1-2) [16]. In the included articles, the term incomplete surgery is used for any amount of tumor residue, and complete surgery is used to indicate no macroscopic residual disease.

2.2. Inclusion and Exclusion Criteria

According to the PICOS criteria (population, intervention, comparison, outcome, and study design), randomized clinical studies in patients with relapsed ovarian cancer comparing two treatment groups—chemotherapy alone vs. surgery plus chemotherapy—and assessing DFS and OS outcomes were selected. We included studies published in the last 5 years in the Spanish and English languages and excluded articles lacking complete cytoreduction data and with the presence of extra-abdominal disease.

2.3. Selection Process

Two review authors independently evaluated the eligibility of the papers and resolved their disagreements by discussion or by appeal to a third review author.

The search was performed using the following filters:

- Languages: English and Spanish
- Date: the last 5 years
- Type of study: randomized controlled trial

2.4. Statistical Analysis

The objective of the study is the assessment of OS and DFS using the association measure hazard ratio through the model fixed effect regardless of the heterogeneity due to the small number of articles included in the statistical analysis. The results obtained are represented using the forest plot graph. The results are considered statistically significant when the $p > 0.05$.

The heterogeneity of the articles included is assessed using the I2 tool, with a value of less than 25% being considered low heterogeneity, 50% intermediate, and greater than or equal to 75% being considered high heterogeneity.

All the results were evaluated using RevMan 5 software (Review Manager [RevMan] Version 5.4, The Cochrane Collaboration, 2020).

3. Results

3.1. Selected Studies

The search strategy uncovered a total of 6212 results in PubMed Research and 68 in Cochrane Research. After filtering articles with electronic tools and eliminating duplicates, 3 articles in PubMed and 1 article in Cochrane were selected. Finally, three articles were included in the review. Figure 1 shows the selection process carried out and the reasons for the exclusion of the articles.

The three randomized clinical trials (RCTs) selected included a study population of 1249 patients. Tables 1 and 2 show highlights of the included studies. Bias analyses are detailed in Figures 2 and 3.

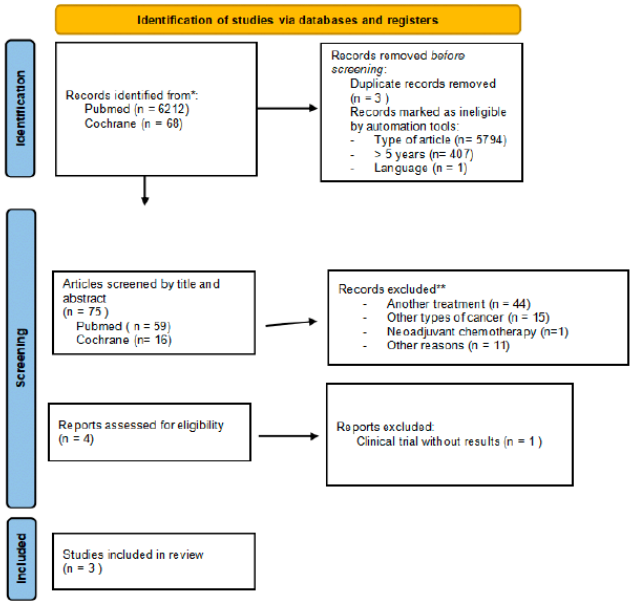


Figure 1. PRISMA diagram showing the selection process of the articles included in the study.

Table 1. Principal results of included randomized clinical trials.

	Groups	N of Patients	Selection Criteria	CTC %	Survival in SCS	Survival in No SCS
DESKTOP III	SCS No SCS	206 201	AGO score	76%	53.7 m (OS)	46 m (OS)
GOG 0213	SCS No SCS	240 245	None	67%	50.6 m (OS)	64.7 m (OS)
SOC-1	SCS No SCS	182 175	IModel + PET TC	77%	58.1 m (OS)	53.9 m (OS)

CTC, complete tumor cytoreduction; PFS, progression-free survival; OS, overall survival; SCS, secondary cytoreductive surgery; No SCS, chemotherapy alone; PET TC, positron emission tomography—computed tomography.

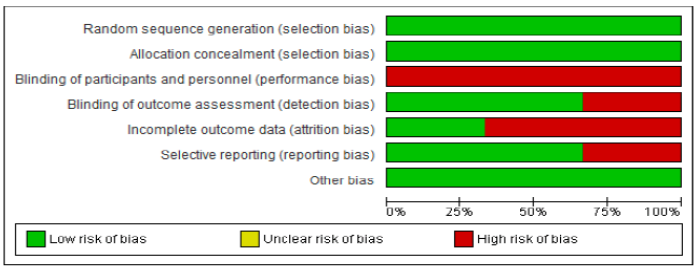


Figure 2. Risk of bias summary.

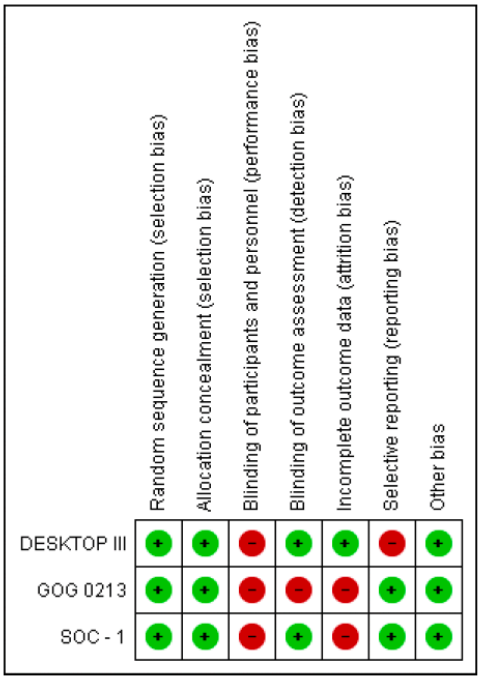


Figure 3. Risk of bias graph.

Table 2. Characteristics of patients in randomized clinical trials.

	Age	FIGO	Platinum-Free Interval	Previous Bevacizumab	Histology
DESKTOP III	SCS 60.8 (54.2–67.3)	III 145 (70.4%) IV 16 (7.8%)	6–12 m 48 (23.6%) >12 m 155 (76.4%)	33 (16%)	Serous 177 (85.9%) Other 23 (14.1%)
	No SCS 62.2 (54.2–69.9)	III 143 (71.1%) IV 13 (6.5%)	6–12 m 47 (23.7%) >12 m 151 (76.3%)	31 (15.4%)	Serous 161 (80.1%) Other 40 (19.9%)
GOG 0213	SCS <60 years 135 (56.2%) >60 years 105 (43.8%)	NE	NE	25 (10.4%)	Serous 211 (87%) Other 29 (12.3%)
	No SCS <60 years 145 (59.1%) >60 years 100 (40.8%)			30 (12.2%)	Serous 207 (84.5%) Other 38 (15.5%)
SOC-1	SCS <54 years 80 >54 years 102	III 128 IV 20	NE	NE	Serous 158 Another 24
	No SCS <54 years 90 >54 years 85	III 121 IV 25			Serous 145 Another 30

3.2. Overall Meta-Analyses of OS and DFS

The three articles showed OS and DFS. The results obtained from each study are represented in Table 3.

Table 3. Main results of the included articles.

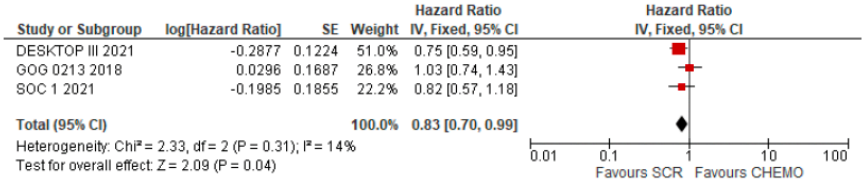
	Groups	DFS (Median Months)	HR	IC 95%	*P*	OS (Median Months)	HR	IC 95%	*P*
DESKTOP III	SCS	18.4	0.66	12.7–20.8	NE	53.7	0.75	0.59–0.96	0.02
	No SCS	14				46			
GOG 0213	SCS	18.9	0.62	0.48–0.80	NE	50.6	1.03	0.74–1.43	0.08
	No SCS	16.2				64.7			
SOC-1	SCS	17.4	0.58	0.45–0.74	<0.0001	58.1	0.82	0.57–1.19	NE
	No SCS	11.9				53.9			

Analysis of the data obtained exhibited an improvement in OS in the secondary cytoreductive surgery group of patients compared to standard chemotherapy treatment. (HR 0.83, IC 95% 0.70–0.99, $p = 0.04$) (Figure 4a).

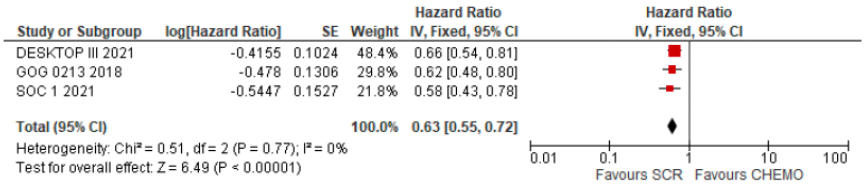
Additionally, the DFS analysis showed statistically significant differences between two groups, with an improvement in the group of patients who underwent CRS (Figure 4b) (HR 0.63, IC 95% 0.55–0.72, $p < 0.000001$).

3.3. Subgroup Analysis

OS and DFS results were collected and analysed according to whether complete resection was achieved. Only two studies showed relevant results. These studies suggested a statistically significant improvement in both OS (HR = 0.65, IC 95% 0.49–0.86, $p = 0.002$) and DFS (HR = 0.67, IC 95% 0.36–0.72, $p = 0.0008$) when complete resection was achieved (Figure 4c,d).

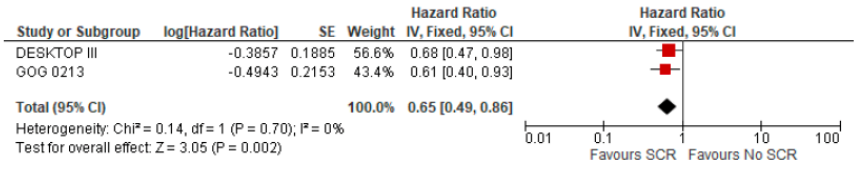


(**a**)

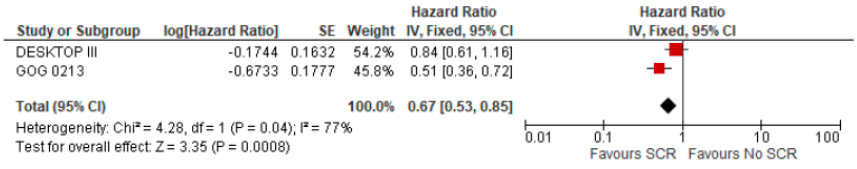


(**b**)

Figure 4. *Cont.*



(**c**)



(**d**)

Figure 4. (**a**): Statistical study OS: Results obtained from all studies included in the review. (**b**): Statistical study DFS: Results obtained from all studies included in the review. (**c**): Subgroup analysis of overall survival with complete cytoreductive surgery vs. residual tumor. (**d**): Subgroup analysis of disease-free survival with complete cytoreductive surgery vs. residual tumor.

4. Discussion

The principal findings of our meta-analysis suggest that in patients with ROC, SCS plus chemotherapy could improve OS and DFS, and this benefit is greater in those patients without tumor residue.

The results of DESKTOP III and SOC-1 showed an improvement in overall survival and disease-free interval in the first two studies, while GOG 0213 only shows a benefit in disease-free interval in the complete resection surgery population.

It is necessary to determine whether this benefit is intrinsic to the surgery or whether it derives from the selection of patients with a better prognosis [18,19]. In addition to determining the benefit derived from surgery that offsets those secondary to the economic cost of these highly complex surgeries, hospital stays, complications, and possible delays in the initiation of chemotherapy treatment.

Moreover, it is necessary to determine the patient groups most likely to benefit from this treatment. [16,18,20]

The ability to select ideal candidates for secondary surgery represents a clinical challenge, as has already been seen in primary cytoreductive surgery [1,3,4,9,13].

Two of the articles analyzed used methods for selecting patients for secondary cytoreduction. Coincidentally, the same two articles showed the best results for OS and DFS in the SCS group (DESKTOP III and SOC-1) [19,21]. In the GOG 0213 study, the selection criterion was the surgeon's decision; these differences in OS between the two groups were not evident, but a better prognosis was observed in the chemotherapy group [7]. However, better results for DFS were evidenced in the SCS group. These are the data used in the statistical analysis because the complete debulking rate in this article was the lowest of the three, there was an unspecified percentage of cross-over between the non-surgical and surgical groups that could benefit the chemotherapy group alone, and patient selection was based on surgeon judgment. Therefore, to minimize heterogeneity, it was decided to use this hazard ratio value.

The method of patient selection was an important difference between the studies. The DESKTOP-III trial used the selection method described in DESKTOP-I (AGO score) [6]. This method is based on presenting a performance status of 0 according to the Eastern cooperative oncology group (ECOG) scale, the presence of ascites at recurrence, and

complete resection at primary surgery. This algorithm has a predicted rate of complete cytoreduction in patients with recurrence of more than 66% [4,9,19].

By contrast, in the SOC-1 article, the algorithm is based on the following clinical data: FIGO stage at diagnosis, presence of residual tumor at primary surgery, platinum sensitivity interval, performance status (ECOG), Ca 125 level at relapse, and the presence of ascites at recurrence, with the addition of PET CT findings [1,21].

The selection criteria in the models used in DESKTOP III and SOC-1 are different, so the selected population differs between them. The iMODEL in SOC-1 selected more candidates; moreover, these patients are younger compared with those enrolled in DESKTOP III and GOG 0213 [22–24]. That fact could explain the improvement in results and the higher selection of patients for the experimental group in SOC-1. However, the platinum-free interval in the SOC-1 study is the shortest of all, being 16 months, compared to 20.4 months in GOG 0213 and 21.1 in DESKTOP III, which could translate into a worse prognosis profile.

The DESKTOP-III and SOC-1 trials led to complete resection in 74.5% and 77% of the patients, respectively, higher percentages than obtained in the GOG-0213 trial (67%) [1,5,19,24]. Due to the aforementioned, it seems that an objective model for selecting patients who are candidates for SCS could be the reason for the higher rates of complete cytoreduction and evidence of impact on OS and DFS in the SCS group in both trials (DESKTOP-III and SOC-1), in contrast to the GOG-0213 trial.

Another factor to consider in the selection of patients for SCS is that it is based on patient selection models that do not include laparoscopic assessment. Llueca et al. show that for proper selection of patients for primary surgery, the addition of diagnostic laparoscopy increases the accuracy of patient selection [18,22–24]. Similarly, Gallota et al. show that the use of laparoscopy in selected patients with ROC allows cytoreduction to be performed in addition to assessment of the extent of disease [14,25]. It is possible that the addition of diagnostic laparoscopy in the previous selection model increased the number of patients with complete resection.

Another difference is the use of adjuvant therapy in three articles, specifically the use of bevacizumab. The activity of bevacizumab is not comparable to the beneficial effect of surgery in patients with recurrence [5,26,27]. Bevacizumab was used in 84% of patients in the GOG-0213 trial, while it was only used in 23% and 1% of patients in DESKTOP III and SOC-1, respectively, in the non-surgical chemotherapy group. It should be noted that the latter two trials were mainly surgical, while GOG-0213 performed a mixture of chemotherapy and surgery in patients with ROC.

To assess the effect of bevacizumab, GOG 0213 conducted an analysis in the group of patients who had not received maintenance bevacizumab. This subgroup showed persistent improvement in the benefit of chemotherapy over SCR regardless of bevacizumab use, with an OS of 67 months in the first group compared to 32.4 months in the SCR group [2,9,24].

However, it should be noted that these results were obtained in a subgroup of patients that corresponds to less than 20% of the total number of patients included, this subgroup not having been defined prospectively and before the article was written [7,9].

Moreover, only 6% of patients enrolled had not received bevacizumab at the time of randomization. A detriment in OS was observed in the surgery group that did not receive bevacizumab (HR: 2.29, 95% IC: 1.31–3.88); meanwhile, this difference was not that evident in the surgery and no surgery groups plus bevacizumab: 61.7 months *vs.* 58.5 months, respectively. It is possible that the non-use of bevacizumab makes subsequent lines of therapy less likely to affect long-term outcomes [26,27].

Although the subgroup of patients who did not receive bevacizumab in the DESKTOP III and in the SOC-1 trials (77% and 99% of the trial population, respectively) was larger than that in the GOG-0213 trial, the analysis of this subgroup was neither blind nor placebo-controlled, and the analysis of this subgroup was not established in the initial study design, which created a substantial bias, and the results are of low confidence [5,19,24].

Chemotherapy treatment after CRS is not standardized and was different in the included studies.

It is possible that the choice of one treatment or another is influenced by different factors, such as postoperative complications, randomization outcome, residual tumor, or the preferences of patients or investigators.

Therefore, it is not possible to draw conclusions about the benefit of bevacizumab in patients with incomplete surgery or whether the effect of bevacizumab is comparable to the benefit of surgery in relapsed ovarian cancer [23].

Another key point is that the overall survival of patients in the chemotherapy group in GOG 0213 is longer than expected in that population group, at 64.7 months, based on the results of published retrospective studies [7].

The OS obtained in GOG 0213 in the SCR group is 56 months, with no statistically significant differences compared to the chemotherapy group [7,9]. This decrease in survival could be a consequence of the delay in starting chemotherapy after surgery. In SOC-1, the period from surgery to the start of chemotherapy was 16 days, while in GOG 0213 it was 40 days. In this same study, a post hoc study was performed showing an increased risk of death after 25 days with a delay in chemotherapy [7]. This worsening in survival due to the delay of chemotherapy had already been demonstrated in retrospective studies.

Another limitation of the included studies is the cross-over of patients from the standard treatment group to the SCR group, which in SOC-1 reaches up to 37% of patients. This fact is a selection bias, decreasing the statistical power of the study to detect a negative result in OS in the control group [24].

All three studies are multicenter studies, and it is convenient to highlight the need to perform complete cytoreduction surgeries in reference centers to ensure excellence in the procedure [28–30]. In DESKTOP-III and SOC-1, it is specified in the material and methods that the centers chosen to be included in the study were selected according to the number of procedures they had performed on patients with advanced ovarian cancer and previous experience in studies in ovarian cancer, which possibly also influenced the rates of complete cytoreduction. GOG 0213 does not specify the method of selection used by the centers included in the study.

In the present meta-analysis, there are a few limitations, as we have observed during the discussion. First, several criteria were used to select patients for randomization, which could lead to selective bias. Second is the absence of standardization of complementary treatment after surgery (addition of bevacizumab or iPARP to conventional chemotherapy).

There are other factors to consider in the ROC, such as tumor histology, somatic or germline mutation, homologous recombination deficiency (HRD) or BRCA status, previous use or relapse during use of antiangiogenic drug (bevacizumab) or PARP inhibitor (PARPi) treatment, and the pattern of relapse presentation [13,26,27,31–33], which could change the management of the ROC [33–36]. Some of these treatments have shown a DFS benefit among patients with ROC.

Moreover, it has been shown that in a certain group of patients with BRCA1/BRCA2 wild type, they present an immune profile of the tumor showing the expression of PD-1/PDL-1 that would benefit from the treatment of iPARP associated with immunotherapy directed at these two biomarkers. That is why, currently, the genomic analysis of the tumor is a fundamental step in the treatment of patients with ovarian cancer [35,37,38].

A weakness of the included studies is that none of them specify the pattern of relapse or the mutational status of BRCA. This could imply a selection bias because the somatic or germline mutation in BRCA 1/2 confers chemosensitivity. In addition, BRCA status plays a role in the treatment of patients with relapse [38,39]. BRCA mutational status appears to determine the possibility of secondary cytoreduction in patients with liver metastases showing better PFS, which is relevant information to know in patients with ovarian cancer [38].

The principal strength of this meta-analysis is that it is the only study that includes the final results of three RCTs, which gives the results of this study the highest level of evidence to date in the surgical treatment of ROC. Another strength of this study is that the

low percentage of heterogeneity obtained when comparing the RCTs offers a high level of evidence for the results of the meta-analysis.

The results of this review show an improvement in OS and DFS in those patients who underwent SCR. This benefit is increased in those in which complete cytoreduction is achieved.

These findings are consistent with the benefit of chemotherapy in patients with complete debulking in primary surgery due to the hypothesized potential effect of chemotherapy in patients without residual tumors.

5. Conclusions

In conclusion, SCR might result in improved DFS and OS in patients with ROC. Complete cytoreductive surgery could bring survival benefits. The achievement of complete surgery highlights the need for the development of a selection model for secondary cytoreductive surgery. These findings redefine a new standard of care for patients with recurrent, platinum-sensitive ovarian cancer. However, it is worth considering the possibility of a change in the recurrence type in patients on targeted maintenance therapy, as platinum sensitivity classification may not be sufficient to determine whether a patient is amenable to surgery for ovarian cancer relapse.

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CAPITULO 4

Should we abandon the use of intraperitoneal chemotherapy in the treatment of ovarian cancer? A meta - analysis.

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CAPITULO 4: Should We Abandon Intraperitoneal Chemotherapy in the Treatment of Advanced Ovarian Cancer? A Meta – Analysis.

1. Abstract:

Background:

Ovarian cancer is the gynaecological malignancy with the highest mortality and diagnosis often occurs in its advanced stages. Standard treatment in these cases is based on complete cytoreductive surgery with adjuvant intravenous chemotherapy. Other types of treatment are being evaluated to improve the prognosis of these patients, including intraperitoneal chemotherapy and antiangiogenic therapy. These may improve survival or time to relapse in addition to intravenous chemotherapy.

Objective:

The aim of this meta-analysis is to determine whether treatment with intravenous chemotherapy remains the gold standard, or whether the addition of intraperitoneal chemotherapy has a benefit in overall survival (OS) and disease-free interval (DFS).

Materials and methods:

A literature search was carried out in Pubmed and Cochrane, selecting clinical studies and systematic reviews published in the last 10 years. Statistical analysis was performed using the hazard ratio measure in the RevMan tool.

Results: Intraperitoneal chemotherapy shows a benefit in OS and DFS compared with standard intravenous chemotherapy. The significant differences in OS (HR: 0.81 CI 95% 0.74–0.88) and in DFS (HR: 0.81 CI 95% 0.75–0.87) are statistically significant ($p < 0.00001$). There were no clinical differences in toxicity and side-effects. Conclusion**:** Intraperitoneal chemotherapy is an option that improves OS and DFS without significant toxicity regarding the use of intravenous chemotherapy alone. However, prospective studies are needed to determine the optimal dose and treatment regimen that will maintain the benefits while minimising side effects and toxicity and the profile of patients who will benefit most from this treatment.

Simple Summary:

Ovarian cancer is the third most common gynaecological cancer but also the cancer with the highest mortality. It is usually diagnosed during the advanced stages and the standard treatment is primary surgery followed by adjuvant intravenous chemotherapy. Three randomised studies have shown that the intraperitoneal chemotherapy increased overall survival and disease-free interval in patients with ovarian cancer; however, its use has not been generalised, and it has not been established as a part of clinical treatment guidelines. Here, we perform a meta-analysis of the last ten years of bibliographic evidence comparing the application of intraperitoneal chemotherapy with standard treatment. Six articles were used for the evaluation of overall survival and five for disease-free interval. Our results show better outcomes with statistically significant differences in those patients treated with intraperitoneal chemotherapy. The main limitations of the selected studies are the inclusion of a retrospective study; the use of different dosages; and different chemotherapy regimens. It is necessary to design prospective studies to determine which patients will benefit from this treatment and to determine the optimal chemotherapy regimen to maintain benefits while minimising side-effects.

Keywords: advanced ovarian cancer; intraperitoneal chemotherapy; overall survival; disease-free survival; primary cytorreductive surgery

2. Introduction

Ovarian cancer is one of the most frequent gynaecological tumours, ranking third. Ovarian cancer has a five-year survival of less than 20% [1,2]. Diagnosis is often delayed due to non-specific or absent symptoms, with most patients (70–80%) being diagnosed in the advanced stages of the disease [1–3]. The principal histological type is serous with a frequency of 75–80% [3].

The treatment of choice for advanced ovarian cancer (AOC) is cytoreductive surgery with the aim of achieving the absence of tumour residue (R0) followed by adjuvant intravenous chemotherapy treatment based on the combination of carboplatin and paclitaxel [4,5].

Due to delays in the diagnosis of ovarian cancer and the high probability of relapse in these patients, only 10–15% have a large disease-free interval [6]. It is necessary to find the best treatment to minimise the possibility of relapse and to increase overall survival.

Surgery aiming for the absence of tumour residue remains the primary objective in the management of advanced ovarian cancer. The definition of optimal cytoreductive surgery has evolved over the years. Currently, the absence of macroscopic tumoral residue is the objective in the primary cytoreductive surgery [4,7–9].

Chemotherapy treatment has been a controversial topic. The debate revolves around whether to administer the intravenous regimen (IV) alone (standard regimen) or with additional therapies such as intraperitoneal chemotherapy (IP) or other medications such as bevacizumab and PARP inhibitors (iPARP) with the aim of increasing survival and delaying the relapse [5,10,11].

The mechanism of action and the theoretical benefit of intraperitoneal chemotherapy lies in increasing the effect of the drugs in the peritoneal cavity and decreasing systemic toxicity [12,13].

There is a high degree of controversy surrounding the intraperitoneal administration of the chemotherapy agents, as well as a lack of consensus among different clinical guidelines [14–16].

Three randomised studies, (GOG 104 [17], GOG 114 [12], and GOG 172 [18]), published in 2001 and 2006, respectively, show statistically significant benefits in overall survival (OS) and disease-free interval (DFS) in intraperitoneal chemotherapy groups. The use of intraperitoneal chemotherapy has not been widespread, despite it showing the greatest increase in overall survival in ovarian cancer, reaching 16 months. Arguments for not using this treatment are based on concerns regarding toxicity symptoms, including asthenia, neurotoxicity, and abdominal pain. There are also difficulties associated with its administration and the use of the intraperitoneal chemotherapy catheter [12,19].

Currently, there is no quality evidence to recommend the use of intraperitoneal chemotherapy in the primary treatment of advanced ovarian cancer. It could be reserved for patients with FIGO stage III with complete or optimal cytoreductive surgery (absence of tumour or residual tumour less than 1 cm, respectively), with good performance status or in younger patients [20–24].

That is why the numbers of long-term overall survivors have been stable over the last 20 to 30 years, and there has not been an increase since platinum-based chemotherapy without a significant effect of new target treatments or increased surgical radicality [22].

There is a lack of consensus and high-grade evidence regarding the optimal treatment of advanced ovarian cancer.

The aim of this meta-analysis was to evaluate whether isolated intravenous chemotherapy still is the most efficacious regimen in patients with advanced ovarian cancer undergoing complete primary surgery.

3. Material and Methods

3.1. Search Strategy

This meta-analysis was carried out based on the indications drawn from the reporting items for systematic reviews and meta-analysis (PRISMA) guidelines (PRISMA 2020, http://www.primastatement.org, accessed on 1 Setember 2023). The Prisma Checklist is available in Supplementary Material [23].

Pubmed and Cochrane central register of databases were searched for literature published between 2016 and February 2023 comparing the use of intraperitoneal chemotherapy added to intravenous chemotherapy in advanced ovarian cancer with the use of intravenous chemotherapy alone.

The search terms used were ('Advance ovarian cancer' AND 'intravenous chemotherapy' AND 'intraperitoneal chemotherapy'). Controlled trials and systematic reviews were included. The hazard ratio of the intervention measure and the 95% confidence interval (CI) for OS and DFS were obtained from each study that met the inclusion criteria.

3.2. Inclusion and Exclusion Criteria

Inclusion criteria followed the PICOS criteria (population, intervention, comparison, outcome, and study design). The population studied was patients with advanced ovarian cancer undergoing primary cytoreductive surgery. We compared the adjuvant treatment administered: intravenous chemotherapy versus intravenous chemotherapy plus intraperitoneal chemotherapy and evaluated the outcomes DFS and OS.

Articles published in the last 10 years in English or Spanish were included. We excluded studies that lacked the rate of complete cytoreduction or applied hyperthermia; included the use of other drugs; or included patients with extra-abdominal disease.

3.3. Selection Process

The selection of articles was based on the critical reading of two review authors. Disagreements were resolved by discussion or with the help of a third review author.

The search was performed using the following filters:

Languages: English and Spanish.

Date: published articles since 2013.

Type of study: controlled trial, systematic review, and meta-analysis.

Exclusion of the articles that use hyperthermic intraperitoneal chemotherapy, neoadjuvant chemotherapy, other drugs, patients in the initial stages of ovarian cancer, and patients with extra-abdominal disease.

3.4. Statistical Analysis

The aim of the present study was to analyse whether intraperitoneal chemotherapy in patients with advanced ovarian cancer treated by cytorreductive surgery has a benefit in OS and DFS. The hazard ratio was used as a measure using a fixed-effect model. The results obtained are represented by forest plots graphs.

p-values of less than 0.05 were considered statistically significant.

Heterogeneity was assessed using the I2 tool. A value of less than 25% was considered low, 50% intermediate, and greater than or equal to 75% was considered high heterogeneity.

RevMan software was the tool used to evaluate the results (Review Manager (RevMan) Version 5.4, the Cochrane Collaboration, 2020).

4. Results

4.1. Selected Studies

The search strategy obtained a total of 211 publications in PubMed and 8 in Cochrane. After the removal of duplicates, the filtering of articles with electronic tools, and the critical reading of the abstracts, five articles in PubMed and one article in Cochrane were selected. Six articles were included in this review for overall survival and five articles for disease-free survival. Figure 1 shows the selection process.

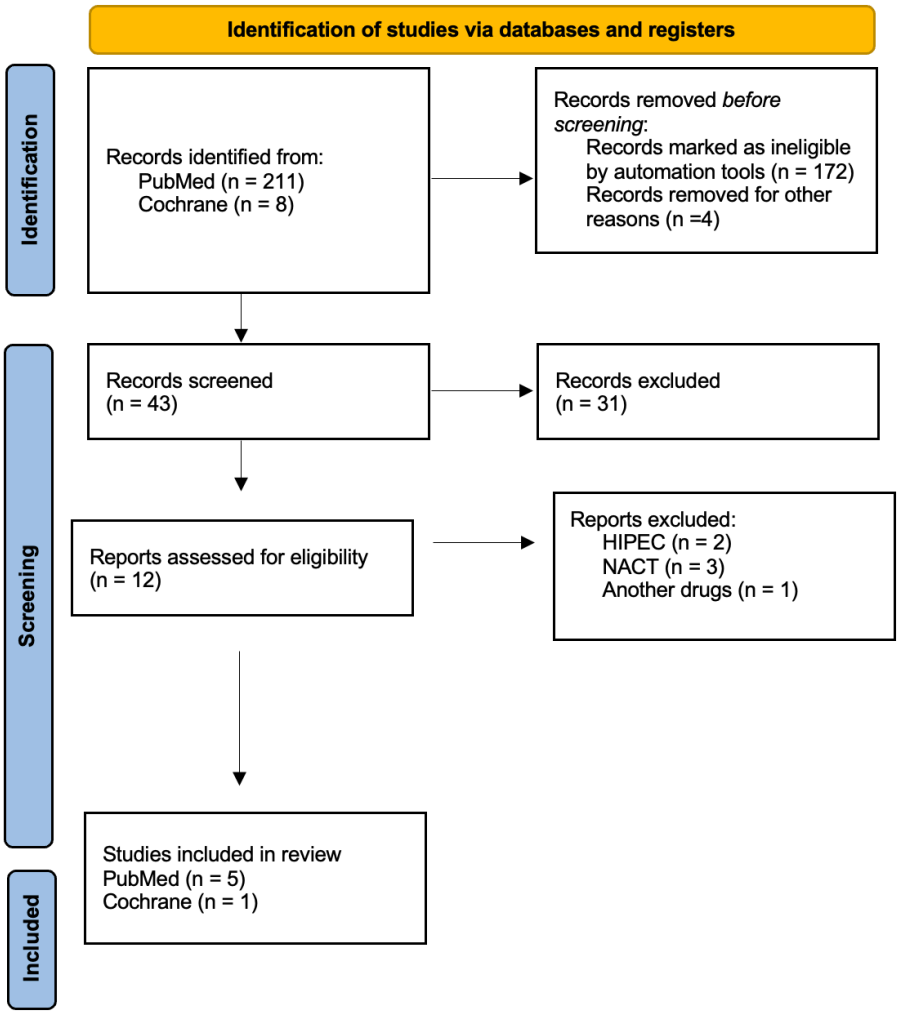


Figure 1. PRISMA diagram showing the selection process of the articles included in the study

The six studies selected had a study population of 4465 patients for the overall survival analysis and 3348 for the disease-free survival analysis.
Tables 1 and 2 show the main features of the study designs and the clinicopathological characteristics of the included population. Bias analyses are detailed in Figures S2 and S3 in the Supplementary Materials.

Table 1. Characteristics of included studies.

Included Studies.	Type of Trial	Participants	Interventions	Primary Outcome
Cochrane 2016[27]	Systematic review	OS (2026) DFS (1311)	IP/IV chemotherapy vs. IV chemotherapy	OS DFS Toxicity
IPocc 2022[24]	Randomised trial of superiority	746	Superiority of IP chemotherapy	DFS
Omali 2022[28]	Three randomised trials: NRG/GOG 104 NRG/GOG 114 NRG/GOG 172	160 (long-term disease-free survivors (LTDFS)	IP/IV chemotherapy vs. IV chemotherapy	Determine independent prognostic factors of LTDFS.

Wright 2015[26]	Prospective cohort study	402	IP/IV chemotherapy vs. IV chemotherapy	OS Toxicity
Yuanming 2022[25]	Retrospective cohort study	255	IP/IV chemotherapy vs. IV chemotherapy	OS DFS Toxicity
Tewari 2015[13]	Two randomised trials: NRG/GOG 114 NRG/GOG 172	876	IP/IV chemotherapy vs. IV chemotherapy	Long-term survival and associated prognostic factors

Table 2. Clinicopathological characteristics of included studies.

Included Studies.	Age (Years)	FIGO Stage (III and IV)	Serous Histology	Cytoreductive Surgery (None or <1 cm)	Chemotherapy Regimen	DFS (HR, CI 95%)	OS (HR, CI 95%)
IPocc 2022[24]	-	87%	64.12%	39.69%	IV: paclitaxel 80 mg/m^2 + IP: carboplatin AUC 6	0.83 (0.69–0.99)	0.81 (0.75–0.91)
Omali 2022[28]	57.2	100%	68.4%	33.6%	IV: cyclophosphamide or carboplatin + paclitaxel iv + IP: cisplatin	1.40 (0.81–2.44)	1.53 (0.69–3.38)
Wright 2015[26]	55–64 (37%)	91%	76%	66%	IV: carboplatin + paclitaxel or docetaxel. IP: cisplatin	N/A	0.68 (0.47–0.99)
Yuanming 2022[25]	53	100%	90.5%	100%	IV: carboplatin + IP: cisplatin 80 mg ip single dose or 75 mg/m^2 every 3 weeks	1.30 (0.71–2.37)	1.21 (0.51–2.91)
Cochrane 2016[27]				N/A		0.78 (0.70–0.86)	0.81 (0.72–0.91)
Tewari 2015[13]	> 55 (485)	100%	72.5%	63.9%	IV: cisplatin + paclitaxel or carboplatin intensive + IP: cisplatin + paclitaxel or paclitaxel	0.79 (0.67–0.93)	0.77 (0.65–0.91)

4.2. Results of Meta-Analysis on Overall Survival and Disease-Free Interval

Six articles included data on overall survival rates, but Wright et al.'s study did not evaluate disease-free survival rates.

The analysis of the included data from each article shows an increase in overall survival in the group of patients treated with intraperitoneal chemotherapy compared with patients treated with standard intravenous chemotherapy only. (HR 0.81 CI 95% 0.74–0.88 $p < 0.00001$) (Figure 2)

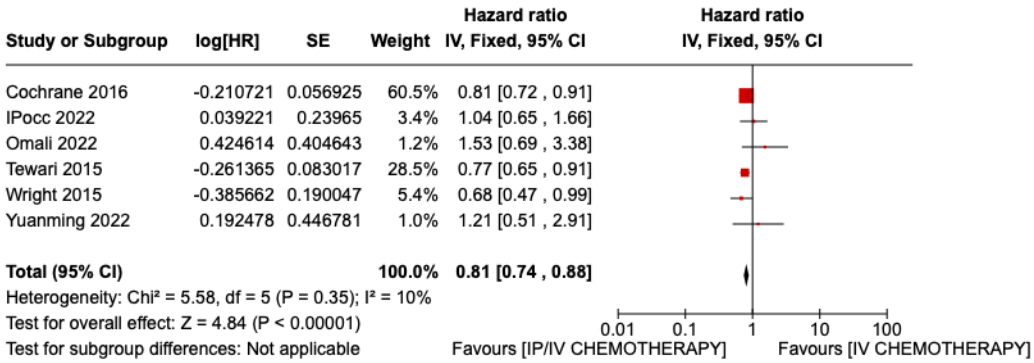


Figure 2. Statistical study of OS: Results obtained from all studies included in the review.

Similarly, the disease-free interval was significantly greater in the group of patients who underwent intraperitoneal chemotherapy in addition to intravenous chemotherapy (Figure 3) (HR 0.81, CI 95% 0.75–0.87, $p < 0.00001$).

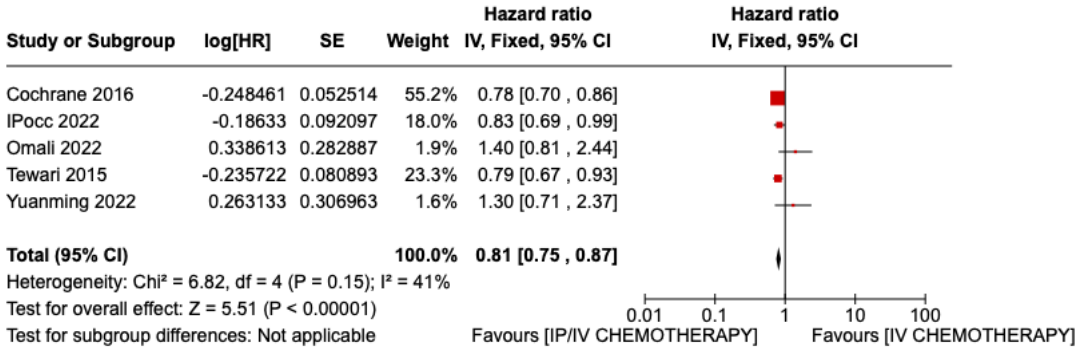


Figure 3. Statistical study of DFS: Results obtained from all studies included except Wright 2015.

The funnel plot showing the absence of publication bias is shown in Figures 4 and 5. Both graphs show a correct symmetry, which supports the selection of articles according to the established inclusion criteria, regardless of their results, and increases the statistical power of the results obtained.

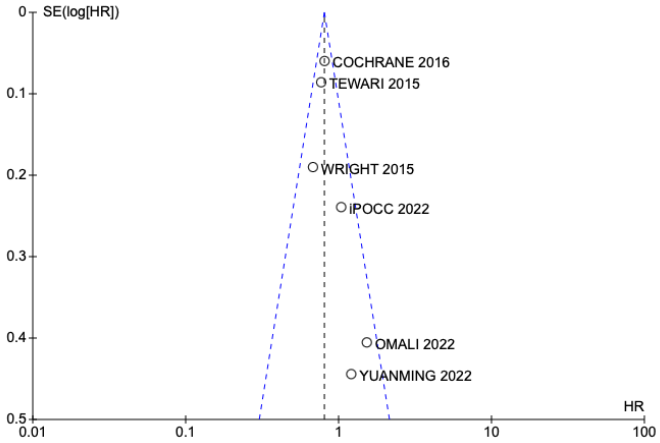


Figure 4. Funnel plot studies included OS.

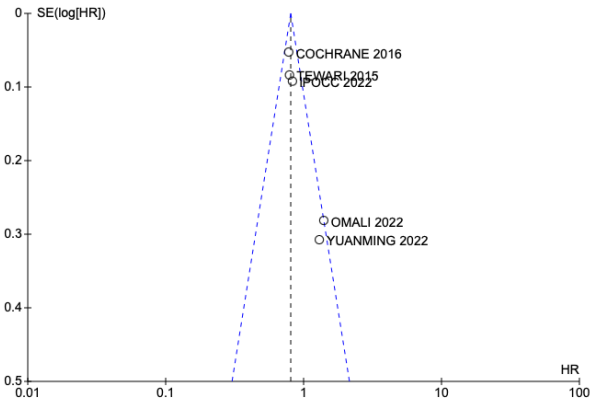


Figure 5. Funnel plot studies included DFS.

Although the aims of three articles included assessing the toxicity associated with intraperitoneal treatment, they did not supply values for relative risk (RR).

The results of the iPocc study [24] are not published enterally, but the results we obtained from the abstract published in the SGO Annual Meeting on Womens' Cancer are, 2022. This abstract specifies similar profiles of toxicity in both groups, but with an increase in catheter-related complications (11.8%).

Yuanming et al. [25] compared the total number of cycles completed in the group with additional IP chemotherapy with those receiving IV chemotherapy. They reported that 93% of intraperitoneal chemotherapy cycles were completed compared with 92% in the intravenous chemotherapy group.

Similarly, Wright et al. [26] reported that the percentage of completed cycles in the intraperitoneal group was 81%, lower than the 91% in the IV chemotherapy group, but with no statistically significant differences in G3/G4 complications.

In contrast, the Cochrane systematic review reported an increased RR of fever, fatigue, infection, gastrointestinal or metabolic disturbances, pain, and hearing loss [27].

5. Discussion

Our study shows a statistically significant increase in overall survival and disease-free survival in those patients with advanced ovarian cancer who have been treated with intraperitoneal chemotherapy.

Of the included studies only two, Omali et al. [28] and Yuanming et al. [25], reported no benefit with the use of intraperitoneal chemotherapy. Omali et al. included patients in the GOG 104, 114, and 172 studies, and they report on long-term survivors (>10 years of survival). The use of intraperitoneal chemotherapy was not found to be an independent survival factor. They also included patients who were treated with cyclophosphamide in the intravenous arm, although this that is not first line in the treatment

of ovarian cancer [28]. Similarly, Yuanming et al. used a lower dose in the IP group than that used in previous studies, and it is possible that the expected benefits of this treatment were not evident as the theoretical positive effect of this route of administration is based on the cumulative effect and dose in peritoneal cavity assuming an increase in side effects. Moreover, 19 patients included in the IP chemotherapy group were randomized to a single IP dose, which was not demonstrated to be clinically efficacious, although there was a decrease in toxicity.

Tewari et al. [13] only included patients from the studies GOG 114 and GOG 172 because, although GOG 104 reported improved survival in the IP chemotherapy group, cyclophosphamide was administered instead of paclitaxel in the IV group, and it can be assumed that the benefit associated with IP administration in the study may be a consequence of this different treatment regimen in the IV arm.

It should be noted that the population evaluated in this study was not the same as in the study by Omali et al.; Tewari et al. evaluated the entire cohort (847 patients), not only the survivors. They reported an improvement in overall survival, with prognostic impact achieving a tumour residue of less than 1 cm, as well as a 12% reduction in the risk of death with each cycle of chemotherapy administered (HR; 0.88 CI 95% 0.83–0.94).

This difference in the results between these two studies is a consequence of the population analysed; Omali et al. selected long-surviving patients, who would have a theoretically better initial prognosis. It is possible that the beneficial effects of IP chemotherapy are not as evident.

The iPocc trial shows a statistically significant benefit in disease-free survival with the addition of IP chemotherapy but no increase in overall survival [24]. Dense doses of paclitaxel were used without bevacizumab, used in GOG 252, in which there was no evidence of improvement with the use of intraperitoneal chemotherapy, possibly because bevacizumab acts as a confounding factor. In addition, only 42% completed treatment in GOG 172. This is the reason that the dose of cisplatin and paclitaxel was decreased, which could reduce the supposed beneficial effect of intraperitoneal chemotherapy. Similarly, the inclusion of patients with suboptimal surgery and stage IV disease may have increased the positive effect of bevacizumab at the expense of IP chemotherapy, which has been shown to be effective in the subgroup of patients with lower tumour residuals [29].

Of note is the inclusion of patients with tumour residues >2 cm in the iPocc study, in whom this reported benefit was maintained. It is possible that the inclusion of patients with suboptimal surgery results and with stage IV disease does not show the survival benefit of using IP chemotherapy, as previous publications included patients with stage III disease and those with primary surgeries with tumour residues of 1 cm or less.

The use of IP carboplatin is also of interest. Cisplatin has been shown to be a drug with good bioavailability in the peritoneal cavity: peritoneal exposure to the drug reaches 20 times the concentration achieved by intravenous administration. However, carboplatin requires higher doses than cisplatin to achieve these concentrations. Markman et al. noted that the response rate was higher in patients treated with intraperitoneal cisplatin than in those treated with carboplatin [30].

In addition, there was a marked variation in the adoption of IP/IV chemotherapy by articles and significant heterogeneity in the IP/IV regimens used.

Wright et al.'s was the first study to evaluate the clinical applicability of intraperitoneal chemotherapy in clinical studies. However, it used a decreased dose of the drug in the intraperitoneal arm [26].

Retrospective studies have documented higher rates of extra-abdominal cancer recurrences in patients treated with intraperitoneal chemotherapy, raising concerns about whether IP and IV chemotherapy provides effective systemic control [31,32].

Wright et al. reported that women treated with IP/IV chemotherapy had higher distant disease at first recurrence (adjusted rates, 58.8% v 29.4%; AOR, 3.14; 95% CI, 1.34 to 7.36), compared with IV chemotherapy [26]. A possible explanation is the poor systemic control of intraperitoneal chemotherapy. We consider this unlikely due to the current administration of IV treatment at the indicated dose for the adjuvant treatment of AOC. A possible cause is the increase in DFS in the IP arm that may reduce early intra-abdominal recurrences but result in distant recurrences due to the increased time to relapse [26].

The Cochrane review of this topic concluded that intraperitoneal chemotherapy increased OS and DFS in advanced ovarian cancer, but reported worse tolerance, especially in catheter-related complications, such as catheter blockage [27].
GOG 172 is the most widely reported study of catheter-related complications; 36% of patients did not complete treatment due to catheter failure or catheter infection [12].
Three randomised controlled phase III trials (GOG 104, 114, and 172) have demonstrated that IP chemotherapy is an effective treatment for patients with advanced ovarian cancer who have undergone primary optimal surgery (the overall risk of death was reduced by 20–30%).
GOG 172 reported the greatest increase in overall survival in these patients, which increased by 16 months [12,13,17,33,34]. However, intraperitoneal chemotherapy is still rarely used as the first-line treatment in clinical practice due to the high toxicity; inconvenience; risk of catheter-related complications; and lack of a widely accepted optimal regimen [26,28].
Another reason for low rates of use is the lack of standardisation in the dose and timing of this approach which diminishes the available scientific evidence [35].
The main criticism of the GOG studies is the lack of standardisation in the optimal regimen of intraperitoneal treatment. These studies show different intravenous treatment regimens and intraperitoneal treatment regimens, even, in some cases, within arms of the same study, which increases heterogeneity [25–27].
GOG 252 showed that reducing the cisplatin dose from 100 to 75 mg/m^2 in intraperitoneal chemotherapy resulted in a significant decrease in toxicity, but compared with intravenous chemotherapy, intraperitoneal chemotherapy with cisplatin or carboplatin did not result in a survival benefit. A possible explanation for this result is the addition of bevacizumab in both arms [36].
However, in the subgroup analysis comparing patients receiving maintenance bevacizumab with patients not receiving maintenance treatment, there was no evidence of superiority of intraperitoneal chemotherapy over the standard chemotherapy regimen [29].
Although the increased toxicity of intraperitoneal chemotherapy is one of the main reasons for its low rate of use, compliance rates have been shown to be as high as 80% with well-tolerated side effects, even in secondary surgery after relapse [37].
Increased toxicity associated with the use of intraperitoneal chemotherapy was evidenced in the GOG 172 study, where approximately half of the patients did not complete cycles of intraperitoneal chemotherapy due to toxicity [12].
The Cochrane review also reported complications, particularly those related to catheters such as blockage, pain, gastro-intestinal disturbances, and infection [27].
However, the other studies did not report higher rates of side effects in the intraperitoneal treatment arm. In GOG 172, there was no difference in quality of life between treatments groups.
Tewari et al. described age as the main factor associated with compliance with treatment, with a 5% decrease as the patient's age increased [13].
The NCCN guidelines, which have included IP chemotherapy treatment in patients with advanced FIGO stage III ovarian cancer and optimal cytoreductive surgery as a category 1 recommendation, make special mention of elderly and medicalised patients in whom treatment tolerance is poor [16].
Although the rate of side effects may be greater with intraperitoneal treatment, there was no increase in G3/4 effects. These effects are usually short term and easily treatable.
To minimise toxicity, the included studies varied the IP chemotherapy regimen, but this minimised the statistical power of meta-analysis [12]. For example, 43% of patients in the Wright et al. study received modified regimens [26]. Based on results from Dash et al., a modified dose of day 2 cisplatin (75 vs. 100 mg/m^2) could reduce toxicity, and 63% of patients received at least five cycles compared with 51% in the GOG 172. However, there are doubts as to whether dose reduction of cisplatin maintains efficacy [38]. To improve tolerance to intraperitoneal treatment, it is necessary to understand the management of complications and to develop an intraperitoneal chemotherapy regimen that combines the described

efficacy with acceptable toxicity. On the other hand, in this meta-analysis, we have not evaluated the role of hyperthermia in this subgroup of patients with advanced ovarian cancer.
Hyperthermic intraperitoneal perfusion chemotherapy (HIPEC) is another mode of intraperitoneal chemotherapy delivery that has been proven to be beneficial in the treatment of patients with advanced ovarian cancer treated with neoadjuvant chemotherapy and interval cytoreductive surgery [39].
Hyperthermia has been associated with increased efficacy in intraperitoneal chemotherapy by enhancing its cytotoxic effect and decreasing its toxicity, avoiding complications of long-term peritoneal access [40–42].
A systematic review published in 2019 shows that the addition of HIPEC to cytoreductive surgery could significantly improve OS of both primary and recurrent ovarian cancer, although the dosage remains unclear [43].
Another systematic review published in 2023 including 674 patients showed that the use of HIPEC in patients with advanced ovarian cancer treated with neoadjuvant chemotherapy associated with interval surgery has an increase in overall survival and disease-free interval. In addition, the drug administered intraperitoneally with the best results was reported to be cisplatin [44].
A multicentre retrospective cohort study comparing two groups of patients with advanced ovarian cancer undergoing interval surgery alone or in association with HIPEC was published in 2023. After a propensity score, 170 patients in each group were analysed, showing no significant difference in OS but with differences in the DFS [45]. One possible reason for not finding differences in survival is that 53% of patients were treated with paclitaxel, a drug that appears to be less effective than cisplatin, as well as being associated with greater abdominal pain and rates of catheter-related complications.
These results in patients with worse prognosis at baseline who had better survival and disease-free interval outcomes with HIPEC appear to support the potential benefit of first-line IP therapy in advanced ovarian cancer.
A trial studying the role of HIPEC after primary surgery in patients with advanced ovarian cancer is currently in the recruitment phase (OVHIPEC-2) and may provide more information [46].
Another point that has not been evaluated in the present meta-analysis is the role of the BRCA mutation. BRCA status has not been assessed in this review due to the absence of BRCA status in the included studies. This is one of the main limitations of the study, as previous publications describe a higher sensitivity to intraperitoneal chemotherapy in the subgroup of patients with BRCA mutations [47–49].
The use of poly (ADP-ribose) polymerase inhibitors (iPARP) is associated with an increase in DFS, although the magnitude of this effect varies between different patient profiles, showing the best results in the treatment of patients with AOC in the first line and as maintenance treatment in patients with the BRCA mutation or homologous recombination deficiency (HDR) [50].
In the PRIMA and VELIA studies, niraparib is used as a maintenance treatment for patients at a high risk of relapse in the former, excluding patients with complete surgery, and veliparib as the first-line and maintenance treatment in patients regardless of biomarker or type of surgery [51,52].
Treatment with other drugs has also been studied, such as bevacizumab, an anti- vascular endothelial growth factor (anti-VEGF) that is associated with an increase in DFS in patients at high risk of recurrence; FIGO IV; or suboptimal surgery in stage III.
In the PAOLA-1 study, olaparib was added to bevacizumab treatment and was associated with an improvement in DFS regardless of BRCA status [53].
Despite the above results, none of the above therapeutic options have been shown to increase overall survival in patients with advanced ovarian cancer.
Further studies are needed to determine the role of IP chemotherapy in patients; however, it should be noted that since the introduction of IV platinum and taxane-based chemotherapy, prior to GOG 172, no such significant increase has ever been achieved in patients with advanced ovarian cancer.
Limitations*:*

The main limitation of this study is the heterogeneity resulting from the inclusion of studies whose design did not standardise the chemotherapy treatment used. Different chemotherapy treatment regimens; doses; treatment regimens; and different medications were utilised in the experimental arm.
Another notable limitation is the absence of data on toxicity and side effects. This is the main limitation to the use of intraperitoneal chemotherapy, in addition to the fact that no cost-effectiveness study has been carried out to evaluate the additional costs associated with the use of intraperitoneal chemotherapy.
Strengths:
The main strength of this study is the inclusion of recent studies showing a clear trend of improvement in survival and disease-free period in patients with low tumour residue after optimal cytoreductive surgery, without assuming an increase in toxicity. The side-effects are the main reason that the use of intraperitoneal chemotherapy has not been standardised.
Despite heterogeneity in the treatment regimen and the limitations of our study, we observed a significant survival benefit associated with IP/IV compared with IV chemotherapy. There were few differences in treatment-related toxicities between groups, suggesting that IP/IV chemotherapy is feasible to use in clinical practice.
The optimal treatment of patients with advanced ovarian cancer should be developed by a multidisciplinary team that achieves a good cytoreduction rates, followed by optimal treatment based on platinum and taxane, and to select those patients who benefit from intraperitoneal treatment [7].
Further studies are needed to establish the profile of patients who would benefit from this treatment, to avoid toxicity in patients who would not benefit from it.
Another reason that intraperitoneal chemotherapy has not been a widely used treatment, despite showing an increase in survival comparable to that observed following platinum- and taxane-based chemotherapies, is possibly due to the low amount of promotion of it by pharmaceutical companies, unlike other targeted drugs with a greater economic benefit.
Moreover, the low utilisation of intraperitoneal chemotherapy is due to catheter-related complications such as obstruction or abdominal pain during treatment. These complications and the lack of training of oncologists in their management mean that a large part of the medical oncology community is reluctant to use intraperitoneal chemotherapy in patients with advanced ovarian cancer despite the scientific evidence and the recommendations of clinical guidelines [54].
Improved knowledge of the peritoneum has led to knowledge of the best drug and the optimal intraperitoneal chemotherapy regimen with acceptable toxicity. It should be noted that the benefit observed with intraperitoneal administration has been developed with the use of intravenously administered drugs and it is possible that this improvement in the prognosis of these patients will increase with the development of drugs designed for peritoneal administration considering the physiology of the peritoneum.
In our opinion and based on the results obtained, intraperitoneal chemotherapy should be a treatment to be considered in young patients with little associated morbidity in which complete cytoreduction is achieved or with a tumor residue of less than 1 cm. This patient profile seems to have the most benefit from the treatment and presents the most tolerable toxicity. Likewise, the chemotherapeutic agent of choice would be cisplatin due to its bioavailability at the peritoneal level and the reduced irritation of the peritoneum that it causes.

6. Conclusions

In conclusion, this meta-analysis is not based on many articles due to the limited number of publications on this topic in the last 10 years and the heterogenicity in the design of these studies; the results obtained show that IP/IV chemotherapy is a treatment that increases the survival and the time of recurrence. However, it is underused, despite a growing amount of evidence supporting a survival advantage for ovarian cancer patients. There are still issues to be solved, such as the optimal regimen and dosage, the best moment of HIPEC, the optimal patient profile, and the role of biomarkers.

Research is needed on new drugs with a peritoneal route of administration, increasing their effect and decreasing the side effects and their combination with intravenous drugs.
Similarly, it is necessary to determine the possible toxicity associated with the different treatment regimens and establish the best pattern of treatment and the profile of patients who benefit from this treatment.

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8. ANNEXO: Original Publication "Should we Abandon Intraperitoneal Chemotherapy in the Treatment of Advanced Ovarian Cancer? A Meta – Analysis.

Journal of *Personalized Medicine*

MDPI

Systematic Review

Should We Abandon Intraperitoneal Chemotherapy in the Treatment of Advanced Ovarian Cancer? A Meta-Analysis

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Abstract: Background: Ovarian cancer is the gynaecological malignancy with the highest mortality and diagnosis often occurs in its advanced stages. Standard treatment in these cases is based on complete cytoreductive surgery with adjuvant intravenous chemotherapy. Other types of treatment are being evaluated to improve the prognosis of these patients, including intraperitoneal chemotherapy and antiangiogenic therapy. These may improve survival or time to relapse in addition to intravenous chemotherapy. Objective: The aim of this meta-analysis is to determine whether treatment with intravenous chemotherapy remains the gold standard, or whether the addition of intraperitoneal chemotherapy has a benefit in overall survival (OS) and disease-free interval (DFS). Materials and methods: A literature search was carried out in Pubmed and Cochrane, selecting clinical studies and systematic reviews published in the last 10 years. Statistical analysis was performed using the hazard ratio measure in the RevMan tool. Results: Intraperitoneal chemotherapy shows a benefit in OS and DFS compared with standard intravenous chemotherapy. The significant differences in OS (HR: 0.81 CI 95% 0.74–0.88) and in DFS (HR: 0.81 CI 95% 0.75–0.87) are statistically significant ($p < 0.00001$). There were no clinical differences in toxicity and side-effects. Conclusion: Intraperitoneal chemotherapy is an option that improves OS and DFS without significant toxicity regarding the use of intravenous chemotherapy alone. However, prospective studies are needed to determine the optimal dose and treatment regimen that will maintain the benefits while minimising side effects and toxicity and the profile of patients who will benefit most from this treatment.

Keywords: advanced ovarian cancer; intraperitoneal chemotherapy; overall survival; disease-free survival; primary cytorreductive surgery

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1. Introduction

Ovarian cancer is one of the most frequent gynaecological tumours, ranking third. Ovarian cancer has a five-year survival of less than 20% [1,2]. Diagnosis is often delayed due to non-specific or absent symptoms, with most patients (70–80%) being diagnosed in the advanced stages of the disease [1–3]. The principal histological type is serous with a frequency of 75–80% [3].

The treatment of choice for advanced ovarian cancer (AOC) is cytoreductive surgery with the aim of achieving the absence of tumour residue (R0) followed by adjuvant intravenous chemotherapy treatment based on the combination of carboplatin and paclitaxel [4,5].

Due to delays in the diagnosis of ovarian cancer and the high probability of relapse in these patients, only 10–15% have a large disease-free interval [6]. It is necessary to find the best treatment to minimise the possibility of relapse and to increase overall survival.

Surgery aiming for the absence of tumour residue remains the primary objective in the management of advanced ovarian cancer. The definition of optimal cytoreductive surgery

has evolved over the years. Currently, the absence of macroscopic tumoral residue is the objective in the primary cytoreductive surgery [4,7–9].

Chemotherapy treatment has been a controversial topic. The debate revolves around whether to administer the intravenous regimen (IV) alone (standard regimen) or with additional therapies such as intraperitoneal chemotherapy (IP) or other medications such as bevacizumab and PARP inhibitors (iPARP) with the aim of increasing survival and delaying the relapse [5,10,11].

The mechanism of action and the theoretical benefit of intraperitoneal chemotherapy lies in increasing the effect of the drugs in the peritoneal cavity and decreasing systemic toxicity [12,13].

There is a high degree of controversy surrounding the intraperitoneal administration of the chemotherapy agents, as well as a lack of consensus among different clinical guidelines [14–16].

Three randomised studies, (GOG 104 [17], GOG 114 [12], and GOG 172 [18]), published in 2001 and 2006, respectively, show statistically significant benefits in overall survival (OS) and disease-free interval (DFS) in intraperitoneal chemotherapy groups. The use of intraperitoneal chemotherapy has not been widespread, despite it showing the greatest increase in overall survival in ovarian cancer, reaching 16 months. Arguments for not using this treatment are based on concerns regarding toxicity symptoms, including asthenia, neurotoxicity, and abdominal pain. There are also difficulties associated with its administration and the use of the intraperitoneal chemotherapy catheter [12,19].

Currently, there is no quality evidence to recommend the use of intraperitoneal chemotherapy in the primary treatment of advanced ovarian cancer. It could be reserved for patients with FIGO stage III with complete or optimal cytoreductive surgery (absence of tumour or residual tumour less than 1 cm, respectively), with good performance status or in younger patients [20–24].

That is why the numbers of long-term overall survivors have been stable over the last 20 to 30 years, and there has not been an increase since platinum-based chemotherapy without a significant effect of new target treatments or increased surgical radicality [22].

There is a lack of consensus and high-grade evidence regarding the optimal treatment of advanced ovarian cancer.

The aim of this meta-analysis was to evaluate whether isolated intravenous chemotherapy still is the most efficacious regimen in patients with advanced ovarian cancer undergoing complete primary surgery.

2. Material and Methods

2.1. Search Strategy

This meta-analysis was carried out based on the indications drawn from the reporting items for systematic reviews and meta-analysis (PRISMA) guidelines (PRISMA 2020, http://www.primastatement.org, accessed on 1 September 2023). The Prisma Checklist is available in Supplementary Materials [23].

Pubmed and Cochrane central register of databases were searched for literature published between 2016 and February 2023 comparing the use of intraperitoneal chemotherapy added to intravenous chemotherapy in advanced ovarian cancer with the use of intravenous chemotherapy alone.

The search terms used were ('Advance ovarian cancer' AND 'intravenous chemotherapy' AND 'intraperitoneal chemotherapy'). Controlled trials and systematic reviews were included. The hazard ratio of the intervention measure and the 95% confidence interval (CI) for OS and DFS were obtained from each study that met the inclusion criteria.

2.2. Inclusion and Exclusion Criteria

Inclusion criteria followed the PICOS criteria (population, intervention, comparison, outcome, and study design). The population studied was patients with advanced ovarian cancer undergoing primary cytoreductive surgery. We compared the adjuvant

treatment administered: intravenous chemotherapy versus intravenous chemotherapy plus intraperitoneal chemotherapy and evaluated the outcomes DFS and OS.

Articles published in the last 10 years in English or Spanish were included. We excluded studies that lacked the rate of complete cytoreduction or applied hyperthermia; included the use of other drugs; or included patients with extra-abdominal disease.

2.3. Selection Process

The selection of articles was based on the critical reading of two review authors. Disagreements were resolved by discussion or with the help of a third review author.

The search was performed using the following filters:

- Languages: English and Spanish.
- Date: published articles since 2013.
- Type of study: controlled trial, systematic review, and meta-analysis.
- Exclusion of the articles that use hyperthermic intraperitoneal chemotherapy, neoadjuvant chemotherapy, other drugs, patients in the initial stages of ovarian cancer, and patients with extra-abdominal disease.

2.4. Statistical Analysis

The aim of the present study was to analyse whether intraperitoneal chemotherapy in patients with advanced ovarian cancer treated by cytorreductive surgery has a benefit in OS and DFS. The hazard ratio was used as a measure using a fixed-effect model. The results obtained are represented by forest plots graphs.

p-values of less than 0.05 were considered statistically significant.

Heterogeneity was assessed using the I2 tool. A value of less than 25% was considered low, 50% intermediate, and greater than or equal to 75% was considered high heterogeneity.

RevMan software was the tool used to evaluate the results (Review Manager (RevMan) Version 5.4, the Cochrane Collaboration, 2020).

3. Results

3.1. Selected Studies

The search strategy obtained a total of 211 publications in PubMed and 8 in Cochrane. After the removal of duplicates, the filtering of articles with electronic tools, and the critical reading of the abstracts, five articles in PubMed and one article in Cochrane were selected. Six articles were included in this review for overall survival and five articles for disease-free survival. Figure 1 shows the selection process.

The six studies selected had a study population of 4465 patients for the overall survival analysis and 3348 for the disease-free survival analysis.

Tables 1 and 2 show the main features of the study designs and the clinicopathological characteristics of the included population. Bias analyses are detailed in Figures S2 and S3 in the Supplementary Materials.

Table 1. Characteristics of included studies.

Included Studies	Type of Trial	Participants	Interventions	Primary Outcome
Cochrane 2016 [25]	Systematic review	OS (2026) DFS (1311)	IP/IV chemotherapy vs. IV chemotherapy	OS DFS Toxicity
IPocc 2022 [24]	Randomised trial of superiority	746	Superiority of IP chemotherapy	DFS

Table 1. *Cont.*

Included Studies	Type of Trial	Participants	Interventions	Primary Outcome
Omali 2022 [26]	Three randomised trials: NRG/GOG 104 NRG/GOG 114 NRG/GOG 172	160 (long-term disease-free survivors (LTDFS)	IP/IV chemotherapy vs. IV chemotherapy	Determine independent prognostic factors of LTDFS.
Wright 2015 [27]	Prospective cohort study	402	IP/IV chemotherapy vs. IV chemotherapy	OS Toxicity
Yuanming 2022 [28]	Retrospective cohort study	255	IP/IV chemotherapy vs. IV chemotherapy	OS DFS Toxicity
Tewari 2015 [13]	Two randomised trials: NRG/GOG 114 NRG/GOG 172	876	IP/IV chemotherapy vs. IV chemotherapy	Long-term survival and associated prognostic factors

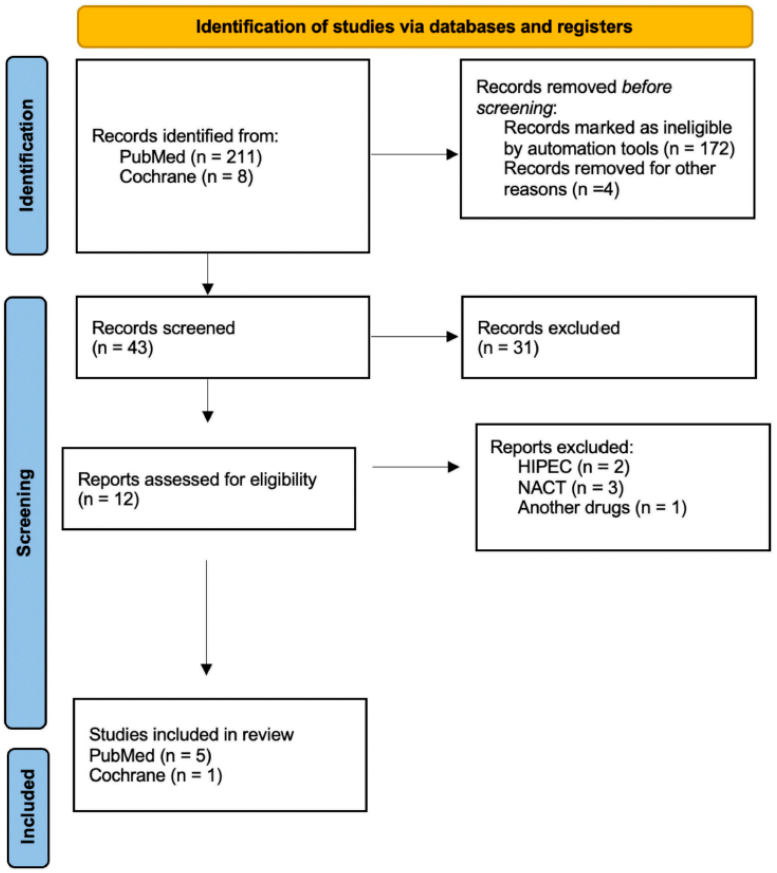


Figure 1. PRISMA diagram showing the selection process of the articles included in the study.

Table 2. Clinicopathological characteristics of included studies.

Included Studies	Age (Years)	FIGO Stage (III and IV)	Serous Histology	Cytoreductive Surgery (None or <1 cm)	Chemotherapy Regimen	DFS (HR, CI 95%)	OS (HR, CI 95%)
IPocc 2022 [24]	-	87%	64.12%	39.69%	IV: paclitaxel 80 mg/m^2 + IP: carboplatin AUC 6	0.83 (0.69–0.99)	0.81 (0.75–0.91)
Omali 2022 [26]	57.2	100%	68.4%	33.6%	IV: cyclophos-phamide or carboplatin + paclitaxel iv + IP: cisplatin	1.40 (0.81–2.44)	1.53 (0.69–3.38)
Wright 2015 [27]	55–64 (37%)	91%	76%	66%	IV: carboplatin + paclitaxel or docetaxel. IP: cisplatin	N/A	0.68 (0.47–0.99)
Yuanming 2022 [28]	53	100%	90.5%	100%	IV: carboplatin + IP: cisplatin 80 mg ip single dose or 75 mg/m^2 every 3 weeks	1.30 (0.71–2.37)	1.21 (0.51–2.91)
Cochrane 2016 [25]			N/A		IV: cisplatin + paclitaxel or carboplatin intensive + IP: cisplatin + paclitaxel or paclitaxel	0.78 (0.70–0.86)	0.81 (0.72–0.91)
Tewari 2015 [13]	>55 (485)	100%	72.5%	63.9%		0.79 (0.67–0.93)	0.77 (0.65–0.91)

3.2. Results of Meta-Analysis on Overall Survival and Disease-Free Interval

Six articles included data on overall survival rates, but Wright et al.'s study did not evaluate disease-free survival rates.

The analysis of the included data from each article shows an increase in overall survival in the group of patients treated with intraperitoneal chemotherapy compared with patients treated with standard intravenous chemotherapy only. (HR 0.81 CI 95% 0.74–0.88 $p < 0.00001$) (Figure 2).

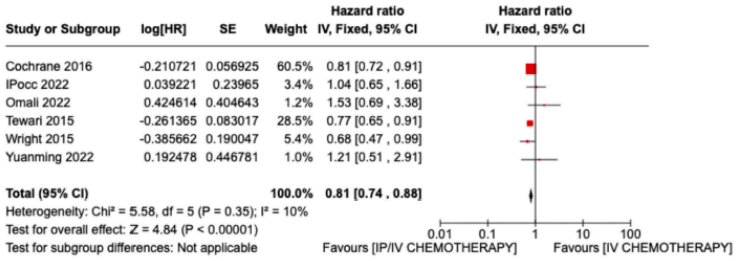


Figure 2. Statistical study of OS: Results obtained from all studies included in the review [13,24–28].

Similarly, the disease-free interval was significantly greater in the group of patients who underwent intraperitoneal chemotherapy in addition to intravenous chemotherapy (Figure 3) (HR 0.81, CI 95% 0.75–0.87, $p < 0.00001$).

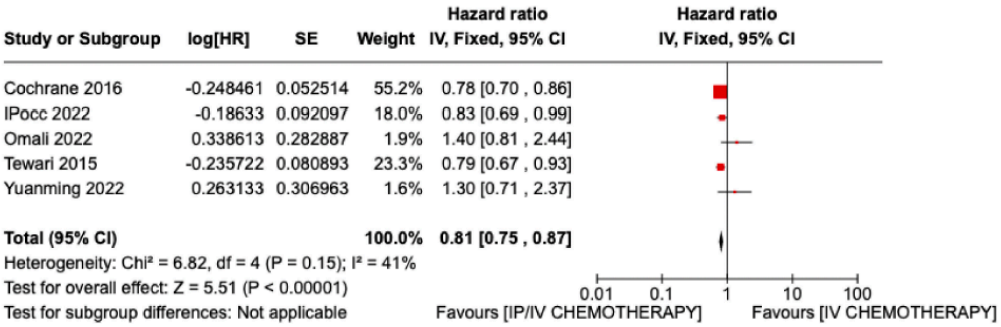


Figure 3. Statistical study of DFS: Results obtained from all studies included except Wright 2015 [13,24–26,28].

The funnel plot showing the absence of publication bias is shown in Figures 4 and 5. Both graphs show a correct symmetry, which supports the selection of articles according to the established inclusion criteria, regardless of their results, and increases the statistical power of the results obtained.

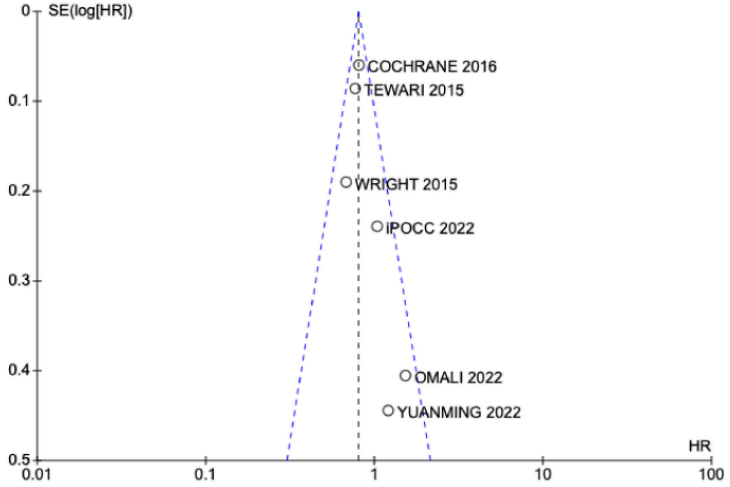


Figure 4. Funnel plot studies included OS [13,24–28].

Although the aims of three articles included assessing the toxicity associated with intraperitoneal treatment, they did not supply values for relative risk (RR).

The results of the iPocc study [24] are not published enterally, but the results we obtained from the abstract published in the SGO Annual Meeting on Womens' Cancer are, 2022. This abstract specifies similar profiles of toxicity in both groups, but with an increase in catheter-related complications (11.8%).

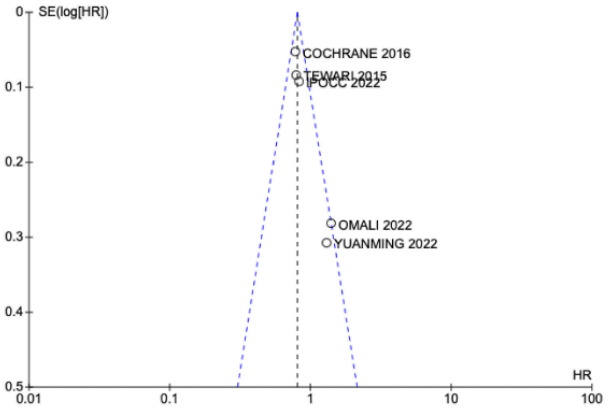


Figure 5. Funnel plot studies included DFS [13,24–26,28].

Yuanming et al. [28] compared the total number of cycles completed in the group with additional IP chemotherapy with those receiving IV chemotherapy. They reported that 93% of intraperitoneal chemotherapy cycles were completed compared with 92% in the intravenous chemotherapy group.

Similarly, Wright et al. [27] reported that the percentage of completed cycles in the intraperitoneal group was 81%, lower than the 91% in the IV chemotherapy group, but with no statistically significant differences in G3/G4 complications.

In contrast, the Cochrane systematic review reported an increased RR of fever, fatigue, infection, gastrointestinal or metabolic disturbances, pain, and hearing loss [25].

4. Discussion

Our study shows a statistically significant increase in overall survival and disease-free survival in those patients with advanced ovarian cancer who have been treated with intraperitoneal chemotherapy.

Of the included studies only two, Omali et al. [26] and Yuanming et al. [28], reported no benefit with the use of intraperitoneal chemotherapy. Omali et al. included patients in the GOG 104, 114, and 172 studies, and they report on long-term survivors (>10 years of survival). The use of intraperitoneal chemotherapy was not found to be an independent survival factor. They also included patients who were treated with cyclophosphamide in the intravenous arm, although this that is not first line in the treatment of ovarian cancer [26]. Similarly, Yuanming et al. used a lower dose in the IP group than that used in previous studies, and it is possible that the expected benefits of this treatment were not evident as the theoretical positive effect of this route of administration is based on the cumulative effect and dose in peritoneal cavity assuming an increase in side effects. Moreover, 19 patients included in the IP chemotherapy group were randomized to a single IP dose, which was not demonstrated to be clinically efficacious, although there was a decrease in toxicity.

Tewari et al. [13] only included patients from the studies GOG 114 and GOG 172 because, although GOG 104 reported improved survival in the IP chemotherapy group, cyclophosphamide was administered instead of paclitaxel in the IV group, and it can be assumed that the benefit associated with IP administration in the study may be a consequence of this different treatment regimen in the IV arm.

It should be noted that the population evaluated in this study was not the same as in the study by Omali et al.; Tewari et al. evaluated the entire cohort (847 patients), not only the survivors. They reported an improvement in overall survival, with prognostic impact

achieving a tumour residue of less than 1 cm, as well as a 12% reduction in the risk of death with each cycle of chemotherapy administered (HR; 0.88 CI 95% 0.83–0.94).

This difference in the results between these two studies is a consequence of the population analysed; Omali et al. selected long-surviving patients, who would have a theoretically better initial prognosis. It is possible that the beneficial effects of IP chemotherapy are not as evident.

The iPocc trial shows a statistically significant benefit in disease-free survival with the addition of IP chemotherapy but no increase in overall survival [24]. Dense doses of paclitaxel were used without bevacizumab, used in GOG 252, in which there was no evidence of improvement with the use of intraperitoneal chemotherapy, possibly because bevacizumab acts as a confounding factor. In addition, only 42% completed treatment in GOG 172. This is the reason that the dose of cisplatin and paclitaxel was decreased, which could reduce the supposed beneficial effect of intraperitoneal chemotherapy. Similarly, the inclusion of patients with suboptimal surgery and stage IV disease may have increased the positive effect of bevacizumab at the expense of IP chemotherapy, which has been shown to be effective in the subgroup of patients with lower tumour residuals [29].

Of note is the inclusion of patients with tumour residues >2 cm in the iPocc study, in whom this reported benefit was maintained. It is possible that the inclusion of patients with suboptimal surgery results and with stage IV disease does not show the survival benefit of using IP chemotherapy, as previous publications included patients with stage III disease and those with primary surgeries with tumour residues of 1 cm or less.

The use of IP carboplatin is also of interest. Cisplatin has been shown to be a drug with good bioavailability in the peritoneal cavity: peritoneal exposure to the drug reaches 20 times the concentration achieved by intravenous administration. However, carboplatin requires higher doses than cisplatin to achieve these concentrations. Markman et al. noted that the response rate was higher in patients treated with intraperitoneal cisplatin than in those treated with carboplatin [30].

In addition, there was a marked variation in the adoption of IP/IV chemotherapy by articles and significant heterogeneity in the IP/IV regimens used.

Wright et al.'s was the first study to evaluate the clinical applicability of intraperitoneal chemotherapy in clinical studies. However, it used a decreased dose of the drug in the intraperitoneal arm [27].

Retrospective studies have documented higher rates of extra-abdominal cancer recurrences in patients treated with intraperitoneal chemotherapy, raising concerns about whether IP and IV chemotherapy provides effective systemic control [31,32].

Wright et al. reported that women treated with IP/IV chemotherapy had higher distant disease at first recurrence (adjusted rates, 58.8% v 29.4%; AOR, 3.14; 95% CI, 1.34 to 7.36), compared with IV chemotherapy [27]. A possible explanation is the poor systemic control of intraperitoneal chemotherapy. We consider this unlikely due to the current administration of IV treatment at the indicated dose for the adjuvant treatment of AOC. A possible cause is the increase in DFS in the IP arm that may reduce early intra-abdominal recurrences but result in distant recurrences due to the increased time to relapse [27].

The Cochrane review of this topic concluded that intraperitoneal chemotherapy increased OS and DFS in advanced ovarian cancer, but reported worse tolerance, especially in catheter-related complications, such as catheter blockage [25].

GOG 172 is the most widely reported study of catheter-related complications; 36% of patients did not complete treatment due to catheter failure or catheter infection [12].

Three randomised controlled phase III trials (GOG 104, 114, and 172) have demonstrated that IP chemotherapy is an effective treatment for patients with advanced ovarian cancer who have undergone primary optimal surgery (the overall risk of death was reduced by 20–30%).

GOG 172 reported the greatest increase in overall survival in these patients, which increased by 16 months [12,13,17,33,34]. However, intraperitoneal chemotherapy is still rarely used as the first-line treatment in clinical practice due to the high toxicity; incon-

venience; risk of catheter-related complications; and lack of a widely accepted optimal regimen [26,27].

Another reason for low rates of use is the lack of standardisation in the dose and timing of this approach which diminishes the available scientific evidence [35].

The main criticism of the GOG studies is the lack of standardisation in the optimal regimen of intraperitoneal treatment. These studies show different intravenous treatment regimens and intraperitoneal treatment regimens, even, in some cases, within arms of the same study, which increases heterogeneity [25,27,28].

GOG 252 showed that reducing the cisplatin dose from 100 to 75 mg/m^2 in intraperitoneal chemotherapy resulted in a significant decrease in toxicity, but compared with intravenous chemotherapy, intraperitoneal chemotherapy with cisplatin or carboplatin did not result in a survival benefit. A possible explanation for this result is the addition of bevacizumab in both arms [36].

However, in the subgroup analysis comparing patients receiving maintenance bevacizumab with patients not receiving maintenance treatment, there was no evidence of superiority of intraperitoneal chemotherapy over the standard chemotherapy regimen [29].

Although the increased toxicity of intraperitoneal chemotherapy is one of the main reasons for its low rate of use, compliance rates have been shown to be as high as 80% with well-tolerated side effects, even in secondary surgery after relapse [37].

Increased toxicity associated with the use of intraperitoneal chemotherapy was evidenced in the GOG 172 study, where approximately half of the patients did not complete cycles of intraperitoneal chemotherapy due to toxicity [12].

The Cochrane review also reported complications, particularly those related to catheters such as blockage, pain, gastro-intestinal disturbances, and infection [25].

However, the other studies did not report higher rates of side effects in the intraperitoneal treatment arm. In GOG 172, there was no difference in quality of life between treatments groups.

Tewari et al. described age as the main factor associated with compliance with treatment, with a 5% decrease as the patient's age increased [13].

The NCCN guidelines, which have included IP chemotherapy treatment in patients with advanced FIGO stage III ovarian cancer and optimal cytoreductive surgery as a category 1 recommendation, make special mention of elderly and medicalised patients in whom treatment tolerance is poor [16].

Although the rate of side effects may be greater with intraperitoneal treatment, there was no increase in G3/4 effects. These effects are usually short term and easily treatable.

To minimise toxicity, the included studies varied the IP chemotherapy regimen, but this minimised the statistical power of meta-analysis [12]. For example, 43% of patients in the Wright et al. study received modified regimens [27]. Based on results from Dash et al., a modified dose of day 2 cisplatin (75 vs. 100 mg/m^2) could reduce toxicity, and 63% of patients received at least five cycles compared with 51% in the GOG 172. However, there are doubts as to whether dose reduction of cisplatin maintains efficacy [38]. To improve tolerance to intraperitoneal treatment, it is necessary to understand the management of complications and to develop an intraperitoneal chemotherapy regimen that combines the described efficacy with acceptable toxicity. On the other hand, in this meta-analysis, we have not evaluated the role of hyperthermia in this subgroup of patients with advanced ovarian cancer.

Hyperthermic intraperitoneal perfusion chemotherapy (HIPEC) is another mode of intraperitoneal chemotherapy delivery that has been proven to be beneficial in the treatment of patients with advanced ovarian cancer treated with neoadjuvant chemotherapy and interval cytoreductive surgery [39].

Hyperthermia has been associated with increased efficacy in intraperitoneal chemotherapy by enhancing its cytotoxic effect and decreasing its toxicity, avoiding complications of long-term peritoneal access [40–42].

A systematic review published in 2019 shows that the addition of HIPEC to cytoreductive surgery could significantly improve OS of both primary and recurrent ovarian cancer, although the dosage remains unclear [43].

Another systematic review published in 2023 including 674 patients showed that the use of HIPEC in patients with advanced ovarian cancer treated with neoadjuvant chemotherapy associated with interval surgery has an increase in overall survival and disease-free interval. In addition, the drug administered intraperitoneally with the best results was reported to be cisplatin [44].

A multicentre retrospective cohort study comparing two groups of patients with advanced ovarian cancer undergoing interval surgery alone or in association with HIPEC was published in 2023. After a propensity score, 170 patients in each group were analysed, showing no significant difference in OS but with differences in the DFS [45]. One possible reason for not finding differences in survival is that 53% of patients were treated with paclitaxel, a drug that appears to be less effective than cisplatin, as well as being associated with greater abdominal pain and rates of catheter-related complications.

These results in patients with worse prognosis at baseline who had better survival and disease-free interval outcomes with HIPEC appear to support the potential benefit of first-line IP therapy in advanced ovarian cancer.

A trial studying the role of HIPEC after primary surgery in patients with advanced ovarian cancer is currently in the recruitment phase (OVHIPEC-2) and may provide more information [46].

Another point that has not been evaluated in the present meta-analysis is the role of the BRCA mutation.

BRCA status has not been assessed in this review due to the absence of BRCA status in the included studies. This is one of the main limitations of the study, as previous publications describe a higher sensitivity to intraperitoneal chemotherapy in the subgroup of patients with BRCA mutations [47–49].

The use of poly (ADP-ribose) polymerase inhibitors (iPARP) is associated with an increase in DFS, although the magnitude of this effect varies between different patient profiles, showing the best results in the treatment of patients with AOC in the first line and as maintenance treatment in patients with the BRCA mutation or homologous recombination deficiency (HDR) [50].

In the PRIMA and VELIA studies, niraparib is used as a maintenance treatment for patients at a high risk of relapse in the former, excluding patients with complete surgery, and veliparib as the first-line and maintenance treatment in patients regardless of biomarker or type of surgery [51,52].

Treatment with other drugs has also been studied, such as bevacizumab, an anti-vascular endothelial growth factor (anti-VEGF) that is associated with an increase in DFS in patients at high risk of recurrence; FIGO IV; or suboptimal surgery in stage III.

In the PAOLA-1 study, olaparib was added to bevacizumab treatment and was associated with an improvement in DFS regardless of BRCA status [53].

Despite the above results, none of the above therapeutic options have been shown to increase overall survival in patients with advanced ovarian cancer.

Further studies are needed to determine the role of IP chemotherapy in patients; however, it should be noted that since the introduction of IV platinum and taxane-based chemotherapy, prior to GOG 172, no such significant increase has ever been achieved in patients with advanced ovarian cancer.

Limitations:

The main limitation of this study is the heterogeneity resulting from the inclusion of studies whose design did not standardise the chemotherapy treatment used. Different chemotherapy treatment regimens; doses; treatment regimens; and different medications were utilised in the experimental arm.

Another notable limitation is the absence of data on toxicity and side effects. This is the main limitation to the use of intraperitoneal chemotherapy, in addition to the fact that

no cost-effectiveness study has been carried out to evaluate the additional costs associated with the use of intraperitoneal chemotherapy.

Strengths:

The main strength of this study is the inclusion of recent studies showing a clear trend of improvement in survival and disease-free period in patients with low tumour residue after optimal cytoreductive surgery, without assuming an increase in toxicity. The side-effects are the main reason that the use of intraperitoneal chemotherapy has not been standardised.

Despite heterogeneity in the treatment regimen and the limitations of our study, we observed a significant survival benefit associated with IP/IV compared with IV chemotherapy. There were few differences in treatment-related toxicities between groups, suggesting that IP/IV chemotherapy is feasible to use in clinical practice.

The optimal treatment of patients with advanced ovarian cancer should be developed by a multidisciplinary team that achieves a good cytoreduction rates, followed by optimal treatment based on platinum and taxane, and to select those patients who benefit from intraperitoneal treatment [7].

Further studies are needed to establish the profile of patients who would benefit from this treatment, to avoid toxicity in patients who would not benefit from it.

Another reason that intraperitoneal chemotherapy has not been a widely used treatment, despite showing an increase in survival comparable to that observed following platinum- and taxane-based chemotherapies, is possibly due to the low amount of promotion of it by pharmaceutical companies, unlike other targeted drugs with a greater economic benefit.

Moreover, the low utilisation of intraperitoneal chemotherapy is due to catheter-related complications such as obstruction or abdominal pain during treatment. These complications and the lack of training of oncologists in their management mean that a large part of the medical oncology community is reluctant to use intraperitoneal chemotherapy in patients with advanced ovarian cancer despite the scientific evidence and the recommendations of clinical guidelines [54].

Improved knowledge of the peritoneum has led to knowledge of the best drug and the optimal intraperitoneal chemotherapy regimen with acceptable toxicity. It should be noted that the benefit observed with intraperitoneal administration has been developed with the use of intravenously administered drugs and it is possible that this improvement in the prognosis of these patients will increase with the development of drugs designed for peritoneal administration considering the physiology of the peritoneum.

In our opinion and based on the results obtained, intraperitoneal chemotherapy should be a treatment to be considered in young patients with little associated morbidity in which complete cytoreduction is achieved or with a tumor residue of less than 1 cm. This patient profile seems to have the most benefit from the treatment and presents the most tolerable toxicity. Likewise, the chemotherapeutic agent of choice would be cisplatin due to its bioavailability at the peritoneal level and the reduced irritation of the peritoneum that it causes.

5. Conclusions

In conclusion, this meta-analysis is not based on many articles due to the limited number of publications on this topic in the last 10 years and the heterogenicity in the design of these studies; the results obtained show that IP/IV chemotherapy is a treatment that increases the survival and the time of recurrence. However, it is underused, despite a growing amount of evidence supporting a survival advantage for ovarian cancer patients. There are still issues to be solved, such as the optimal regimen and dosage, the best moment of HIPEC, the optimal patient profile, and the role of biomarkers.

Research is needed on new drugs with a peritoneal route of administration, increasing their effect and decreasing the side effects and their combination with intravenous drugs.

Similarly, it is necessary to determine the possible toxicity associated with the different treatment regimens and establish the best pattern of treatment and the profile of patients who benefit from this treatment.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jpm13121636/s1, Figure S1: Prima checklist, Figure S2: Risk of bias summary, Figure S3: Risk of bias graph.

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CAPÍTULO 5

Resultados
Discusión general

CAPITULO 5: RESULTADOS. DISCUSIÓN GENERAL.

1. Carcinomatosis Scoring Methods in Predicting Resecability and Prognosis in Gynecologic Malignancies

El cáncer de ovario se presenta hasta en un 80% de los casos en estadios avanzados. El tratamiento indicado en pacientes con diagnóstico de carcinomatosis peritoneal de origen ginecológico es la realización de cirugía citorreductora seguida de quimioterapia adyuvante.(87,150) El objetivo de la cirugía es conseguir citorreducción completa, la cual se considera un factor independiente de supervivencia. El tumor residual tras la cirugía se encuentra inversamente relacionado con la supervivencia global (SG). (151)La distribución de la enfermedad y el volumen tumoral son los principales factores relacionados con cirugía completa. El estadio FIGO no se correlaciona con la extensión tumoral.

En este escenario la laparoscopia diagnóstica disminuye la cirugía subóptima en un 10 – 39%.(68,87)

En un estudio no randomizado retrospectivo de cohortes se compara el índice de carcinomatosis peritoneal descrito por Sugarbaker (ICP) con el índice de Fagotti en una población de 34 pacientes con diagnóstico de carcinomatosis sometidas a laparoscopia diagnóstica y posterior laparotomía, ya que la laparotomía sigue considerándose el gold estándar en la valoración de la carga de enfermedad en la carcinomatosis peritoneal. (150)Se comparan ambos scores con el objetivo de determinar la resecabilidad y el pronóstico en estas pacientes. Se evidencia el ICP mayor de 20 como el predictor con mayor exactitud diagnóstica en la valoración de la resecabilidad de estas pacientes.

El score descrito por Sugarbaker presenta mejor correlación con la supervivencia global y la extensión de la enfermedad comparado con el índice de Fagotti, mostrando una mejor supervivencia a ICP más bajos.

Se concluye que el ICP es una herramienta diagnóstica superior que el índice de Fagotti para seleccionar a las pacientes con carcinomatosis peritoneal subsidiarias de citorreducción completa, ya que el índice de Fagotti no realiza una cuantificación de la extensión de la enfermedad.

Hay que destacar la posibilidad de adecuar el valor de corte del ICP según la tasa de citorreducción subóptima de cada equipo quirúrgico, hecho que permite mejorar la selección de las pacientes para el tratamiento óptimo.

En base a los resultados propuestos es necesario realizar estudios prospectivos que permitan determinar el valor de corte óptimo para la mejor selección de las pacientes.

Este estudio contribuye a optimizar la decisión quirúrgica, reduciendo las laparotomías innecesarias y de este modo mejorar los resultados en pacientes con enfermedad oncológica avanzado de origen ginecológico.

En múltiples estudios se evidencia una mayor exactitud diagnóstica mediante la aplicación de ICP laparotómico con un AUC de 0.83. La aplicación del índice predictivo descrito por Fagotti vía laparoscópica presenta un AUC de 0.68 similar al descrito en nuestro artículo. No obstante, la aplicación del ICP vía laparoscópica alcanza 0.79. La exactitud diagnóstica de la laparoscopia comparada con la aplicación de los scores laparoscópicos mediante la prueba de imagen (TC) muestra una disminución de la AUC a 0.64. La aplicación de los scores vía laparoscópica presenta mejor concordancia con resultados quirúrgicos comparado con la evaluación radiológica, probablemente porque el estudio mediante prueba de imagen infraestima la extensión de enfermedad en forma de carcinomatosis diafragmática, omental y peritoneal. No obstante, hay determinadas áreas que son inaccesibles a la laparoscopia como es el pedículo hepático, el área retro – hepática y superficie de intestino delgado. (152)

La enterografía, que incrementa la detección en casos de alta carga de enfermedad presenta un AUC de 0.68, no mostrando diferencias estadísticamente con el TC convencional en aquellos casos con baja carga de enfermedad.(66)

A diferencia de los resultados obtenidos en nuestro artículo, el artículo publicado por Hansen et al. publicado en 2018 muestra la mayor concordancia descrita del índice predictivo, describiéndose una concordancia entre el score laparoscópico y la cirugía de citorreducción que alcanzaba el 96%.

Este estudio es prospectivo e incluye 226 pacientes seleccionadas entre 2013 – 2017. Aquellas pacientes con índice predictivo mayor a 8 se remite a quimioterapia neoadyuvante. Describen un valor predictivo positivo para citorreducción completa del 85.4% con una exactitud en la predicción de citorreducción

completa del 67%. La tasa de citorreducción completa descrita alcanza el 86% (153). Este estudio muestra una tasa de citorreducción mayor que la descrita en nuestro estudio, la cual es del 79.4%; la alta tasa de concordancia para el score laparoscópico descrito por Fagotti probablemente sea poque las pacientes incluidas en nuestro estudio fueron todas sometidas a laparotomía, con lo cual se evaluaron pacientes con índice mayor a 8 y se confirmó si las pacientes fueron irresecables. Este hecho no ocurre en el estudio de Hansen. No obstante, la exactitud diagnóstica en la predicción de citorreducción completa fue del 67%, similar a la exactitud diagnóstica en la predicción de citorreducción subóptima.

Se ha publicado un estudio en el que se realiza una comparación entre ambos índices y su aplicación en cirugía de intervalo, que confirma las conclusiones extraídas en nuestra publicación. (154)

La modificación del índice predictivo de Fagotti incrementando el valor de corte a > 10 con una tasa de citorreducción del 57.5%, un 20% más baja de la descrita en nuestra muestra, parece reducir el porcentaje de laparotomías innecesarias entre un 33.2 – 100%, concluyendo que el incremento del valor de corte para la indicación de cirugía primaria incrementa la exactitud y reduce las cirugías innecesarias. (155).

En la bibliografía revisada se objetivan varios estudios que comparan la laparoscopia con el estudio prequirúrgico por prueba de imagen. Concluyen que la laparoscopia es más exacta en la valoración de la enfermedad peritoneal. No obstante, su principal limitación es la valoración de mesenterio y retroperitoneo. Sin embargo, el uso de la laparoscopia en el estudio prequirúrgico de estas pacientes puede reducir el número de laparotomías innecesarias. (87,152,156,157).

En conclusión, la aplicación de la laparoscopia diagnóstica asociado al estudio por imagen prequirúrgico permite mejorar la selección de las pacientes con el objetivo de conseguir una citorreducción completa en el tratamiento quirúrgico primario, en la cirugía de intervalo, e incluso, en las pacientes con indicación quirúrgica en la recidiva.

2. Surgery in Recurrent Ovarian Cancer: A Meta-Analysis.

El tratamiento del cáncer de ovario en estadios avanzados se basa en el tratamiento quirúrgico con el objetivo de conseguir ausencia de residuo tumoral asociado a quimioterapia adyuvante. (30)
El 80% de las pacientes tratadas de forma óptima presentan una recidiva de su enfermedad. (158)
El tratamiento indicado en estas pacientes es el tratamiento quimioterápico. Sin embargo, estudios retrospectivos han mostrado un beneficio de la cirugía en el tratamiento de la recidiva de cáncer de ovario en pacientes platino – sensibles, mostrando que la citorreducción completa es el principal factor pronóstico en la cirugía primaria y también, en la cirugía de la recidiva. (119,158,159). No obstante, estos estudios presentan elevada heterogeneidad, lo que no permite la obtención de conclusiones fiables.
Es por ello que se plantea la realización de un meta – análisis de los 3 estudios prospectivos randomizados disponibles en la literatura, con el objetivo de evaluar el impacto de la citorreducción secundaria en la supervivencia global (SG) y el intervalo libre de enfermedad (ILE) en estas pacientes.(160–162)
En los estudios evaluados se obtiene una muestra de 1249 pacientes.
Dos de los artículos estudiados utilizan un sistema de selección de las pacientes. DESKTOP III utiliza un algoritmo denominado AGO score basado en un volumen de ascitis en la recurrencia menor a 500 mL, ECOG 0 y una cirugía primaria citorreductora completa. Las pacientes que cumplen estos tres criterios tienen una elevada probabilidad de citorreducción completa (119,120).
El SOC – 1 se basó en el iModel asociado al PET – TC.
En la siguiente tabla se muestran los criterios junto con su evaluación:

Variable	Score
FIGO Stage (I/II vs. III/IV)	0 or 0.8
Residual Disease (Primary surgery)	0 (no residual) or 1.5
Progression-Free Interval (<16 vs. ≥16 months)	2.4 or 0
ECOG Performance Status (0–1 vs. 2–3)	0 or 2.4
CA125 Levels at recurrence (<105 vs. ≥105 U/ml)	0 or 1.8
Ascites (Absent vs. Present)	0 or 3.0

Tabla 1: Algoritmo de selección iModel.
Jiang R, Feng Y, Chen Y, Cheng X, Shi T, Gao W, Jia H, Jiang S, Guo Y, Huang X, Tu D, Zhang Y, Yang H, Zhang P, Liu J, Zhu J, Zang R; SOC-1 Investigators. Surgery versus no surgery in platinum-sensitive relapsed ovarian cancer: final overall survival analysis of the SOC-1 randomized phase 3 trial. Nat Med. 2024 Aug;30(8):2181-2188. doi: 10.1038/s41591-024-02981-0. Epub 2024 Jun 1. PMID: 38824243.

La obtención de un score ≤ 4.7 indica una elevada probabilidad de citorreducción completa. El uso del PET TC complementa el score en la medida que confirma la presencia de enfermedad resecable.
Aplicando los algoritmos de selección comentados en aquellas pacientes platino – sensibles (recidiva > 6 meses tras finalización de tratamiento quimioterápico con platino) con un ECOG 0 – 1 se consigue una tasa de citorreducción completa del 75 y del 77% respectivamente. (162,163)
El último artículo incluido, que corresponde al publicado por Coleman et al. (161), no utiliza un algoritmo de selección para estos pacientes. Basándose en la evidencia por criterios RECIST de recidiva, la respuesta completa tras el tratamiento primario confirmado mediante negativización de Ca 125 y prueba de imagen posterior, un ECOG de 0 – 2 y una enfermedad potencialmente resecable, excluyendo aquellas pacientes con carcinomatosis difusa, enfermedad extra – abdominal y ascitis significativa.
Pese a la aplicación de estos criterios, este estudio presenta la tasa de citorreducción más baja, siendo aproximadamente del 67%, pese a que sólo el 16% de la muestra incluida fue sometida a tratamiento quirúrgico de la recidiva.

En la siguiente tabla se muestran las características de los estudios incluidos:

COMPARACIÓN DE RESULTADOS QUIRÚRGICOS EN LOS ESTUDIOS INCLUIDOS

	GOG 0213 (n = 674)	DESKTOP III (n= 407)	SOC – 1 (n= 357)
Tasa de citorreducción completa	67%	75%	77%
Criterios de selección	Capacidad quirúrgica sin uso de herramientas predictivas	AGO score	iModel score + PET TC
Imagen prequirúrgica	TC convencional o RMN	No establecido, pero criterios clínicos estrictos	PET - TC
Indicación quirúrgica	16% del total de los pacientes incluidos (n = 104)	100% de los pacientes seleccionados por AGO score (n = 206)	30% de los pacientes pre – seleccionados para cirugía (n = 182)
Diseño del estudio	Randomizado para cirugía y uso de bevacizumab	Randomización para cirugía o no cirugía	Randomización para cirugía o no cirugía.
Experiencia de los centros	Centros con experiencia quirúrgica variable	Centros con alto volumen con equipos quirúrgicos especializados.	Centros regionales con alta experiencia quirúrgica.
Resultado SG	1.03 (IC al 95% 0.74 – 1.43)	0.75 (IC al 95% 0.59 – 0.96)	0.82 (0.57 – 1.19)
Resultado ILE	0.62 (IC al 95% 0.48 – 0.88)	0.66 (IC al 95% 12.7 – 20.8)	0.58 (IC al 95% 0.45 – 0.74)

Tabla 2: Comparación de los resultados quirúrgicos obtenidos en los estudios incluidos en el Meta – Análisis.

Los resultados obtenidos en el análisis estadístico de estos tres artículos muestran un incremento en la supervivencia global y en el intervalo libre de enfermedad en aquellas pacientes platino – sensibles con recurrencia por cáncer de ovario avanzado, obteniendo para la supervivencia global HR 0.83 (IC al 95% 0.70 – 0.99 p = 0.04) y para el intervalo libre de enfermedad un HR de 0.63 (IC al 95% 0.55 – 0.72 p < 0.000001).

Posteriormente se evalúa el impacto de la citorreducción completa en este grupo de pacientes observando que el beneficio obtenido en términos de supervivencia e intervalo libre de enfermedad es mayor; en SG HR 0.65 (IC al 95% 0.49 – 0.86 p = 0.0002) y para ILE HR 0.67 (IC al 95% 0.53 – 0.82 p=0.0008), en concordancia con la importancia de la ausencia de residuo tumoral en cirugía primaria. (99,101,164)

No obstante, pese a que los resultados son similares a los publicados en otras revisiones en los que la cirugía de citorreducción secundaria parece presentar un beneficio en estas pacientes, hay que destacar que la heterogeneidad presente entre estos tres estudios es 50 – 75% considerándose moderada.

Los motivos son los siguientes:

- **Selección de pacientes;** la utilización de algoritmos de selección diferentes entre en SOC – 1 y el DESKTOP III. La no utilización de ningún método objetivo de selección en el GOG 0213.
- **Tasa de citorreducción completa;** la ausencia de residuo tumoral es el principal factor pronóstico relacionado con la supervivencia global en pacientes con cáncer de ovario avanzado sometidas a cirugía. Es por ello por lo que la baja tasa de reducción en el estudio GOG 0213 podría influir en los resultados obtenidos.
- **Objetivos;** SOC – 1 y DESKTOP III son dos estudios con un diseño quirúrgico, a diferencia del GOG 0213 en el que el estudio se encuentra dirigido a evaluar el efecto del bevacizumab en estas pacientes. EL objetivo primario del SOC – 1 es evaluar el impacto de la cirugía en las pacientes platino – sensibles con recaída en el intervalo libre de enfermedad, siendo la

supervivencia global un objetivo secundario. A diferencia del DESKTOP III en el que la supervivencia global es su objetivo primario, y el intervalo libre de enfermedad es su objetivo secundario. Por el contrario, el GOG 0213 combina el objetivo de evaluar la supervivencia global para el bevacizumab y la cirugía, realizando una doble randomización.

- **Experiencia quirúrgica de los diferentes centros;** mientras que en el DESKTOP III y en el SOC – 1 participan equipos quirúrgicos con experiencia en la cirugía por cáncer de ovario. En el GOG 0213 participan diferentes centros con experiencia variable.
- **Tratamiento adyuvante**; en el GOG 0213 el 50% de las pacientes del grupo de quimioterapia (337 pacientes) y el 50% de las pacientes del grupo de cirugía (53 pacientes), lo que alcanzaba a aproximadamente el 60% del total de la muestra (674 pacientes), recibieron bevacizumab. Además de que se alcanza el 84% de uso de bevacizumab debido al uso de este en pacientes con progresión a lo largo del estudio (487 pacientes). Mientras que en el DESKTOP III y en el SOC – 1 es sólo del 16% y del 1% respectivamente.

De los estudios incluidos el único que no muestra una ventaja en la supervivencia global en el grupo sometido a cirugía de citorreducción secundaria es el GOG 0213, además de que presenta una supervivencia global de 64.7 meses en el grupo de pacientes tratadas con quimioterapia, muy superior a la publicada en pacientes con características similares, e incluso a las obtenidas en DESKTOP III y en SOC – 1 en el grupo de mejor supervivencia.

Las posibles causas de este hecho probablemente sean secundarias a la selección de pacientes realizada en el estudio GOG 0213, pacientes con mejor pronóstico, ya que el intervalo platino – sensible del 75% de las pacientes incluidas en el grupo de quimioterapia es mayor a 12 meses. Además, a diferencia de otros estudios, algunas pacientes del GOG 0213 habían sido sometidas a una cirugía de citorreducción secundaria con enfermedad residual mínima o nula antes de entrar en el grupo de comparación del grupo de quimioterapia, lo que actuaría beneficiando en la supervivencia a este grupo al ser pacientes de mejor pronóstico.

La aleatorización equilibrada entre los grupos evaluados podría haber conducido inadvertidamente a una mayor proporción de pacientes con pronóstico favorable en el grupo de quimioterapia debido a un error en el cálculo del intervalo libre post – tratamiento, aunque posteriormente se corrigió con un análisis de sensibilidad mostrando una persistencia del beneficio del bevacizumab. Del mismo modo se randomizaron pacientes al grupo de quimioterapia que ya habían sido sometidas a una cirugía de citorreducción secundaria, lo que podría traducirse en un sesgo de aleatorización produciendo una ventaja inintencionada en el grupo de quimioterapia.

Otro punto que destacar es la menor tasa de citorreducción completa. La presencia de residuo tumoral tras el procedimiento quirúrgico tiene peores resultados en términos de supervivencia, este hecho podría haber afectado a la supervivencia global en el grupo quirúrgico no mostrando el efecto beneficioso propio de la cirugía completa como se objetiva en el análisis del subgrupo de cirugía completa en el que se obtiene un HR 0.96 (IC al 95% 0.68 – 1.36). Este hallazgo podría deberse a la escasa muestra quirúrgica que presenta el estudio, ya que, con menos pacientes, es más difícil detectar efectos menores del tratamiento, y los resultados en este subgrupo pueden reflejar una variación aleatoria más que un verdadero efecto del tratamiento con bevacizumab (16% de la muestra; 107 pacientes. 54 randomizadas a cirugía).

En 2024, el SOC – 1 publica una actualización de sus datos con una mediana de seguimiento de 82.5 meses, a diferencia de los 36 meses publicados en 2021. En esta actualización se evidencia una persistencia de la ventaja de la cirugía en términos de supervivencia y de intervalo libre de enfermedad tras ajustar el HR por el cruce de pacientes, ya que hasta el 35% de los pacientes incluidos en el grupo de quimioterapia son sometidas a tratamiento quirúrgico.

Con un HR para supervivencia global 0.76 (IC al 95% 0.58 – 0.99) y 0.55 (IC al 95% 0.44 – 0.69) para ILE. La mediana de supervivencia descrita para aquellas pacientes en las que se obtiene citorreducción completa es de 73 meses, respecto a los 58.1 meses global en el grupo de cirugía. Destaca que aquellas pacientes con residuo tumoral presentan una supervivencia similar al grupo de quimioterapia; 52.1

meses, evidenciando la importancia de la citorreducción completa en estas pacientes derivada de la correcta selección de las pacientes.
Durante el periodo de seguimiento se muestra una supervivencia libre de recaída del 13.2% con una supervivencia mayor a 60 meses en el grupo sometido a cirugía, mientras que sólo el 2.9% de las pacientes del grupo de quimioterapia presentan estos resultados. (165)
En base a los resultados presentados en el meta – análisis realizado y en los estudios evaluados, la citorreducción secundaria en pacientes con recidiva de cáncer de ovario parece una opción con impacto en el pronóstico de las pacientes realizando una correcta selección de estas.
Sin embargo, hay que destacar ciertas limitaciones para la extracción de conclusiones generalizadas, como es la utilización de tratamientos de mantenimiento como los iPARP y su impacto en el intervalo libre de enfermedad o en el patrón de recurrencia en estas pacientes. El SOC – 3 pretende establecer el impacto en término de supervivencia, intervalo libre de enfermedad, calidad de vida y seguridad quirúrgica en pacientes con uso de niraparib como terapia de mantenimiento en pacientes sometidas a tratamiento quirúrgico o no, evaluando una de las cohortes con tratamiento con iPARP previo a la cirugía. (163), ya que estudios previos con Niraparib en tratamiento primario no han mostrado ventajas en términos de supervivencia, aunque sí en intervalo libre de enfermedad(141,142)
Por último, en ninguno de los estudios publicados se evalúa el perfil molecular de las pacientes, aunque en diversas publicaciones se ha demostrado un mejor pronóstico en pacientes BRCA mutadas con periodos de platino – sensible más largos, o en pacientes con déficit en la recombinación homóloga en la que el uso de iPARP como el niraparib presenta mayor beneficio. El SOC – 3 aportará información a este respecto al estratificar a las pacientes en BRCA mutadas y no mutadas.
La Cochrane también ha presentado un protocolo para la evaluación del papel de la citorreducción secundaria en la recidiva del cáncer de ovario, pendiente de la publicación de los resultados de la revisión sistemática. (166)

3. **Should We Abandon Intraperitoneal Chemotherapy in the Treatment of Advanced Ovarian Cancer? A Meta-Analysis.**

El uso de la quimioterapia intraperitoneal (IP) es un tema de gran interés en el tratamiento del cáncer de ovario avanzado debido a la posibilidad de conseguir mayor concentración de los fármacos quimioterápicos directamente en la cavidad peritoneal.
El histórico estudio de Armstrong et al. publicado en el New England Journal of Medicine en 2006 aportó pruebas convincentes en apoyo de este enfoque. Evidenció con el uso de la quimioterapia intraperitoneal el incremento más notable en la supervivencia en cáncer de ovario avanzado, con una mediana de supervivencia de 65.6 meses en el grupo de quimioterapia intraperitoneal, versus 49.7 meses en el grupo de quimioterapia intravenosa sola, con una diferencia en la supervivencia de 16 meses (HR de 0.75 p = 0.03). Observando este beneficio también en el intervalo libre de enfermedad. (23.8 meses vs 18.3 meses en el grupo control.
No obstante, su uso no ha llegado a estandarizarse en la práctica clínica. Los motivos de esto son los siguientes:

- **Efectos secundarios:**
  La quimioterapia intraperitoneal se asocia con toxicidad grado 3 – 4; dolor abdominal, cansancio náuseas, toxicidad hematológica, neurotoxicidad con el uso de paclitaxel. En el artículo de Armstrong establece un 60% de efectos adversos en el grupo de quimioterapia intraperitoneal vs un 40% en el grupo de quimioterapia intravenosa sólo. Además, las complicaciones relacionadas con el catéter, como las infecciones, el bloqueo o la movilización de este, comprometen la administración del tratamiento.
- **Baja tasa de cumplimiento:**
  La toxicidad secundaria al tratamiento y las complicaciones secundarias al uso del catéter dificultan la administración de los 6 ciclos propuestos. En el estudio de Armstrong sólo el 58% de los pacientes completaron el tratamiento.
- **Desarrollo de otros tratamientos:**
  - Inhibidores del PARP: han mostrado un incremento en el intervalo libre de enfermedad en pacientes BRCA mutadas o con deficiencia de la recombinación homóloga (HRd). Estos tratamientos son menos tóxicos y con una facilidad de administración mayor.
  - Anti – angiogénicos: bevacizumab combinado con la quimioterapia intravenosa parece ofrecer los mismos beneficios con una mejor seguridad y tolerabilidad según los resultados del GOG 252. (167)
- **Logística de administración:**
  El uso de la quimioterapia intraperitoneal requiere un entrenamiento especializado y un equipo de administración específico; catéter intraperitoneal y protocolos de infusión.

En el escenario expuesto es necesario evaluar el impacto de la quimioterapia intraperitoneal, y si los efectos adversos descritos justifican la sustitución de esta por otros tratamientos.

Por este motivo se desarrolla un meta – análisis que pretende evaluar la supervivencia global y el intervalo libre de enfermedad de las pacientes tratadas con quimioterapia intravenosa vs aquellas en las que al tratamiento estándar intravenoso se añade la quimioterapia intraperitoneal.
Para ello se analizan 6 artículos en los que se aplica la quimioterapia intraperitoneal en pacientes sometidas a cirugía primaria. (168–173)
En la siguiente tabla se muestran las características más relevantes de cada estudio.

CARACTERÍSTICAS RELEVANTES DE LOS ESTUDIOS INCLUIDOS					
ESTUDIO	OBJETIVO	COHORTE	RESULTADOS	TASAS DE CUMPLIMIENTO	LIMITACIONES
Tewari (2015)	Mediana SG e ILE en cirugía óptima	Cirugía óptima (≤ 1 cm) en estadio III de cáncer de ovario	SG en IP (61.8 m vs 51.4 m). ILE en IP (25 m vs 20 m	42% completan 6 ciclos.	Elevada toxicidad. Falta BRCA estatus.
Omali(2022)	Supervivientes ≥ 10 años. Estadio III de cáncer de ovario	Estadio III con supervivencia ≥ 10 años.	18% supervivencia libre de enfermedad ≥ 10 años. Edad único factor pronóstico. (No diferencias IP vs IV.)	N/A	Retrospectivo. Análisis sólo de largos supervivientes. Falta BRCA estatus
Yuanming (2022)	Pacientes chinas con cáncer de ovario avanzado	Estadio III cáncer de ovario con cirugía con residuo ≤ 1 cm.	No diferencias: ILE (20 vs 22 m.) SG 3 años (80% vs 78%)	Mediana 5.6 ciclos (94% de ciclos completados)	Falta BRCA status. Dosis de cisplatino menor (75 mg/m^2)
Cochrane (2016)	Eficacia y seguridad	Estadio III de cáncer de ovario	IP mejora SG e ILE	Variable. Alta toxicidad.	Heterogeneidad. Falta de estandarización de regímenes de tratamiento
Wright (2015)	Tasas de cumplimiento y resultados SG e ILE en la práctica clínica.	Pacientes tratados con IP	IP beneficio en SG.	Tasa baja de cumplimiento. Baja adherencia.	Variabilidad en práctica clínica
iPocc trial (2022)	Eficacia de carboplatino IP	Diagnóstico de cáncer de ovario avanzado (III/IV)	Carboplatino IP mejor tolerado que cisplatino con SG similar.	Mejor tolerancia que series previas con cisplatino	Muestra limitada.

Tabla 3: Resultados relevantes de los estudios incluidos en el meta – análisis

Los resultados obtenidos mediante el análisis de los estudios presentados muestran un beneficio en la supervivencia global con un HR de 0.81 (IC al 95% 0.74 – 0.88) y un intervalo libre de enfermedad HR 0.81 (IC al 95% 0.75 – 0.87), ambos con diferencias estadísticamente significativas a favor del uso de la quimioterapia intraperitonal.

De los 6 artículos incluidos sólo 2 no muestran beneficio en la supervivencia global y el intervalo libre de enfermedad, el publicado por Yuanming et al. y el publicado por Omali et al. (170,172)

El estudio de Yuanming es un estudio retrospectivo en el que se realiza un propensity score 1:2 incluyendo a 85 pacientes con quimioterapia intraperitoneal y 107 con quimioterapia intravenosa con una mediana de seguimiento de 41 meses, sin mostrar diferencias significativas en ninguno de los dos grupos, probablemente porque en este estudio sólo realizan 1 ciclo de quimioterapia intraperitoneal durante la cirugía empleando dosis inferiores de cisplatino a las reportadas en otros artículos. Este factor podría justificar la ausencia de una ventaja terapéutica notable asociada con la quimioterapia intraperitoneal. (172)

El estudio de Omali et al., analiza las pacientes con supervivencias mayores a 10 años del GOG 104, GOG 114 y GOG 172 evaluando los factores independientes relacionados con la supervivencia ≥10 años y la

supervivencia libre de enfermedad ≥ 10 años, Los resultados revelan que una edad más joven al momento del diagnóstico es el único factor independientemente relacionado con ambos desenlaces. (174–176)

Aunque la quimioterapia intraperitoneal parece mostrar una tendencia a aumentar la supervivencia global en pacientes con supervivencias prolongadas, las diferencias observadas no alcanzan significación estadística.

Es probable que factores como el uso de regímenes quimioterápicos en primera línea, como la ciclofosfamida, la falta de estandarización en el fármaco empleado (paclitaxel versus cisplatino) o las diferencias en el número de ciclos de quimioterapia intraperitoneal (3 ciclos en el GOG 114 frente a 6 ciclos en el GOG 104 y GOG 172) hayan contribuido a una heterogeneidad que podría reducir la potencia estadística del estudio, dificultando la demostración del beneficio de la quimioterapia intraperitoneal.

El estudio de Tewari et al., basado en pacientes de los ensayos GOG 114 y GOG 172, confirma una ventaja significativa en términos de supervivencia global e intervalo libre de enfermedad a favor del tratamiento con quimioterapia intraperitoneal. En comparación con la quimioterapia intravenosa, se observa un incremento de 10 meses en la supervivencia global y de 5 meses en el tiempo hasta la recidiva. Sin embargo, solo el 50% de los pacientes completaron los 6 ciclos de tratamiento debido a la toxicidad y a problemas asociados con el catéter. A pesar de ello, el estudio destaca que cada ciclo de quimioterapia intraperitoneal administrado reduce el riesgo de muerte en un 12%.(173)

Aunque ambos estudios analizan pacientes de los mismos ensayos, su selección difiere significativamente. Omali et al. se centra exclusivamente en los largos supervivientes, lo que reduce el tamaño de la muestra y limita la potencia estadística de sus resultados. En cambio, Tewari et al. incluye a toda la cohorte de pacientes, proporcionando un análisis más amplio y representativo.

Es posible que Omali haya seleccionado un grupo de mejor pronóstico por sus características y que, por tanto, no se evidencie el beneficio de la quimioterapia intraperitoneal. Es probable que el hecho de que la edad sea el único factor pronóstico independiente identificado esté relacionado con la inclusión de pacientes con mutaciones en BRCA. Estas pacientes tienden a desarrollar cáncer de ovario a edades más tempranas y suelen mostrar una mayor quimiosensibilidad, así como períodos más prolongados de sensibilidad al platino.

El GOG 252, aunque es un estudio randomizado de fase III, no se incluyó en el meta-análisis debido a que en su diseño se incorpora el uso de bevacizumab, lo cual introduce una variable adicional que podría afectar la comparabilidad de los resultados. Los resultados obtenidos no muestran diferencias en supervivencia global ni intervalo libre de enfermedad entre aquellas pacientes tratadas con quimioterapia intravenosa asociado a bevacizumab que aquellas tratadas con cisplatino o carboplatino intraperitoneal asociado a bevacizumab. Concluyendo que el uso del bevacizumab presenta el mismo beneficio que el uso de la quimioterapia intraperitoneal. (167)

Sin embargo, hay ciertos aspectos que deben tenerse en cuenta respecto al diseño del estudio;

- Menor dosis de cisplatino que la usada en otros estudios (75 mg/m^2, a diferencia de 100 mg/m^2).
- Incluye pacientes en estadio II (10.4%) y en estadio IV (6%): ninguna de estas pacientes se incluyó en los otros estudios. Sólo estadios III.
- Incluyen pacientes sometidas a cirugía de intervalo, sin establecer el uso de tratamientos de mantenimiento que podrían haber recibido con anterioridad. (16%)
- Un 7% de las pacientes incluidas presentan residuo tumoral > 1 cm. Un criterio de inclusión en el resto de los estudios presentados es la cirugía de citorreducción sin residuo o con residuo ≤ 1 cm.
- Tres estudios fase III evidencian que el uso del bevacizumab se relaciona con un incremento en el intervalo libre de enfermedad, pero no en la supervivencia global, sobretodo en pacientes consideradas de mal pronóstico (estadio FIGO IV y residuo tumoral > 1 cm). (177–179).

Aproximadamente el 20% de las pacientes incluidas presentan estas características, por lo que los resultados obtenidos podrían haberse visto influenciados por este hecho.

En 2024, Tang et al., ha publicado un artículo basado en un estudio de cohorte que compara 57 pacientes sometidas a quimioterapia intraperitoneal (cisplatino 100 mg/m^2 + paclitaxel 60 mg/m^2) con 23 pacientes tratadas con quimioterapia intravenosa con carboplatino + paclitaxel + bevacizumab (7.5 mg/Kg) (IVB). Los resultados obtenidos evidencian un beneficio en la supervivencia global (HR de 0.34) y en intervalo libre de enfermedad (HR de 0.45) a favor del uso de la quimioterapia intraperitoneal pese a que se incluye un 25% de estadio IV y 11% de estadio II en el grupo de IP vs un 22% y 4% respectivamente en el grupo IVB. Incluyen también pacientes con residuo tumoral > 1 cm, 35% en el grupo IP y 65% en el grupo IVB.(180)

Pese a estas modificaciones de perfil de paciente incluido respecto al estudio de Armstrong muestran una superioridad notable de las pacientes tratadas con quimioterapia intraperitoneal, evidenciando que los factores relacionados con el pronóstico es el estadio FIGO avanzado, un Ca 125 elevado y la administración de pocos ciclos de quimioterapia. No obstante, la dosis utilizada de bevacizumab es menor que la utilizada en GOG 252 (7.5 mg/Kg vs 15 mg/Kg). Este hecho junto con el carácter retrospectivo de los datos, y la muestra pequeña evaluada disminuye la potencia estadística de los resultados obtenidos.

Padilla et al., realiza un estudio retrospectivo multicéntrico en el que en el que evalúa el impacto de la mutación en BRCA (BRCAmt) en la respuesta al tratamiento intraperitoneal, bajo la premisa de la mejor respuesta de estas pacientes al tratamiento quimioterápico basado en platino, respecto a las pacientes no mutadas (BRCAwt). (181,182). Se evaluó la respuesta al tratamiento quimioterápico intravenoso e intraperitoneal en pacientes BRCAmt frente a aquellas BRCAwt. Los resultados mostraron un mayor beneficio en la supervivencia global y en el intervalo libre de enfermedad en las pacientes BRCAmt tratadas con quimioterapia intraperitoneal, con un hazard ratio (HR) de 0.17 frente a 0.35, respectivamente. En contraste, en las pacientes BRCAwt no se observó ninguna ventaja, independientemente de la vía de administración, a pesar de las altas tasas de citorreducción completa, superiores al 90%.

Respecto a los efectos secundarios presentan un incremento en síntomas gastro – intestinales y complicaciones relacionadas con el catéter en el grupo de quimioterapia intraperitoneal, no obstante, los efectos secundarios a largo plazo son comparables en ambos grupos.

En base a estos hallazgos, es posible que aquellas pacientes con deficiencia en la recombinación homóloga presenten beneficio con el uso de la quimioterapia intraperitoneal. Aquellas pacientes BRCAwt pueden no obtener el beneficio esperado con este tratamiento, siendo necesario realizar estudios prospectivos que evalúen con mayor potencia estadística este tratamiento u otras armas terapéuticas en este grupo de pacientes de peor pronóstico.

En la actualidad, la inmunoterapia está siendo aplicada en diversos tipos de cáncer, incluidos los tumores ginecológicos. Recientemente, se publicó un estudio basado en las pacientes del ensayo iPocc, en el cual se evaluaron las muestras tumorales. Este análisis incluyó la infiltración por células inmunes y la expresión génica, clasificando a las pacientes en dos categorías: alta actividad inmune (immune hot) y baja actividad inmune (immune cold).

Las pacientes con una elevada infiltración tumoral de células T citotóxicas o células Natural Killer (NK), junto con una alta expresión génica de genes relacionados con la inmunidad, puntos de control inmunitario o moléculas supresoras, mostraron un beneficio en la supervivencia global y en el intervalo libre de enfermedad al ser tratadas con quimioterapia intraperitoneal en comparación con la intravenosa. Este perfil se asemeja al de las pacientes clasificadas como "immune hot". Sin embargo, aunque existe una relación entre una mejor respuesta inmune y las pacientes con mutaciones en BRCA (BRCAmt), no se encontró una asociación directa entre la mutación BRCA y la clasificación "immune hot".(169)

Actualmente, se están investigando numerosos factores moleculares e inmunológicos en pacientes con cáncer de ovario, lo que permite identificar y perfilar diferentes subtipos de pacientes. Estos avances contribuyen a una mejor comprensión de la heterogeneidad del tumor, facilitando la personalización de

los tratamientos y optimizando los resultados clínicos. Son necesarios estudios que permitan establecer el perfil de pacientes que más se benefician de las diferentes alternativas terapéuticas disponibles.

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CAPITULO 6

CONCLUSIONES

CAPITULO 6: CONCLUSIONES.

Los artículos publicados ofrecen un marco integral para abordar el manejo del cáncer de ovario avanzado y su recurrencia. Las conclusiones son:

- La cirugía agresiva con objetivo de eliminación de residuo tumoral, acompañada del uso de la quimioterapia intraperitoneal en casos seleccionados, es esencial para mejorar la supervivencia global y el intervalo libre de enfermedad en pacientes con buen estado funcional y estadio III de cáncer de ovario.

- El uso de herramientas que permitan catalogar a las pacientes para la indicación quirúrgica en cirugía primaria o secundaria, tales como el ICP laparoscópico y los diferentes algoritmos de selección en cirugía secundaria, son esenciales para identificar a las pacientes que se beneficiaran de este tratamiento quirúrgico. Esto conduce al establecimiento de nuevos protocolos en los que se incluye el ICP laparoscópico.

- La integración de herramientas predictivas y la evaluación del perfil inmunológico y molecular de cada tumor son cruciales para establecer diferentes perfiles de pacientes y de este modo maximizar los beneficios de los tratamientos aplicados y minimizar los riesgos y los costes asociados de cada intervención.

Este enfoque multidisciplinar y personalizado tiene el potencial de transformar el manejo del cáncer de ovario y mejorar el pronóstico de nuestras pacientes.