UNIVERSIDAD DE LAS PALMAS
DE GRAN CANARIA

Facultad de Ciencias de la Salud

Escuela de Doctorado de la ULPGC

Programa de Doctorado Investigación Aplicada a las Ciencias Sanitarias

Departamento de Ciencias Clínicas

TESIS DOCTORAL

Pedro de Pablos Rodríguez

Las Palmas de Gran Canaria 2024

UNIVERSIDAD DE LAS PALMAS DE GRAN CANARIA

ESCUELA DE DOCTORADO DE LA ULPGC

Departamento de Ciencias Clínicas

PROGRAMA DE DOCTORADO

INVESTIGACIÓN APLICADA A LAS CIENCIAS SANITARIAS POR LA UNIVERSIDAD DE LAS PALMAS DE GRAN CANARIA Y LA UNIVERSIDAD DE LEÓN

Título de la Tesis

UTILIDAD DEL VERDE DE INDOCIANINA EN LA LINFADENECTOMÍA POR CÁNCER DE PRÓSTATA. FACTORES PRONÓSTICOS EN EL CÁNCER DE PRÓSTATA AVANZADO.

Tesis Doctoral presentada por D. Pedro de Pablos Rodríguez

Dirigida por el Dr. Juan Francisco Loro Ferrer

Codirigida por el Dr. Miguel Ramírez Backhaus

El Director, **El Codirector** **El Doctorando,**

Las Palmas de Gran Canaria, a 15 de marzo de 2024

DEDICATORIA

A mi familia, por su desinteresado apoyo constante. Papá (Pedro), mamá (Fátima), hermana (Marta), hermano (Luis), me siento agradecido y afortunado.

A mis tutores, por ser una inspiración profesional inmejorable. Gracias Dr. Ramírez por contagiarme “con tu prurito” por la investigación. Gracias Dr. Loro por tu apoyo durante este proceso.

A mis docentes, por la paciencia que requiere enseñar, incentivar, repetir. Tiene un valor sobreañadido en un medio que no incentiva esta labor.

A los pacientes, por vuestro compromiso con la ciencia y la confianza que depositan en los médicos. Esta confianza es un pilar necesario para nuestra motivación.

ÍNDICE DE CONTENIDO

1. GLOSARIO DE ABREVIATURAS

BCR = Recurrencia bioquímica

CP = Cáncer de próstata

CPRC = Cáncer de próstata resistente a la castración

ECA = Ensayo clínico aleatorizado

ePLND = Linfadenectomía pélvica extendida

HR = Hazard ratio

PET = Tomografía por emisión de positrones

PLND = Linfadenectomía pélvica

PR = Prostatectomía radical

PSA = Antígeno prostático específico

RIC = Rango intercuartílico

RMN = Resonancia magnética nuclear

RR = Riesgo relativo

SCE = Supervivencia cáncer específica

SG = Supervivencia global

SLP = Supervivencia libre de progresión

TAC = Tomografía axial computarizada

TPA = Terapia de privación androgénica

2. INTRODUCCIÓN

2.1 Conceptos generales

El cáncer de próstata (CP) es el cáncer más frecuentemente diagnosticado [1] y la tercera causa de muerte por cáncer en varones en España [2]. A nivel estatal, en el año 2023 se diagnosticaron 29.002 pacientes de CP, seguido por el cáncer pulmón (22.266), vejiga (21.694) y colon (28.465) [1]. Mientras, en los Estados Unidos, es el cáncer más comúnmente diagnosticado en los hombres, representando el 19% de todos los casos [3]. En el año 2018, 164.690 norteamericanos fueron diagnosticados de CP y 39.430 murieron por esta enfermedad en el mismo año [3].

El CP es una enfermedad sumamente heterogénea cuya mortalidad viene condicionada especialmente por el PSA, el Gleason y el estadio tumoral [4]. En España, se estima que entorno al 90% de los CP se diagnostican en estadio localizado frente a un 10% en estadio localmente avanzado o metastásico [5]. La muerte cáncer específica a 5 años en pacientes con CP localizado tratados mediante cirugía o radioterapia es inferior al 5%, frente al 30% en un escenario metastásico [6,7].

Los factores de riesgo de la enfermedad los podemos agrupar en no modificables (edad, historia familiar, predisposición genética, etc.) y modificables (ingesta dietética, medicación, infecciones, etc.). En general, los factores modificables se asocian débilmente con el cáncer existiendo además cierta heterogeneidad en los estudios [7].

En ausencia de directrices claras en la prevención del CP se hace imperativa su detección precoz y estudiar los factores pronósticos que puedan impactar negativamente sobre la evolución de la enfermedad. En el escenario metastásico que, como hemos indicado, es donde se produce la mayor mortalidad cáncer específica, los factores pronósticos más estudiados son los relacionados con la carga tumoral: número y localización de las metástasis óseas, presencia de metástasis viscerales, Gleason, PSA y fosfatasa alcalina [8-11]. Interesa, sin embargo, dilucidar aquellos factores pronósticos modificables que permitan aumentar la supervivencia de estos pacientes.

La alta prevalencia del cáncer de próstata, así como su asociada mortalidad, obligan a mantener la más alta calidad en la atención de estos pacientes. Es imperativo optimizar el manejo de la enfermedad en cada momento y según los diferentes escenarios clínicos a los que nos enfrentamos, desde su estadio localizado a su evolución metastásica.

2.2 Introducción artículo 1

Actualmente concurren dos circunstancias: una reducción de los programas de despistaje poblacional del CP junto con la popularización de la vigilancia activa en pacientes de bajo riesgo. Por ello, la PR que clásicamente era el tratamiento de elección

para los pacientes de muy bajo o bajo riesgo, se traslada a escenarios de riesgo clínico intermedio y alto [12].

El registro nacional sueco objetivó que el propio CP era la principal causa de muerte en los pacientes que padecían este tipo de enfermedad [13]. Posiblemente porque algunos de estos pacientes con riesgo clínico intermedio o alto, en realidad, ya padecen una enfermedad localmente avanzada, incluso con metástasis adenopáticas pélvicas asociadas. De hecho, se ha observado que hasta el 20- 30% de los pacientes con riesgo clínico intermedio o alto padecen afectación ganglionar pN1 [14-17].

La PR es una de las opciones terapéuticas para el control local de la enfermedad en estos estadios clínicos [18]. Tiene como virtud, además, que la linfadenectomía que se puede asociar supone la mejor de las opciones para estadificar regionalmente la enfermedad. La información sobre la presencia de metástasis en los ganglios linfáticos al diagnóstico es importante para la correcta estadificación y el consecuente tratamiento de los pacientes de riesgo clínico alto y la mayor parte de los de riesgo clínico intermedio.

La probabilidad o riesgo de tener ganglios linfáticos pélvicos metastásicos al diagnóstico del cáncer de próstata se puede estimar de dos modos:

- Con pruebas de imagen de nueva generación como el Ga68PSMA. Alrededor del 80% de los ganglios metastásicos en CP son menores de 8 mm [19]. Por lo tanto, la sensibilidad de TAC y RNM son bajas [20]. La tomografía por emisión de positrones es una nueva modalidad de imagen basada en información molecular. Recientemente, el uso cada vez más frecuente del PSMA PET-TAC marcado con 68Ga o 18F, impresiona de que va a revolucionar la estadificación del cáncer de próstata [21]. Sin embargo, una revisión sistemática reciente que incluyo doce estudios con un total de 322 demostró una excelente especificidad, pero baja y variable sensibilidad [22].
- Con nomogramas basados en parámetros que incluyen: PSA, puntuación Gleason, numero de cilindros afectos por cáncer en la biopsia positivos o características de la resonancia magnética multiparamétrica [23,24,25]. De hecho, las guías clínicas recomiendan la utilización de estas calculadoras para

conocer de manera preoperatoria el riesgo de que el paciente padezca una enfermedad pN1 y la toma de decisiones (linfadenectomía sí o no) en función de la probabilidad calculada para cada caso. Las europeas apuestan por el nomograma de Briganti y cols y recomiendan la linfadenectomía extendida cuando el riesgo calculado de tener metástasis es mayor al 5% [24]. Las guías de la NCCN abogan por el modelo de Cagiannos y cols y establecen un punto de corte del 2% [26].

Independientemente de la opción que se tome para el cálculo del riesgo de tener metástasis ganglionares, es obvio que la linfadenectomía es la mejor estrategia para la estadificación de la enfermedad y, por tanto, el resultado de la misma, el mejor marcador pronóstico para estos pacientes. Varios estudios han demostrado que el número de metástasis ganglionares en la linfadenectomía constituyen un factor pronostico [27, 28]. El comportamiento bioquímico y la supervivencia libre de metástasis es significativamente peor cuando se objetivan más de dos metástasis [27, 28]. Además, un antiguo estudio aleatorizado que incluyo solo 100 pacientes con linfadenectomías positivas para metástasis demostró que el uso precoz de terapia de privación androgénica tenía un beneficio en supervivencia cuando lo comparábamos con el uso tardío de dicha estrategia [29]. Por tanto, la información que deriva de la linfadenectomía supondría un beneficio oncológico, cuanto menos, indirecto.

La extensión de la linfadenectomía también ha sido objeto de debate y estudio. La ePLND supone una exquisita disección del tejido linfograso de la pelvis, incluyendo, obviamente los ganglios que cubren la arteria y la vena iliaca externas hasta el cruce del uréter, de la fosa obturatriz y los ganglios medial y lateral a la arteria iliaca interna desde el Cloquet hasta la fosita de Marcille. Dicho procedimiento supone un consumo de tiempo y un aumento de la iatrogenia. Se estima que entre el 87% [30] y el 94% [31] de los pacientes quedarían bien estadificados según el anterior esquema. La linfadenectomía limitada a la fosa obturatriz presupone insuficiente [30, 31], para la correcta estadificación de los pacientes. Desde el punto de vista oncológico, los estudios retrospectivos han observado la superioridad de la ePLND frente a la limitada. Pero recientemente se han presentado los resultados de ensayo clínico americano con 1500

pacientes aleatorizados a una linfadenectomía ampliada versus a una limitada y no se objetivaron diferencias en la evolución bioquímica de los subgrupos [32].

De forma paralela, surgieron los primeros estudios que exploraron el papel del ganglio centinela durante la prostatectomía radical [33]. El ganglio centinela se define como el primero que recibe el drenaje de un tumor. Se basa en la suposición de una invasión progresiva y ordenada de las células tumorales en los ganglios linfáticos. Implica que el racimo de ganglios está libre de infiltración tumoral si el primer nodo no está afecto y este concepto se usa habitualmente en el cáncer de mama y el melanoma. El beneficio potencial seria obviar el tiempo quirúrgico y la iatrogenia de una ePLND cuando el ganglio centinela no fuera metastásico, además de la localización de ganglios centinela fuera de la pelvis. Sin embargo, en cáncer de próstata muchos autores argumentan que el ganglio centinela no sería aplicable en la próstata por la multifocalidad del tumor [34], la falta de un ganglio centinela único de la glándula prostática [31], la dificultad para la inyección del trazador alrededor del tumor y la falta de una técnica fiable para el análisis intraoperatorio del ganglio centinela. El grupo alemán de Wawroschek y Winter con más de 1200 casos de experiencia objetivaron una razón de verosimilitud negativa menor al 10% [35], lo que supone que es una técnica fiable para conocer el estado ganglionar de los pacientes. Son varios los inconvenientes de susodicha técnica: el incremento de los costos que suponen las pruebas de imagen preoperatorias, la toxicidad que supone la irradiación, la toxicidad de la inyección transrectal del trazador en régimen ambulatorio el día previo a la intervención, la multidisciplinariedad de la técnica y, sobre todo, la falta de un análisis peroperatorio fiable del ganglio centinela.

En los últimos años se introdujeron mejoras como las sondas para el uso endoscópico [36], el uso de fluorescencia intraoperatoria [37] y trazadores híbridos que combinan coloide 99m Tc marcado con un fluoróforo como el verde de indocianina (ICG) para la navegación intraoperatoria [38]. El potencial de visualizar los ganglios involucrados en el drenaje linfático ha supuesto un creciente interés por el uso del ICG.

Nuestro grupo demostró en 84 pacientes a los que les practicamos una linfadenectomía guiada por ICG seguida de una ePLND de validación que la exéresis selectiva de los ganglios fluorescentes estadificó correctamente el estadio ganglionar del 97% de los

pacientes [39]. La técnica de linografía con ICG libre tiene ventajas frente al ganglio centinela con el trazador Tc99. La posibilidad de aplicarlo durante el procedimiento quirúrgico ahorra los sobrecostes del SPECT y del ingreso previo, así como la potencial iatrogenia de la irradiación y la inoculación del trazador el día previo.

2.3 Introducción artículo 2

La sarcopenia es una enfermedad progresiva y musculoesquelética vinculada a la edad cronológica de la persona [40,41] caracterizada por la pérdida de masa muscular y su función asociada, lo que se relaciona con una mayor probabilidad de resultados adversos, incluidas caídas, fracturas, discapacidad física y mortalidad [41]. Específicamente, la sarcopenia es probable cuando se detecta una baja fuerza muscular. El diagnóstico de sarcopenia se confirma por la presencia de baja cantidad o calidad muscular. Cuando se detecta baja fuerza muscular, baja cantidad/calidad muscular y bajo rendimiento físico, se considera que la sarcopenia es grave [41]. Existe una disminución inherente en las concentraciones séricas de testosterona a medida que aumenta la edad, lo que afecta directamente al desarrollo de la masa muscular y la masa grasa. En consecuencia, el proceso de envejecimiento acelera el desarrollo de la sarcopenia [40].

Además, uno de los enfoques terapéuticos en los diferentes escenarios de cáncer de próstata puede involucrar la TPA , que produce cambios en la composición corporal y la función física [42]. Por lo tanto, la pérdida relacionada con la edad de la masa muscular y grasa y, por lo tanto, la sarcopenia, se acentúa en estos pacientes por el efecto de la castración química [42].

Se ha identificado la sarcopenia como un factor pronóstico desfavorable para la progresión de la enfermedad y la mortalidad en pacientes con cáncer de ovario [43], cáncer de mama [44], cáncer de pulmón [45] o cáncer colorrectal [46], entre otros. En el caso del cáncer de próstata, aunque se han establecido diferentes factores pronósticos para la progresión de la enfermedad y la mortalidad, incluido el Gleason, el estadio clínico, el PSA, la presencia de metástasis viscerales y el número de sitios metastásicos [47], falta una conclusión clara o consenso sobre el papel pronóstico de la

sarcopenia. Determinar esta asociación puede incentivar el diseño de estrategias específicas y adaptadas para mejorar el pronóstico de los pacientes con cáncer de próstata y la efectividad de los tratamientos de primera línea.

3. OBJETIVOS

3.1 Objetivos del artículo 1

Primarios

Demostrar que la linfadenectomía selectiva de los ganglios teñidos con ICG (ICG-PLND) disminuye el riesgo de complicaciones que asocia la ePLND.

Secundarios

Determinar si la linfadenectomía de los ganglios teñidos por ICG tiene una capacidad equivalente para estadificar a los pacientes diagnosticados de CP subsidiarios de prostatectomía radical. Demostrar que la linfadenectomía selectiva tiene una equivalente capacidad citorreductora en el caso de los pacientes que tengan metástasis ganglionares, lo que supondrá un igual control bioquímico de la enfermedad.

3.2 Objetivos del artículo 2

Los objetivos del estudio fueron identificar, evaluar críticamente y sintetizar la evidencia científica disponible sobre el impacto de la sarcopenia en la progresión de la enfermedad y la mortalidad en pacientes con cáncer de próstata avanzado.

4. METODOLOGÍA

4.1 Metodología del artículo 1

4.1.1 Criterios de valoración

Primarios

- Porcentaje de complicaciones estratificadas por la clasificación de Clavien.

Secundarios

- Porcentaje de complicaciones grado 3, según la clasificación de Clavien [48].

- Media de días de estancia.
- Mediana de días de estancia.
- Porcentaje de pacientes estadiados como pN1. Pacientes con, al menos una, metástasis ganglionar o número absoluto de ganglios metastásicos en cada grupo.
- Número de ganglios disecados por grupo: número de ganglios analizados en el informe de anatomía patológica.
- Ratio número de ganglios metastásicos/número de ganglios absoluto.
- Porcentaje de pacientes con PSA<= 0,01 ng/ml a los 3 meses.
- Porcentaje de pacientes con PSA<= 0,01 ng/ml a los 12 meses de la intervención.
- Porcentaje de pacientes con PSA <= 0,01 ng/ml a los 24 meses de la intervención.
- Porcentaje de pacientes con privación androgénica a los 2 años. Análogo de la GnRH o cualquier tratamiento antitumoral hormonal.
- Tiempo a la recidiva bioquímica (PSA>0,2 ng/ml en dos mediciones consecutivas separadas entre sí 2 semanas).
- Porcentaje de pacientes en recidiva bioquímica a los dos años (PSA>0,2 ng/ml en dos mediciones consecutivas separadas entre sí 2 semanas).

4.1.2 Selección de la muestra a estudio

Criterios de inclusión

Varones diagnosticados de CP, mayores de 18 años, subsidiarios de tratamiento con PR que deseen participar en el estudio y estén capacitados para firmar el consentimiento informado. CP de riesgo clínico intermedio y alto según la clasificación de las guías NCCN. Puntuación de la Eastern Cooperative Oncology Group ECOG=0 en el momento del diagnóstico de CP. Puntuación ASA, I, II o III.

Criterios de exclusión

TPA previa a la cirugía. Se permite el uso de finasteride o Dutasteride. Índice de masa corporal mayor a 40. Grupos de riesgo muy bajo, bajo y muy alto. Otro tumor, excluyendo los basocelulares o espinocelulares de la dermis. Si se permite otros tumores

si el paciente está >2 años Libre de enfermedad. Historia de cirugía mayor del recto o sigma. Diverticulitis activa. Alteraciones psicológicas, o condiciones familiares, socioculturales o geográficas que, a juicio del investigador, impidan al paciente dar su consentimiento o completar el estudio. Tratamiento con radioterapia o braquiterapia previa. Si se permite el tratamiento focal previo a la indicación de prostatectomía radical.

4.1.3 Diseño del estudio

Estudio aleatorizado (1:1), unicéntrico. Comparará la proporción de complicaciones y el control bioquímico, en pacientes con CP de riesgo intermedio o alto, subsidiarios de PR y linfadenectomía. A los pacientes se les practicará una linfadenectomía selectiva de los ganglios teñidos de ICG versus una ePLND.

El estudio tiene las siguientes fases: Despistaje, tratamiento quirúrgico, seguimiento postoperatorio inmediato, postoperatorio intermedio, tardío.

4.1.4 Asignación del tratamiento

Los pacientes serán aleatorizados a linfadenectomía selectiva o ePLND en una proporción de 1 a 1 con el software informático R. El software será preparado antes de la puesta en marcha del ensayo clínico.

4.1.5 Medicación, toxicidad esperada o factible, modificaciones de la dosis

La droga incluida en el presente estudio es verde de indocianina. El verde de indocianina es un colorante soluble en agua con la absorción espectral de pico a 800 nm. Características que la hacen idónea para la técnica de linografía.

Una vez reconstituido en agua bidestilada tiene un pH de aproximadamente 6.5. Está comercializado como un polvo verde estéril liofilizado que contiene 25 mg de verde de indocianina sin más de yoduro de sodio al 5%. Se diluye con agua y se administra por vía endovenosa o percutánea.

Después de la inyección intravenosa, el verde de indocianina se une rápidamente a la albumina que es su principal transportador (95%). No está descrita circulación extrahepática o enterohepática. Las mediciones simultaneas de ICG en sangre venosa y arterial sugieren que la acumulación renal, pulmonar, cerebral es insignificante. Su metabolización es hepática casi en exclusiva lo que hace que sea un marcador útil de la función hepática.

Está descrito su uso para determinar el gasto cardiaco, la función hepática, el flujo sanguíneo hepático, para angiografía oftálmica, la linografía y la perfusión renal.

No hay descritas complicaciones para el uso percutáneo del producto.

Las preparaciones de heparina que contengan bisulfito de sodio pueden reducir el pico de absorción de ICG. Dicha circunstancia debe tenerse presente si se utiliza el ICG como marcador de función hepática, no para el uso percutáneo que se dará en el presente estudio. Carcinogénesis, mutagénesis, alteración de la fertilidad: no se han realizado estudios para evaluar la carcinogenicidad, mutagenicidad o deterioro de la fertilidad.

Se han reportado reacciones urticariales en pacientes con o sin antecedentes de alergia al yodo, con el uso endovenoso, no con el uso percutáneo. Si tales reacciones ocurren, es conveniente el tratamiento con los fármacos habituales. Solo hay reportados 3 casos de reacción anafiláctica en 4046 pacientes [49, 50]. Y solo con el uso endovascular. En nuestro ensayo se utilizará ICG con aplicación percutánea intersticial, hasta la fecha no hay descritas complicaciones mayores asociadas a este acceso. Además, el hecho de una aplicación percutánea transperineal tampoco aumenta el riesgo de infección o contaminación del campo quirúrgico.

En el hipotético caso que algún paciente presentara una reacción adversa al fármaco, el evento se notificará a las autoridades competentes en materia de farmacovigilancia siguiendo los cauces y plazos establecidos por dichas autoridades.

No hay datos disponibles que describan los signos y síntomas de una potencial sobredosis. Para el uso endovenoso, el LD50 se calculó con un rango de 60 y 80 mg / kg

en ratones, 50 y 70 mg / kg en ratas y 50 y 80 mg / kg en conejos. No se contempla la posibilidad de sobredosis con el uso percutáneo del producto.

4.1.6 Fases de diagnóstico clínico, tratamiento y seguimiento

Desde la fase del despistaje hasta el tratamiento

La fase de despistaje o "screening" supone el periodo comprendido desde el diagnóstico hasta el tratamiento hasta los 6 meses e incluye la aleatorización. Tiene una duración mínima de 4 semanas y máxima de hasta 6 meses. Durante esta fase:

- El paciente recibirá el consentimiento informado, así como la explicación verbal del estudio.
- El paciente se quedará con una copia del consentimiento informado.
- El paciente tendrá la oportunidad de preguntar las dudas pertinentes.

Una vez aleatorizado recibirá un número.

Se deben cumplimentar los siguientes documentos:

1. Consentimiento informado firmado y fechado
2. Datos demográficos
3. Antecedentes clínicos
4. Datos clínicos de su CP
5. ECOG performance status
6. ASA
7. Estudio de extensión
8. Medicación habitual

Fase de tratamiento

El paciente acude al hospital el día de la intervención o la noche previa. Se confirmará que el paciente cumple los criterios de inclusión y que los datos precisados en el epígrafe anterior están debidamente cumplimentados en la base de datos. Se confirmará que la aleatorización está hecha y se conocerá el grupo.

En el grupo 1. Linfadenectomía selectiva de los ganglios fluorescentes. Tras la inducción de la anestesia se administra de manera percutánea, transperineal ecodirigida, 25 mg de ICG diluidos en 5 ml de agua destilada. Se aplicarán de 2 a 4 punciones por glándula y se inocularán de 3 a 5 ml de dilución. Por vía laparoscópica trans o intraperitoneal se accederá al retroperitoneo donde se disecarán y extirparán solo los ganglios fluorescentes. Dichos ganglios se representarán gráficamente en una plantilla diseñada con tal motivo.

En el grupo 2. Se hará una ePLND, al menos, hasta el cruce con los uréteres, siendo recomendable la disección de los ganglios presacros y de las arterias y venas iliacas comunes, hasta la bifurcación.

Fase de seguimiento

Postoperatorio inmediato

A los siete días se pormenorizará y registrará:

- El día de alta para el cálculo de la estancia.
- Se pormenorizarán todas las alteraciones del postoperatorio estrictamente normal y se categorizarán de acuerdo con la clasificación de Clavien Dindo [48]
- Día de retirada de sonda para el cálculo de la duración de la sonda uretral.

Seguimiento hasta el quinto año

En cada seguimiento se registrará la fecha del seguimiento y el PSA total. La periodicidad será trimestral el primer año. Semestral el segundo año y anual hasta el quinto año.

4.1.7 Criterios de evaluación

Evaluación de las complicaciones

La variable primaria es la toxicidad de cualquier grado en la escala de Clavien-Dindo [48] en los 3 meses que siguen a la prostatectomía radical. La toxicidad, independientemente

del grado, se registrará por el subinvestigador responsable del seguimiento de los pacientes durante el ingreso, y por uno de los investigadores principales. A los siete días de la intervención y a los 3 meses de la intervención.

Evaluación de los datos patológicos

De los datos de la biopsia de próstata se recogen: Número de cilindros disponibles para el análisis. Número de cilindros afectos por tumor. Gleason primario y Gleason secundario. Porcentaje de patrón 4 en los grados 3+4 y 4+3. Las variables de la pieza de prostatectomía se ajustan a los recomendados por el Colegio Americano de Patólogos [51].

Evaluación de los datos bioquímicos

El análisis del PSA se recoge con el kit MODULAR ANALYTICS E170, cobas e 601 y cobas e 602.

4.1.8 Análisis estadístico

Para el cálculo del tamaño muestral tomamos en consideración las siguientes cifras que proceden de datos propios no publicados. La probabilidad de complicaciones en el grupo de linfadenectomía limitadas en será del 10% (cualquier tipo de complicación). La probabilidad de complicaciones en las ePLND en el 35% (cualquier tipo de complicación o desviación del curso postoperatorio habitual). Asumiendo un error alfa del 0,05 y una potencia estadística del 80%, se calcula que necesitamos 100 casos para observar las diferencias antes expuestas.

Todos los pacientes aleatorizados se incluirán en el conjunto de datos a estudiar (análisis por intención de tratar). Todas las variables de interés se analizarán utilizando el conjunto de datos. Sin embargo, aquellos pacientes que son aleatorizados, pero que sufren una violación relevante del protocolo, que impactarían de manera significativa en los resultados del estudio podrán ser revisados por el Investigador Principal. Por ejemplo, paciente que es aleatorizado a ePLND pero que intraoperatoriamente se objetivan adherencias o no tolera la posición de trendelemburg, necesaria para la

cirugía, y se hace la prostatectomía sin linfadadenectomía. Dicho caso podrá ser excluido del estudio.

4.1.9 Ética

Este estudio se llevará a cabo bajo los principios rectores de la Declaración de Helsinki de la Asociación Médica Mundial. El estudio será conducido por personas científicamente y medicamente cualificadas. Los beneficios anticipados del estudio son proporcionales a los riesgos; Se respetarán los derechos y el bienestar de los pacientes. Cada paciente proporcionará un consentimiento informado por escrito antes de que se realicen pruebas o evaluaciones específicas del protocolo. Antes de iniciar el estudio, el investigador obtendrá la aprobación del CEIm y la autorización de la Agencia Española del Medicamento y Productos Sanitarios (AEMPS).

4.1.10 Información al paciente y consentimiento informado

Se obtendrá de cada paciente un consentimiento informado escrito, debidamente redactado, de conformidad con la Declaración de Helsinki, ICH, Buenas Prácticas Clínicas (GCP), para la protección de pacientes humanos (21 CFR 50.25 [a, b], CFR 50.27, y CFR Parte 56, Subparte A).

El investigador proporcionará copias del formulario de consentimiento informado firmado a cada paciente y mantendrá el documento original firmado dentro del registro clínico del paciente según los requisitos locales. El investigador también documentará completamente el proceso de consentimiento informado en los documentos fuente del paciente. Todos los informes y muestras de pacientes se identificarán solo con un número de identificación para mantener la confidencialidad del paciente.

4.1.11 Calidad de los datos

Gestión de los datos

La gestión de los datos clínicos será realizada por el investigador principal. El plan de gestión de datos incluirá procedimientos para procesar los datos de este estudio y describirá las responsabilidades de cada persona que tenga acceso a los mismos.

Cuidado de los registros

El investigador debe hacer que los datos originales del estudio (impresos o electrónicos) estén disponibles para eventuales requerimientos de los inspectores de las agencias reguladoras. Se debe mantener un archivo para cada paciente que incluya el formulario de consentimiento informado firmado y copias de toda la documentación de la fuente relacionada con ese paciente.

El investigador debe garantizar la confiabilidad y disponibilidad de los documentos de origen de los cuales se derivó la información en el formulario de informe del caso.

La información de identidad del paciente registrada se mantendrá durante al menos 15 años en el registro de confidencialidad del paciente o durante más tiempo si así lo exigen las normativas locales.

Medios y recursos materiales disponibles

El Instituto Valenciano de Oncología (IVO) es un centro monográfico de pacientes oncológicos. El servicio de urología cuenta con una *datamanager*, un estadístico y una coordinadora de ensayos clínicos. Además del personal estructural, el servicio dispone de *fellows* y residentes externos que han colaborado y colaboran en la investigación. El verde de indocianina es una sustancia económica y fácil de usar. Los reactivos para el análisis del PSA y del fluoróforo son práctica habitual. Como se comentado previamente, el departamento de urología cuenta con una amplia experiencia en su aplicación.

4.2 Metodología del artículo 2

4.2.1 Adquisición de Evidencia

Se realizó una revisión sistemática siguiendo el Grupo de Métodos de Pronóstico de Cochrane [52] y la presentación siguió la declaración de Elementos de Reporte Preferidos para Revisiones Sistemáticas y Metaanálisis (PRISMA) [53]. El protocolo está registrado en la base de datos PROSPERO (número de referencia CRD42021248645).

4.2.2 Fuentes de Información y Estrategia de Búsqueda

Se realizaron búsquedas en las bases de datos de Medline (utilizando la plataforma Ovid), EMBASE y Web of Science (26 de marzo de 2021). La estrategia de búsqueda se desarrolló inicialmente en Medline, incluyendo tanto vocabulario controlado como términos de palabras de texto relacionados con sarcopenia y neoplasias de próstata, y luego se adaptó para cada una de las otras bases de datos. Las búsquedas se restringieron a los idiomas inglés y español y no se pusieron límites de tiempo. Se examinaron las listas de referencias de todos los documentos relevantes para identificar posibles estudios adicionales que cumplieran con los criterios de selección.

4.2.3 Proceso de Selección de Estudios

Los estudios fueron elegibles para su inclusión si cumplían con los siguientes criterios:
(a) Tipo de estudio: Se incluyeron cualquier estudio observacional longitudinal (por ejemplo, estudios de cohortes, estudios de casos y controles, o estudios de enlace de bases de datos) y análisis secundarios de estudios experimentales (aleatorizados o no) que investigaran el significado pronóstico de la sarcopenia en pacientes con CP para predecir la mortalidad o la progresión de la enfermedad. Para que un estudio experimental fuera elegible, debía haber utilizado solo el grupo de control o toda la muestra del estudio ajustada para la intervención. Se excluyeron los estudios transversales, las series de casos o los estudios de casos y las revisiones sistemáticas o narrativas.
(b) Población: Se incluyeron estudios que evaluaron a hombres de sesenta años o más diagnosticados con CP avanzado. Se consideraron avanzados a los pacientes si tenían CP metastásico, sensible a hormonas o resistente a la castración (ganglionar, óseo y/o visceral) definido como cTxNxM1. Se incluyeron estudios que contemplaran otros pacientes aparte de los relevantes para la pregunta de revisión siempre que los resultados de los pacientes que cumplían con los criterios de inclusión se informaran por separado o representaran más del 80% de la población objetivo. Se excluyeron los estudios realizados con voluntarios sanos o animales.
(c) Factor pronóstico índice: la presencia de sarcopenia definida como la pérdida progresiva y generalizada de masa y función muscular esquelética evaluada por resonancia magnética (RM), tomografía computarizada (área o volumen muscular o

índice músculo esquelético), absorciometría con rayos X de doble energía, o análisis de impedanciometría bioeléctrica.

(d) Comparador: ausencia de sarcopenia.

(e) Medidas de resultado: los estudios debían informar sobre la supervivencia global, la supervivencia cáncer específica, la tasa de respuesta global al tratamiento del cáncer, la supervivencia libre de progresión, las complicaciones del cáncer o la calidad de vida relacionada con la salud.

(f) Temporalidad: la medición de la sarcopenia debía realizarse durante o después del diagnóstico. No se excluyó ningún estudio según la duración del seguimiento.

(g) Contexto: se incluyeron estudios realizados en atención primaria o secundaria.

(h) Idioma: solo se incluyeron estudios publicados en inglés o español.

4.2.4 Proceso de Selección de Estudios

El proceso de selección de estudios fue llevado a cabo por dos revisores de la siguiente manera: primero, los revisores examinaron de forma independiente y en duplicado los títulos y resúmenes de todas las citas recuperadas; en segundo lugar, los revisores, nuevamente de forma independiente y en duplicado, leyeron y evaluaron para su inclusión los artículos de texto completo que parecían cumplir con los criterios de selección predefinidos. Los revisores compararon y discutieron los resultados en ambas fases y consultaron a un tercer revisor en caso de duda y discrepancia.

4.2.5 Proceso de Recolección de Datos

Se preparó un formulario de extracción de datos (en formato Excel) por parte de los autores, se realizó una prueba piloto en tres estudios antes del inicio del proceso de extracción de datos y se ajustó en consecuencia. Dos revisores extrajeron de forma independiente y en duplicado los siguientes datos de los estudios incluidos: identificación del artículo (autor, año de publicación, país y financiación), diseño y metodología (objetivo, número de centros y duración del seguimiento), población y sus características demográficas (por ejemplo, tamaño de la muestra, edad, grado/etapa del cáncer y metástasis), sarcopenia (definición, método de medición, momento y punto de corte) y resultados del estudio (medias, recuentos de eventos, cociente de

riesgos—HR, o cociente de probabilidades—OR, con especial atención a la variabilidad en los resultados presentados (desviación estándar, varianza, valores de p, etc.)). Se extrajeron HR y OR de análisis univariante y multivariante. Posteriormente, un tercer revisor verificó los datos extraídos.

4.2.6 Evaluación del Riesgo de Sesgo

Nuevamente, dos revisores evaluaron de manera independiente y duplicada el potencial riesgo de sesgo en los estudios incluidos utilizando la herramienta *Quality in Prognosis Studies* (QUIPS) [54]. Cada uno de los seis dominios utilizados por QUIPS incluye múltiples ítems que se evalúan por separado. Basándose en las calificaciones de los ítems, se realizó un juicio conclusivo sobre el riesgo de sesgo dentro de cada dominio y se expresó en una escala de tres grados (bajo, moderado o alto riesgo de sesgo). En la revisión sistemática, el riesgo general de sesgo se consideró bajo si hasta un dominio se clasificaba como de riesgo moderado de sesgo. Si uno o más dominios del estudio se clasificaban como de alto riesgo o si tres o más se clasificaban como de riesgo moderado, entonces el estudio se clasificaba como de alto riesgo. Todos los estudios intermedios se clasificaron como riesgo moderado de sesgo [55]. El acuerdo interevaluador utilizando el kappa ponderado y el acuerdo porcentual fue evaluado. Las discrepancias en los juicios entre los revisores fueron discutidas y, en caso de no lograr un consenso, se consultó a un tercer revisor. Los archivos QUIPS están disponibles bajo solicitud de los autores.

4.2.7 Evaluación del Sesgo de Publicación

Según las recomendaciones de la Colaboración Cochrane [56], el sesgo de publicación se examinó mediante la construcción de un gráfico de embudo y el cálculo de la prueba de Egger, con un nivel de significancia establecido en 0.05, utilizando los comandos metafunnel y metabias en STATA versión 16 (StataCorp LLC, College Station, TX, EE. UU.).

4.2.8 Análisis y Síntesis de Resultados

Se realizó un metaanálisis para los resultados informados por dos o más estudios. El metaanálisis y el gráfico forestal para la tasa de sarcopenia se calcularon utilizando el comando metaprop en STATA versión 16. El hazard ratio y el intervalo de confianza del 95% correspondiente para la supervivencia global, la supervivencia específica por cáncer y la SLP se agruparon con una estimación de varianza indirecta en metaanálisis utilizando el programa estadístico Review Manager (RevMan, versión 5.4.1. Copenhague: Centro Nórdico Cochrane, La Colaboración Cochrane, 2020), y los resultados se mostraron en gráficos forestales. Se evaluó la heterogeneidad utilizando la estadística I2. Cuando había heterogeneidad (I2 ≥ 50% o P < 0.1), se realizaron metaanálisis utilizando un modelo de efectos aleatorios. Se realizó un análisis de sensibilidad omitiendo cada estudio individualmente para determinar la estabilidad de la estimación general del efecto. Se exploraron los efectos del estadio de la enfermedad (CP sensible o CPRC) y el tipo de tratamiento (TPA con/sin quimioterapia o quimioterapia) utilizando análisis de subgrupos. La naturaleza de los datos reportados para la edad, presencia de metástasis y etapa de sarcopenia no permitió agruparlos para el análisis. La meta-regresión tampoco fue posible debido al pequeño número de estudios evaluados.

4.2.9 Evaluación de la Certeza de la Evidencia

Se realizó una evaluación de la certeza de la evidencia por resultado basada en el enfoque de la Gradación de Recomendaciones, Evaluación, Desarrollo (GRADE). La certeza podría clasificarse para la baja considerando cinco dominios: riesgo de sesgo, inconsistencia, incertidumbre sobre que la evidencia sea directa, imprecisión y sesgo de publicación; o clasificada al alza considerando tres dominios: efecto grande, gradiente dosis-respuesta y confusión plausible. Se construyeron perfiles de evidencia y la certeza general de la evidencia se clasificó desde muy baja (poca confianza en la estimación; es probable que el verdadero pronóstico sea sustancialmente diferente de la estimación) hasta alta (muy seguro de que el verdadero pronóstico está cerca de la estimación).

5. RESULTADOS

5.1 Resultados del artículo 1

Se reclutaron un total de 108 pacientes en este ensayo clínico aleatorizado, con una mediana de seguimiento de 16 meses (10-24); 54 de ellos fueron incluidos en el grupo de ICG-PLND y 54 fueron incluidos en el grupo de ePLND. La mediana de edad fue de 65 años, la mediana del nivel de PSA preoperatorio fue de 8 ng/mL, y el 46% de los pacientes tenían CP de riesgo intermedio. Las características basales de la cohorte se presentan en la Tabla 1.

Table 1 Baseline characteristics.

Variable	Total	ePLND	ICG-PLND
Patients, *n*	108	54	54
Age, years, median (IQR)	65 (60–69)	65 (61–68)	65 (60–69)
PSA, ng/mL, median (IQR)	8 (6–12)	8 (5–11)	9 (6–12)
Gleason score, *n* (%)			
6	5 (4.6)	2 (3.7)	3 (5.6)
3 + 4	30 (28)	15 (28)	15 (28)
4 + 3	35 (32)	15 (28)	20 (37)
8	28 (26)	18 (33)	10 (19)
9–10	10 (9.3)	4 (7.4)	6 (11)
Clinical T stage, *n* (%)			
cT1	64 (60)	31 (57)	33 (61)
cT2	22 (20)	13 (24)	9 (17)
cT3	22 (20)	10 (19)	12 (22)
NCCN risk group, *n* (%)			
Intermediate	50 (46)	24 (44)	26 (48)
High	58 (54)	30 (56)	28 (52)

En total, 55 pacientes de la cohorte total (51%) presentaron al menos una complicación postoperatoria. En cuanto al objetivo principal, la tasa de complicaciones postoperatorias fue significativamente mayor en el grupo de ePLND (70%) en comparación con el grupo de ICG-PLND (32%) ($P < 0.001$). Cuatro pacientes (11%) del grupo de ePLND presentaron una complicación importante frente a dos pacientes (12%) del grupo de ICG-PLND. Esta diferencia no fue estadísticamente significativa ($P = 0.7$). Las complicaciones fuertemente relacionadas con la PLND fueron más frecuentes en el grupo de ePLND (riesgo relativo 4.00, IC del 95% 1.62–9.88; $P < 0.05$). Esta asociación fue estadísticamente significativa pero más débil en los grupos probable e

improbablemente relacionados con la PLND. Estos hallazgos se resumen en las Tablas 2 y 3.

Table 2 Complication rates according to Clavien–Dindo classification.

Variable	Total	ePLND	ICG-PLND	P
Clavien–Dindo, *n* (%)				
0	53 (49)	16 (30)	37 (69)	<0.001
I	33 (31)	22 (41)	11 (20)	
II	16 (15)	12 (22)	4 (7.4)	
IIIb	5 (4.6)	4 (7.4)	1 (1.9)	
IVa	1 (0.9)	0 (0)	1 (1.9)	
Clavien–Dindo Grade, *n* (%)				
0	53 (49)	16 (30)	37 (69)	<0.001
>0	55 (51)	38 (70)	17 (31)	
Clavien–Dindo Grade, *n* (%)				
I–II	49 (89)	34 (89)	15 (88)	1
III–IV	6 (1.9)	4 (10)	2 (12)	
Complications for patient, *n*, mean (SD)	0.76 (0.91)	1.2 (1)	0.35 (0.55)	<0.001

Table 3 Type and severity of complications.

	Clavien–Dindo Grade I		Clavien–Dindo Grade II		Clavien–Dindo Grade IIIa		Clavien–Dindo Grade IIIb		Clavien–Dindo Grade IVa		Total
	ePLND	ICG-PLND	ePLND	ICG-PLND	ePLND	ICG-PLND	ePLND	ICG-PLND	ePLND	ICG-PLND	
Strongly PLND related (RR 4.00, 95% CI 1.62–9.88) *P* < 0.05											
Lymphoedema	19	4	–	–	–	–	–	–	–	–	23
Lymphocele	1	1	–	–	–	–	–	–	–	–	2
Likely PLND related (RR 2.57, 95% CI 1.17–5.65) *P* = 0.021											
Sensory disturbances	7	3	2	–	–	–	–	–	–	–	12
Bleeding	5	–	–	–	–	–	2	1	–	–	8
Motor dysfunction	2	2	1	–	–	–	–	–	–	–	5
Ureteric injury	–	–	–	–	–	–	1	–	–	–	1
Pulmonary embolism	–	–	–	–	–	–	–	–	–	1	1
Unlikely PLND related (RR 2.22, 95% CI 1.11–4.43) *P* = 0.017											
UTI	–	–	3	2	–	–	–	–	–	–	5
Haematuria	3	1	1	–	–	–	–	–	–	–	5
Urinary leak	1	–	1	2	–	–	–	–	–	–	4
Fever	2	–	1	–	–	–	–	–	–	–	3
Pain	1	1	1	–	–	–	–	–	–	–	3
Diarrhoea	1	–	1	–	–	–	–	–	–	–	2
Evisceration	–	–	–	–	–	–	1	–	–	–	1
Renal function impairment	1	–	–	–	–	–	–	–	–	–	1
Seroma	–	1	–	–	–	–	–	–	–	–	1
Ileus	–	–	–	1	–	–	–	–	–	–	1
Pneumonia	–	–	–	1	–	–	–	–	–	–	1
Haemorrhoids	–	–	1	–	–	–	–	–	–	–	1
Allergic reaction	1	–	–	–	–	–	–	–	–	–	1
Total	**57**		**18**		**0**		**5**		**1**		**81**

Las complicaciones más frecuentes fueron linfedema (29%), trastornos sensoriales (15%) y sangrado (10%). El linfedema fue la única complicación significativamente mayor en el grupo de ePLND (RR 4.75, IC del 95% 1.73–13.04; P < 0.05). Los trastornos sensoriales y el sangrado no alcanzaron significación (RR 3.00, IC del 95% 0.86–10.48, P = 0.1; y RR 7.00, IC del 95% 0.89–54.98, P = 0.06, respectivamente).

Un paciente en el grupo de ePLND tuvo una lesión en la vena ilíaca que se consideró la única complicación intraoperatoria en la cohorte general. El tiempo operatorio fue más largo en el grupo de ePLND, con una mediana (RIC) de 270 minutos (243–300) frente a 240 minutos (210–252) en el grupo de ICG-PLND, lo cual fue estadísticamente significativo (P < 0.001). No hubo diferencias en la mediana (RIC) de la estancia hospitalaria, que fue de 3 (3–4) días en ambos grupos (P = 0.9). Dos pacientes en el grupo de ICG-PLND tuvieron un drenaje colocado después de la cirugía frente a uno en el grupo de ePLND. Ningún paciente llevó el drenaje por más de 14 días.

La mediana (RIC) del número de ganglios linfáticos disecados fue de 7 (4–9) en el grupo de ICG-PLND y de 24 (18–27) en el grupo de ePLND (P < 0.001). La tasa de detección de pN1 fue mayor en el grupo de ICG-PLND (28%; n = 15) que en el grupo de ePLND (22%; n = 12), aunque esta diferencia no fue estadísticamente significativa (P = 0.7). Como se muestra en la Tabla 4, el análisis de las muestras de próstata arrojó hallazgos comparables entre ambos grupos.

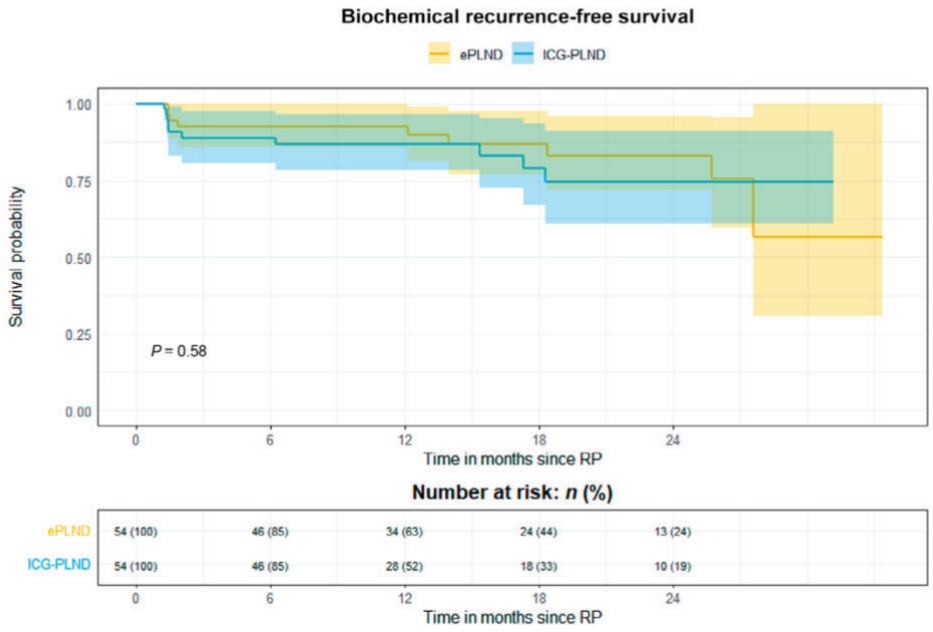
Table 4 Histopathological findings.

Variable	Total	ePLND	ICG-PLND	*P*
Dissected nodes, median (IQR)	14 (7–23)	23 (18–27)	7 (4–9)	<0.001
Positive LNs, *n* (%)				
0	81 (75)	42 (78)	39 (72)	0.733
1	17 (16)	6 (11)	11 (20)	
2	4 (3.7)	2 (3.7)	2 (3.7)	
3	2 (1.9)	1 (1.9)	1 (1.9)	
4	2 (1.9)	1 (1.9)	1 (1.9)	
5	1 (0.9)	1 (1.9)	0 (0)	
17	1 (0.9)	1 (1.9)	0 (0)	
pN1, *n* (%)	27 (25)	12 (22)	15 (28)	0.657
Gleason score, *n* (%)				
6	2 (1.9)	1 (1.9)	1 (1.9)	0.28
3 + 4	35 (32)	15 (28)	20 (37)	
4 + 3	38 (35)	24 (44)	14 (26)	
8	11 (10)	6 (11)	5 (9.3)	
9–10	22 (20)	8 (15)	14 (26)	
R1 status, *n* (%)	34 (32)	17 (31)	17 (31)	1
Locally advanced disease, *n* (%)	75 (70)	39 (72)	36 (67)	0.676

A los 3, 12 y 24 meses, el 98% (IC del 95% 88%–99%), el 83% (IC del 95% 68%–91%) y el 64% (IC del 95% 45%–78%) de los pacientes, respectivamente, presentaron PSA indetectable en el grupo de ICG-PLND. Del mismo modo, en el grupo de ePLND, las tasas de PSA indetectable fueron del 94% (IC del 95% 84%–98%), el 76% (IC del 95% 62%–86%), y el 56% (IC del 95% 38%–71%), respectivamente. No se observaron diferencias estadísticamente significativas entre los grupos (P = 0.5).

La tasa de pacientes con TPA a los 24 meses fue del 8% (IC del 95% 3%–20%) en el grupo de ICG-PLND y del 4% (IC del 95% 1%–4%) en el grupo de ePLND (P = 0.2). En total, el 87% (IC del 95% 78%–96%) y el 75% (IC del 95% 61%–91%) de los pacientes en el grupo de ICG-PLND experimentaron recurrencia bioquímica, frente al 93% (IC del 95% 86–99%) y al 83% (IC del 95% 71–96%) de los pacientes en el grupo de ePLND a los 12 y 24 meses después de la cirugía, respectivamente. Como se señala en la Figura 3, no se observaron diferencias estadísticamente significativas en términos de supervivencia libre de BCR entre los grupos. En el momento del análisis, dos pacientes se perdieron durante el seguimiento, y se registró una muerte debido a otras causas que no fueron el CP.

Fig. 3 Biochemical recurrence-free survival.



5.2 Resultados del artículo 2

5.2.1 Síntesis de la Evidencia

Los resultados de la búsqueda bibliográfica y el proceso de selección de estudios se muestran en la Figura 1. De un total de 861 referencias identificadas inicialmente después de eliminar duplicados, se seleccionaron 164 artículos potencialmente relevantes para una evaluación del texto completo. Finalmente, nueve estudios fueron elegibles para su inclusión según los criterios de selección preestablecidos [57-65], y

ocho de ellos fueron seleccionados para síntesis cuantitativa [57–61, 63-65]. Todos los estudios seleccionados se publicaron en inglés entre 2015 y 2021.

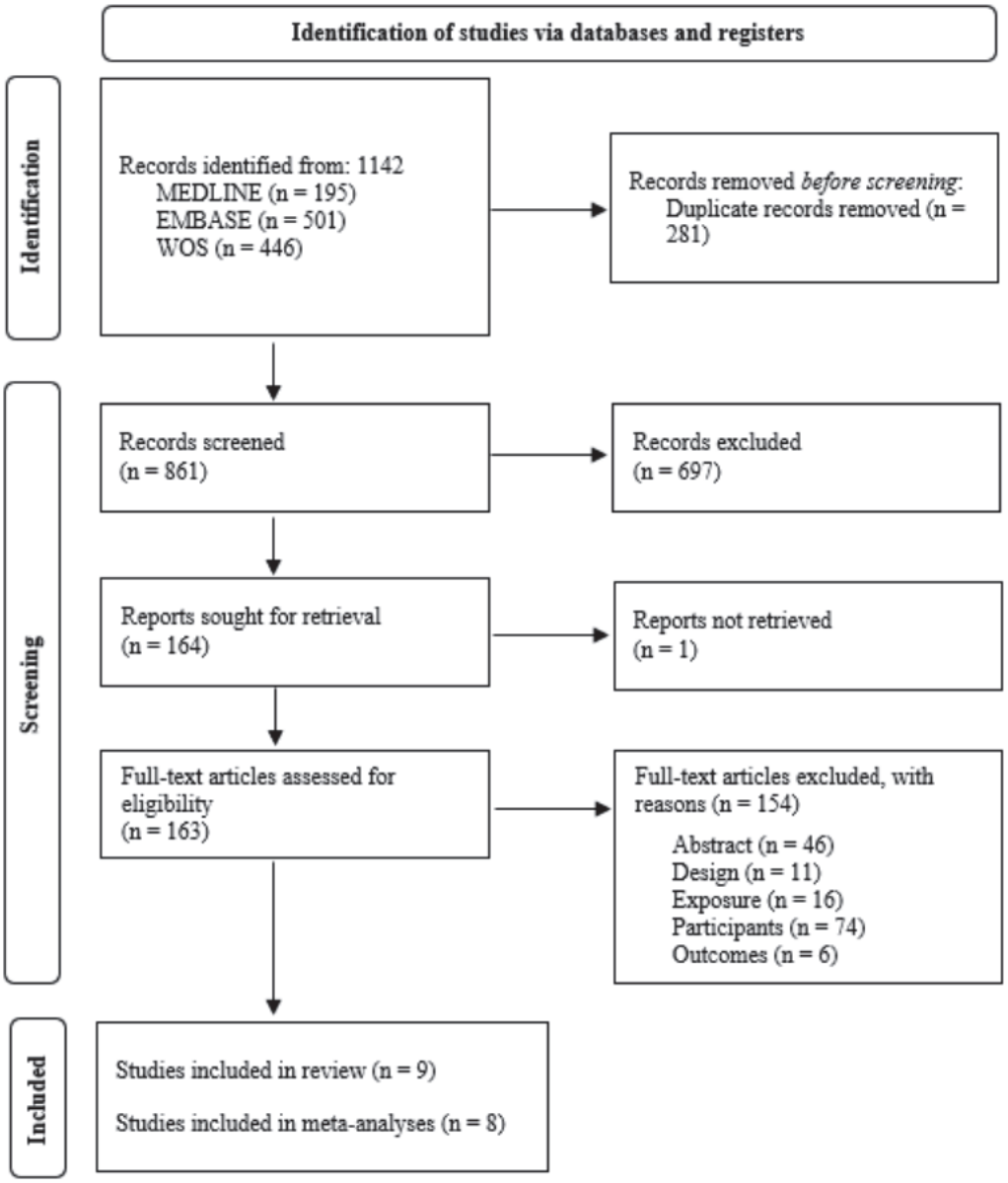


Figure 1. PRISMA flow chart detailing the screening process.

5.2.2 Descripción de los Estudios Incluidos

Las características principales de los estudios seleccionados se resumen en la Tabla 1. Siete estudios fueron revisiones retrospectivas de historias clínicas [57, 60-65], y dos fueron cohortes retrospectivas [58,59]. Los estudios se llevaron a cabo en Corea del Sur [59-61], Japón [59,63], el Reino Unido [58], Finlandia [57], España [62], Austria [65], y Australia [64]. La cantidad total de participantes reclutados en los nueve estudios fue

de 1659 hombres. El estudio más grande incluyó a 411 hombres [61], mientras que el estudio más pequeño tenía solo 59 hombres [62].

Table 1. Characteristics of included studies.

First Author, Year (Country)	Design	N	Patient					Sarcopenia			Outcomes	Follow-Up Time (Months)
			Age [a]	Inclusion Criteria	Exclusion Criteria	Metastases (N)	Cancer Treatment (%)	Definition	Prevalence (%)	Diagnosis Method		
Antoun, 2015 [18] (France)	RRR	127	69 (63–74) *	Metastatic CRPCa	NR	Visceral: 15	1. Enzalutamide + prednisolone: 62 2. Abiraterone + prednisolone: 24	SMI < 43 cm^2/m^2 (BMI < 25 kg/m^2) SMI < 53 cm^2/m^2 (BMI > 25 kg/m^2)	66.14	At L3 by CT scan	OS	16 (95% CI: 12–19)
											PFS	Sarcopenia: 4 (95% CI: 3–6) Non-sarcopenia: 5 (95% CI: 3–6)
Fischer, 2020 [19] (UK)	RCS	90	69 (NR) *	Starting treatment (enzalutamide or abiraterone) for metastatic CRPCa	No imaging data	Bone: 15 Bone and lymph node: 17 Lymph node: 10 Visceral: 1	Previous ADT: 100% 1. Enzalutamide + prednisolone: 69% 2. Abiraterone + prednisolone: 31%	SMI < 52.4 cm^2/m^2	NR	At L3 by CT scan	OS	NR
Ikeda, 2020 [20] (Japan)	RCS	197	73 (66.0–78.0) *	1. Metastatic hormone-sensitive PCa 2. No previous treatments	Missing clinical or imaging data at diagnosis	Bone: 127 Distant lymph node: 29 Other locations: 9	Previous ADT:100% 1. Docetaxel: 39.6% 2. Cabazitaxel: 6.7% 3. Enzalutamide: 30.6% 4. Abiraterone: 34.3% 5. Other treatment: 17.1%	SMI < 33 cm^2/m^2 (BMI < 25 kg/m^2) SMI < 53 cm^2/m^2 (BMI >25 kg/m^2)	82.74	At L3 by CT scan	OS	Sarcopenia: 72 (IQR: 50–84) Non-sarcopenia: NR (IQR: 52-NR)
											CSS	Sarcopenia: 77 (IQR: 62-NR) Non-sarcopenia: NR (IQR: 75-NR)
Lee, 2018 [21] (Republic of Korea)	RRR	282	67.0 (61.0–72.0) *	CRPCa progression	1. Incomplete clinical data 2. Loss to follow-up 3. Unknown cause of death	Bone: 155 Lymph node: 118 Visceral: 10	Previous ADT: 100% 1. Docetaxel + prednisolone: NR 2. Enzalutamide + prednisolone: NR 3. Abiraterone + prednisolone: NR	SMI < 52.4	NR	At L3 by CT scan)	CSS	15
											PFS	3.7
Lee, 2020 [22] (Republic of Korea)	RRR	411	70 (65–76) *	CRPCa progression	1. Insufficient imaging data 2. Lost to follow-up 3. Unknown cause of death	Bone: 344 Lymph node: 199 Visceral:70	Previous ADT:100% 1. Docetaxel + prednisolone: NR 2. Cabazitaxel + prednisolone: NR 3. Enzalutamide + prednisolone: NR 4. Abiraterone + prednisolone: NR	SMI < 45.2 cm^2/m^2 SMA < 32.4 HU	50.36	At L3 by CT scan	OS	Sarcopenia: 19 Non-sarcopenia: 24
Muñoz-Rodríguez, 2021 [23] (Spain)	RRR	59	72.74 (12.25)	Metastatic onset PCa + first-line ADT	No imaging data	Bone: 52 Retroperitoneal lymphadenopathy: 30 Visceral: 6	1. ADT: 100%	European Working Group on Sarcopenia in Older People criteria [5]	NR	CT scan	OS	32.3 (95% CI: 17.1–47.16)

Table 1. *Cont.*

First Author, Year (Country)	Design	N	Patient					Sarcopenia			Outcomes	Follow-Up Time (Months)
			Age [a]	Inclusion Criteria	Exclusion Criteria	Metastases (N)	Cancer Treatment (%)	Definition	Prevalence (%)	Diagnosis Method		
Ohtaka, 2019 [24] (Japan)	RRR	77	70 (65–76) *	CRPCa + docetaxel chemotherapy	NR	Bone: 55 Lymph node: 34 Visceral: 12	1. Previous ADT + docetaxel+ prednisolone: 100%	Psoas muscle index < 5.7 cm^2/m^2	33.77	At L3-psoas muscle by CT scan	OS	16.41 (IQR: 10.85–25.97)
Pak, 2020 [25] (Republic of Korea)	RRR	230	68.3 (9.1)	CRPCa + first-line therapy	1. Insufficient imaging data before starting first-line treatment 2. Patients treated for <2 months 3. Patients followed-up for <6 months	Bone: 196 Lymph node: 122 Solid organ: 28	Previous ADT: 100% 1. Docetaxel + prednisolone: 7.0% 2. Cabazitaxel + prednisolone: 24.3% 3. Enzalutamide + prednisolone: 10.0% 4. Abiraterone + prednisolone: 13.0% 5. Other treatment + prednisolone: 2.1%	SMI < 50 cm^2/m^2	51.30	At L3 by CT scan	OS	Sarcopenia: 16.9 Non-sarcopenia: 24.1
											PFS	Sarcopenia: 9.1 Non-sarcopenia: 14.9
Stangl-Kremser, 2019 [26] (Austria)	RRR	186	68.8 (64.6–75.0) *	CRPCa + chemo hormonal therapy	1. Insufficient imaging data 2. Lost to follow-up	Bone: 146 Distant lymph node: 65 Liver: 16 Visceral (No liver): 19	1. Docetaxel + prednisolone: 100	SMI < 55 cm^2/m^2 (men)	82.80	At L3 by CT scan	OS	26.2 (IQR 13.7–42.4)
											PFS	7.8 (IQR: 4.4–16.3)

[a] Mean (SD) or median (IQR); * as reported. ADT: androgen deprivation therapy; BMI: body mass index; CRPCa: Castration-resistant prostate cancer; CSS: Cancer-specific survival; CT: Computerized Tomography; DSF: Progression-free survival; HU: Hounsfield Units; CI: confidence interval; IQR: interquartile range; NR: not reported; OS: Overall survival; PCa: Prostate cancer; RCS: Retrospective cohort study; RRR: Retrospective record review; SD: standard deviation; SMA: Skeletal Muscle Attenuation; SMI: Skeletal muscle index; UK: United Kingdom.

La edad promedio de los pacientes fue de 69.77 años (desviación estándar: 1.85), con un rango de 61 a 78 años. Cinco estudios se centraron en pacientes con CPRC [60,61,63–65], dos en pacientes con CPRC metastásico [57,58], y dos en pacientes con CP metastásico [59,62].

La prevalencia general de la sarcopenia fue del 61% (IC del 95%: 46–76%; I2 = 97.07%, P > 0.01) (Figura S1 del material suplementario). Sin embargo, tres de los estudios incluidos no informaron el número de participantes con sarcopenia, y los datos de estos estudios no pudieron incluirse en el análisis [58,60,62].

El método más comúnmente utilizado para la detección de la sarcopenia fue la medición del Índice de Masa Muscular Esquelética (SMI) mediante una tomografía computarizada en L3 [57–61,64,65]. Sin embargo, un estudio utilizó el índice del músculo psoas en L3 [63], y otro estudio [62] utilizó los criterios del Grupo de Trabajo Europeo sobre Sarcopenia en Personas Mayores [41]. Los criterios utilizados para definir la sarcopenia se detallan en la Tabla 1.

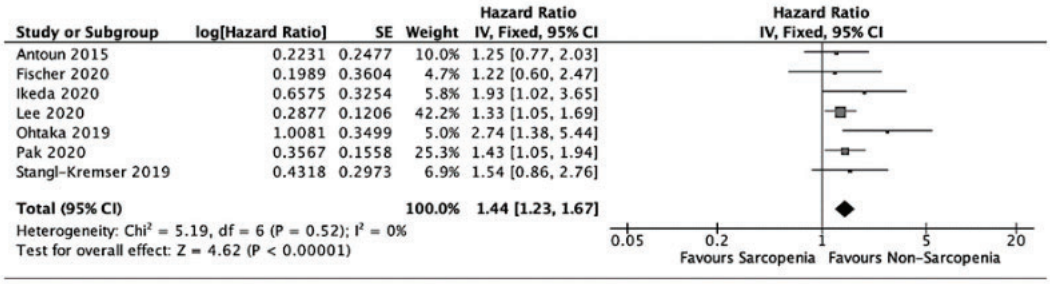
En cuanto al momento de la medición de la sarcopenia, cuatro estudios realizaron la medición en el momento del diagnóstico del CP [62,65], o del CPRC [60,61]. Tres estudios realizaron la medición antes de iniciar los tratamientos [58,59,64] y un estudio la llevó a cabo en la evaluación del tumor [57]. Un estudio no informó sobre el momento de la medición de la sarcopenia [63].

En cuanto a los resultados clínicos, siete estudios consideraron la supervivencia global como variable objetivo [57–59, 61–65], dos consideraron la sce [59,60], y cuatro consideraron la supervivencia libre de progresión [57,60, 64,65]. No se informaron datos sobre tasas de respuesta global, complicaciones del cáncer o calidad de vida relacionada con la salud. La duración media del seguimiento fue de veintinueve semanas [57,59-62,65].

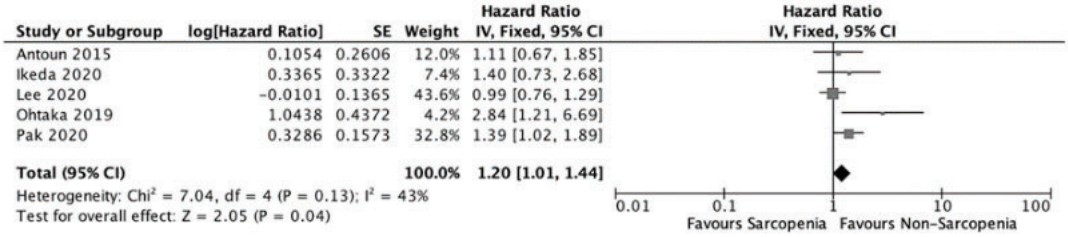
5.2.3 Supervivencia global

El metaanálisis de los datos univariantes [57–59,61,63–65] y multivariantes [58,59,61,63,64] sobre la influencia de la sarcopenia en la SG se muestra en la Figura 2. Los resultados agrupados [58,59,61,63,64] sobre la influencia de la sarcopenia en la SG se muestran en la Figura 2. Los resultados agrupados de los datos univariantes mostraron que los pacientes con CP con sarcopenia tenían un riesgo significativamente mayor de mortalidad por todas las causas (efectos fijos, HR = 1.44, IC del 95%: 1.23, 1.67, P < 0.01, I2 = 0%; k = 7; n = 1081) en comparación con los participantes sin sarcopenia. En el metaanálisis de datos multivariantes (efectos fijos), hubo una asociación escasamente significativa entre la sarcopenia y la SG (efectos fijos, HR = 1.20, IC del 95%: 1.01, 1.44, P = 0.04, I2 = 43%; k = 5; n = 831). El análisis de subgrupos

y sensibilidad no mostró cambios estadísticamente significativos en la estimación general del resultado.



(A) Univariate Analysis.



(B) Multivariate Analysis.

Figure 2. Forest plots for overall survival [10–20,22,24–26].

5.2.4 Supervivencia cáncer específica

Solo dos estudios [59,60] informaron sobre la SCE. En el metaanálisis de los datos univariantes, no hubo una asociación significativa entre la sarcopenia y la SCE (efectos aleatorios, HR = 1.98, IC del 95%: 0.80, 4.90, P = 0.14; I2 = 74%; k = 2; n = 479) (Figura 3). Sin embargo, el único estudio que informó un modelo multivariable [59] encontró que la sarcopenia estaba significativamente asociada con una SCE más corta (HR = 2.18, IC del 95%: 1.07, 7.32, P = 0.04; n = 197). El análisis de subgrupos de datos univariantes indicó una asociación estadísticamente significativa en pacientes con CP hormonosensible (HR = 3.48, IC del 95%: 1.43, 8.47, P = 0.05; n = 197).

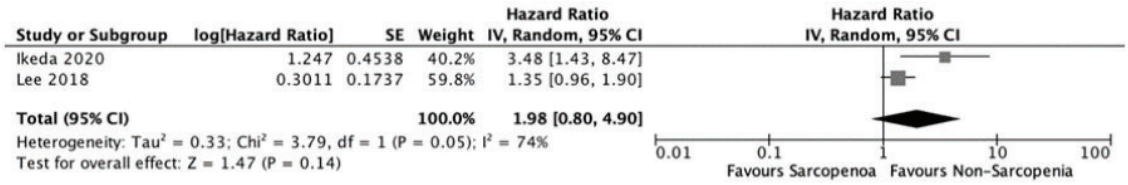
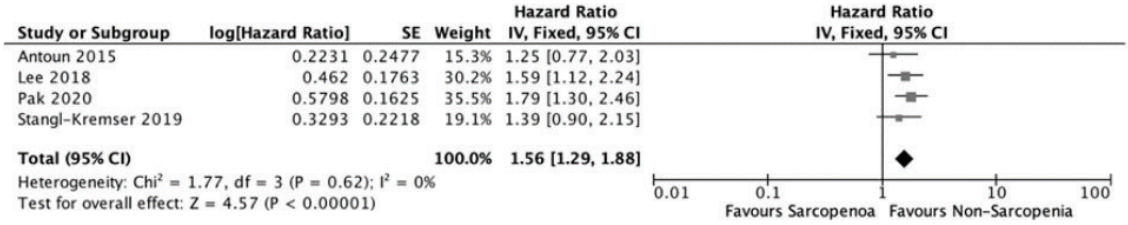


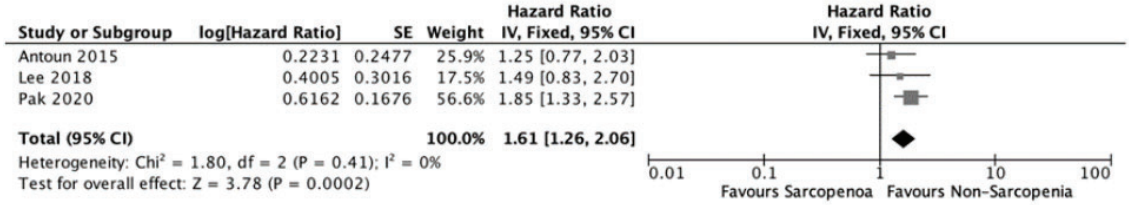
Figure 3. Forest plot for cancer-specific survival—Univariate Analysis [20,21].

5.2.5 Supervivencia libre de progresión

Cuatro estudios proporcionaron datos sobre la SLP [57,60,64,65]. El análisis combinado demostró una asociación entre la sarcopenia y una SLP más corta, y esta asociación existió tanto en el análisis univariante (HR = 1.56, IC del 95%: 1.29, 1.88, P < 0.01; I2 = 0%; k = 4; n = 818) como en el análisis multivariable (HR = 1.61, IC del 95%: 1.26, 2.06, P < 0.01; k = 3; n = 588) (Figura 4). El análisis de subgrupos de datos univariantes sugirió que no había un efecto significativo del tratamiento en la asociación entre la sarcopenia y la SLP.



(A) Univariate Analysis.



(B) Multivariate Analysis.

Figure 4. Forest plots for progression-free survival [18,21,25,26].

6. DISCUSIÓN

6.1 Discusión del artículo 1

Presentamos el primer ensayo clínico aleatorizado que evalúa la seguridad y eficacia de una PLND personalizada guiada por ICG en contraste con la ePLND convencional. Nuestra experiencia inicial muestra resultados prometedores en cuanto a su menor toxicidad con resultados oncológicos similares a corto plazo.

Las complicaciones mayores relacionadas con la PLND son raras, y la mortalidad es casi anecdótica [66]. Sin embargo, considerando todas las complicaciones, hasta el 14% de los pacientes pueden experimentar al menos una después de la cirugía [67]. El hecho de que consideráramos cualquier desviación del curso postoperatorio regular

establecido como una complicación podría explicar la alta prevalencia (51%) de pacientes que experimentaron una o más complicaciones en este estudio.

Una revisión sistemática realizada por Fossati et al. [68] que evaluó la seguridad y los beneficios oncológicos de la PLND resaltó la escasez de evidencia de alta calidad publicada (solo tres ECA de 66 estudios). Uno de ellos, Lestingi et al. [69], no encontró diferencia en la tasa de complicaciones postoperatorias, y los otros dos coincidieron en que los linfoceles eran más probables de ocurrir en la ePLND que en la lPLND, con pequeñas diferencias entre los grupos (2% y 9%) [70,71]. Se encontró, en un ECA, que el linfedema fue otra complicación estadísticamente diferente entre los grupos. Sin embargo, esta diferencia fue solo del 1%, por lo que puede que no sea clínicamente relevante [66]. En nuestro estudio, el linfedema fue la única complicación que fue significativamente mayor en el grupo de ePLND. La formación de linfoceles parece estar relacionada con la extensión de la PLND (RR 0.52, IC del 95% 0.37–0.74; P < 0.001) [25]; sin embargo, no encontramos diferencias entre los grupos con una tasa excepcionalmente baja de desarrollo.

Otro enfoque interesante es el análisis de complicaciones según la probabilidad de estar relacionadas con la PLND. De esta manera, Cacciamani et al. [67] revelaron una marcada diferencia en las complicaciones fuertemente relacionadas con la PLND, favoreciendo a la lPLND (RR 0.46; IC del 95% 0.34–0.61; P = 0.01), mientras que no se encontraron diferencias en los grupos probable y poco probablemente relacionados con la PLND. Encontramos diferencias estadísticamente significativas en los tres grupos a favor del grupo de ICG-PLND. El RR de cada grupo fue mayor, al igual que la probabilidad de relación con la linfadenectomía.

Respecto a los resultados anatomopatológicos, se encontró enfermedad pN1 en el 28% de los pacientes en el grupo de ICG-PLND, en contraste con el 22% detectado en el grupo de ePLND. Este hallazgo es notable si consideramos que hubo una diferencia de 17 ganglios linfáticos disecados entre los dos grupos (siete vs. 24). Aunque esta investigación no fue diseñada para probar la no inferioridad oncológica de la ICG-PLND, estos resultados son prometedores. Dos ECA han mostrado resultados oncológicos comparables entre ePLND y lPLND. Touijer et al. [32], con una gran cohorte de

pacientes, describieron tasas similares de RCP entre ePLND y lPLND. La principal crítica de ese estudio fue que hubo poca diferencia en el recuento de ganglios linfáticos entre ambos grupos. Por otro lado, Lestingi et al. [72] reportaron una mayor diferencia en el número de ganglios linfáticos removidos entre ambos grupos, tres vs. 17. Sin embargo, tampoco encontraron diferencias en la RCP con un seguimiento de 53.9 meses. La gran proporción de pacientes con un perfil de cáncer favorable (un tercio de los pacientes con Gleason preoperatorio 6) podría haber subestimado el beneficio oncológico de ePLND, y puede ser necesaria una observación más prolongada para evaluar los resultados oncológicos.

Interesantemente, si analizamos el número de ganglios disecados y el porcentaje enfermedad pN1 en estos ensayos clínicos dilucidamos un comportamiento similar. En el estudio de Touijer et al. [32], encontraron un 14% de enfermedad pN1 en el grupo de ePLND con una mediana de 14 ganglios linfáticos resecados. En el grupo de lPLND, encontraron un 12% de enfermedad pN1 con una disección mediana de 12 ganglios linfáticos. El mismo hallazgo se detectó en el ensayo de Lestingi et al. [72], donde disecaron 17 ganglios y encontraron un 17% de pacientes pN1 en el grupo de ePLND. En lPLND, la mediana de número de ganglios disecados fue de tres, y la tasa de pN1 fue precisamente del 3.4%.

En el presente estudio, detectamos enfermedad pN1 en el 28% de los pacientes en el grupo de ICG-PLND, con una extracción mediana de solo siete ganglios linfáticos. Este hallazgo sugiere la viabilidad oncológica de una disección guiada por ICG al aumentar la probabilidad de remover los ganglios linfáticos con mayor riesgo de afectación. Nuestra experiencia previa con ICG mostró un valor predictivo negativo del 97% [73]. Solo cinco de 219 pacientes (2%) fueron estadificados incorrectamente. Decidimos realizar el presente ensayo clínico para evaluar las tasas de complicaciones y para evaluar la relevancia clínica de la ausencia de ganglios linfáticos positivos en pacientes adecuadamente estadificados, ya que esta pregunta aún no está clara.

La sensibilidad se presenta como el principal objetivo de la linfadenectomía del CP, y en el contexto de la linfadenectomía guiada por ICG, se informa una alta variabilidad del 50% al 100% en la literatura [74-77]. Se han propuesto varias razones para estos

resultados discordantes. En primer lugar, la sensibilidad se ha calculado tanto en función del número de ganglios linfáticos removidos como en la estadificación de los pacientes. La naturaleza del presente ensayo clínico dificulta el análisis de la sensibilidad o el valor predictivo negativo. En segundo lugar, se han descrito diferentes técnicas, sistemas de visión y dosificación. Manny et al. [74] realizaron una inyección percutánea robotizada de 0.4 mL de una solución de ICG al 2.5 mg/mL. Describen una sensibilidad del 100% en este estudio piloto con 50 pacientes. Hruby et al. [75] realizaron el mismo enfoque que nosotros, pero con una concentración más baja de la solución (0.25 mg de ICG disueltos en 2.5 mL de agua). La mayor sensibilidad se obtuvo en el grupo de ICG, seguido por el super-ePLND y el ePLND, 97.7%, 87.8% y 80.5%, respectivamente. Por último, también se han validado combinaciones de ICG con coloides radiactivos, como el 99mTc [76,78]. El grupo de Van der Poel [76] describe tres modificaciones de su técnica respecto a la concentración de partículas y el sistema de imágenes, con una sensibilidad incrementada en cada modificación. Aunque la mejor sensibilidad, 93.5%, se logró con el sistema de imagen 1 HUB HD con el sistema D-Light P de KARL STORZ GmbH & Co.KG, los resultados deben tomarse con precaución debido a la pequeña cohorte de pacientes. Este grupo ha publicado recientemente un ensayo clínico de fase II donde describen un mejor rendimiento con la inyección intratumoral del marcador en lugar de la inyección prostática sistemática [78], abriendo una nueva y prometedora línea de investigación.

Recientemente, la linfadenectomía guiada por PSMA también está siendo explorada como una alternativa para sustituir la ePLND en el contexto del CP primario; sin embargo, la evidencia científica aún es escasa [79]. Hasta que nuevas técnicas de imagen surjan para determinar adecuadamente el estado de los ganglios linfáticos de los pacientes con CP, enfoques menos invasivos, como la linfadenectomía guiada por ICG, deben seguir siendo investigados.

El verde de indocianina es una sustancia segura y económica que es accesible para la mayoría de los centros. Se puede inyectar fácilmente dentro de la próstata con la ayuda de un ultrasonido convencional. La linfadenectomía guiada por ICG personalizada ha demostrado ser menos agresiva (en términos de tasas de complicaciones), menos

consumidora de tiempo y ha identificado una tasa similar de pacientes pN1 en comparación con la ePLND. El seguimiento corto y el tamaño de la muestra son las principales limitaciones del estudio, especialmente al informar los resultados oncológicos. Se hace necesaria la validación externa de estos resultados.

6.2 Discusión del artículo 2

Los hallazgos reportados aquí respaldan la sarcopenia como un factor pronóstico importante de la supervivencia libre de progresión en pacientes con CP avanzado. Además, se encontró una asociación menos clara entre la sarcopenia y la supervivencia cáncer específica y la supervivencia global.

Dado que la SLP es un marcador subrogado de la SCE y SG, el hecho de que los resultados de esta revisión solo hayan sido concluyentes para esta variable y no para la SCE y la SG puede estar relacionado con la corta duración del seguimiento en los estudios incluidos (promedio: 29 semanas). Es probable que un seguimiento más prolongado pueda demostrar una asociación más clara entre la sarcopenia y las variables de supervivencia/mortalidad.

Como sucede con los resultados obtenidos para otros tipos de cáncer [43-46], dos metaanálisis recientes identificaron la sarcopenia como un factor pronóstico pobre para la progresión de la enfermedad en el CP [80,81]; sin embargo, ninguno se ha centrado en la sarcopenia como un factor pronóstico para el CP avanzado. Además, el efecto de la sarcopenia sobre la SG fue evaluado en ambos estudios, pero no en la SCE y la SLP. Finalmente, nuestros análisis de subgrupos y la evaluación de la certeza de la evidencia no se llevaron a cabo en estos estudios previos.

La prevalencia de sarcopenia en pacientes con CP estimada por el SMI en los estudios incluidos varió ampliamente, desde el 50.36% [61] al 82.80% [65]. Esto puede deberse al uso de diferentes puntos de corte para el diagnóstico de sarcopenia (45.2–55 cm2/m2), incluyendo el uso de un punto de corte específico para la obesidad. Dado que el punto de corte utilizado para definir la sarcopenia influye directamente en el resultado de las asociaciones entre el SMI y el pronóstico en pacientes con cáncer, es necesario llegar a un consenso sobre esto.

La prevalencia de sarcopenia en pacientes con CP es notablemente alta (61%) en comparación con pacientes afectados por otros tipos de cáncer (38.6%) [82]. Esta mayor prevalencia puede explicarse por dos factores: primero, la avanzada edad media de la muestra (69.77 años), y, en segundo lugar, porque un porcentaje significativo de los pacientes estaban bajo TPA.

El principal resultado obtenido en la presente revisión es la asociación entre sarcopenia y la supervivencia libre de progresión, que podría explicarse por la peor respuesta al tratamiento que experimentan los pacientes con sarcopenia [82].

Es más fácil explicar la relación obtenida entre sarcopenia y la supervivencia global (asociación débil pero estadísticamente significativa en el análisis multivariado). Esta asociación se ha mostrado en otros tumores sólidos [83-86]. La sarcopenia supone una disminución de las reservas funcionales. Las malas reservas funcionales están asociadas con el fenotipo de fragilidad. La estrecha relación entre sarcopenia y el síndrome funcional de fragilidad es probablemente la principal razón detrás de los hallazgos relacionados con la SG.

Además, en pacientes que requieren cirugía, se deben priorizar los procedimientos quirúrgicos que minimicen el riesgo de empeoramiento de la sarcopenia. En este sentido, es ampliamente conocido que la cirugía ambulatoria o la cirugía mínimamente invasiva [87]. Implican menos días de hospitalización en comparación con la cirugía convencional, pueden ayudar a reducir el riesgo de desnutrición y, consecuentemente, el empeoramiento de la sarcopenia que conlleva la hospitalización [88].

Cuando se requiere TPA, la TPA intermitente puede ser una alternativa para reducir el impacto del hipogonadismo en el músculo. Desde el punto de vista oncológico, esta estrategia ha demostrado no inferioridad con respecto a la TPA continua [89,90]. De hecho, las guías de urología europea respaldan la intermitencia como una opción de tratamiento de TPA en un perfil seleccionado de pacientes [91]. De la misma manera que la intermitencia puede atenuar el impacto en la masa ósea [92], podría quizás atenuar su efecto en la masa muscular.

Las actuales guías europeas de urología solo mencionan la sarcopenia como una consecuencia del tratamiento androgénico. Sin embargo, como la sarcopenia podría ser un factor pronóstico desfavorable que puede empeorar con el tratamiento del CP, debe ser sistemáticamente evaluada y, si se detecta, los pacientes deben recibir un tratamiento dirigido [42,91]. Por otro lado, el diagnóstico de sarcopenia debe ir acompañado de otras medidas para reducir el impacto del hipogonadismo en el músculo. Así, estudios preliminares han mostrado que los programas de ejercicio físico pueden mejorar la sarcopenia en pacientes con CP [93], incluso en ausencia de testosterona [94]. También se han obtenido mejoras en la sarcopenia en pacientes con CP suplementados con altas dosis de vitamina D [94,95]. Además, se están llevando a cabo diferentes estudios para evaluar el efecto de la suplementación de proteínas y creatinina, pero los resultados aún no se han publicado [97,98].

La principal limitación de la presente revisión es que la evidencia proviene exclusivamente de estudios retrospectivos, un diseño caracterizado por un control deficiente sobre el factor de exposición, covariables y potenciales factores de confusión y sesgo. Además de los periodos de seguimiento cortos en los estudios incluidos en nuestra revisión, otra limitación importante es, debido a la falta de consenso sobre la definición de sarcopenia, la diversidad de puntos de corte utilizados por los estudios considerados para evaluar la sarcopenia. Además, no se pudieron realizar análisis de subgrupos y de meta-regresión para explorar el efecto de variables importantes como la edad, presencia de metástasis y etapa de sarcopenia en la magnitud de la asociación. Finalmente, otra posible limitación de esta revisión es la posibilidad de que algunos estudios no hayan sido incluidos, porque no están escritos en inglés o español o porque no están indexados en las bases de datos consultadas. A pesar de todas estas limitaciones, el presente estudio se beneficia de métodos rigurosos siguiendo los principios fundamentales de transparencia y replicabilidad, una búsqueda integral, una selección por pares, extracción de datos y evaluación del riesgo de sesgo, una síntesis cuantitativa de resultados con la exploración de importantes fuentes potenciales de heterogeneidad y una evaluación de la certeza de la evidencia sobre la base de un enfoque estructurado y explícito.

Para el diagnóstico de sarcopenia, los siguientes puntos de corte son arbitrarios en este momento. El desarrollo de puntos de corte validados depende de datos normativos y su valor predictivo para puntos finales sólidos, lo cual supone una prioridad alta para estudios de investigación. Además de nuevos estudios con un seguimiento a más largo plazo sobre los efectos de la sarcopenia en la progresión avanzada del CP, las futuras líneas de investigación deben estar relacionadas con el análisis del impacto de diferentes medidas destinadas a eliminar o atenuar la sarcopenia y su efecto en la evolución del CP avanzado, como la nutrición [99], el ejercicio físico [100] o si la intermitencia es una opción de tratamiento con TPA en pacientes con CP avanzado. Otros aspectos en los que la evaluación del papel de la sarcopenia podría ser relevante están relacionados con la decisión de comenzar o no el tratamiento, o si combinarlo o no, así como la decisión sobre el tipo de tratamiento que mejor se adapta a un estado muscular. En este sentido, varios estudios, algunos de los cuales están incluidos en el metaanálisis aquí, respaldan la idea de que los pacientes con sarcopenia sufren una mayor toxicidad y tienen peor tolerancia a la quimioterapia [101,102]. La propuesta de estos estudios es utilizar la sarcopenia como un factor para decidir tratar a los pacientes con una nueva generación de antiandrógenos en lugar de con quimioterapia. Se sabe que los nuevos antiandrógenos también conducen a una reducción en la masa corporal magra [103,104], pero no se ha establecido si esto está relacionado o no con una menor supervivencia o tiempo libre de enfermedad [64].

En conclusión, la evidencia disponible respalda la visión de que la sarcopenia es un factor pronóstico importante de la SLP en pacientes con carcinoma de próstata avanzado. Sin embargo, la sarcopenia tiene una asociación débil con una SG más corta. Finalmente, la evidencia disponible sobre el papel de la sarcopenia en la SCE es insuficiente y, como tal, impide sacar conclusiones definitivas y, además, respalda la necesidad de mayores esfuerzos de investigación.

7. CONCLUSIONES

La linfadenectomía pélvica extendida en pacientes con cáncer de próstata de riesgo intermedio o alto está siendo replanteada como el mejor método de estadificación. En este ensayo clínico, sugerimos que la linfadenectomía guiada por verde de indocianina

puede ser una alternativa a la linfadenectomía extendida. Asocia una menor morbilidad con resultados oncológicos comparables a corto plazo.

La sarcopenia es un factor pronóstico importante de supervivencia libre de progresión en pacientes con cáncer de próstata avanzado. La sarcopenia tiene una relación débil con una supervivencia global más corta. No hay suficiente evidencia sobre la relación entre la sarcopenia y la supervivencia cáncer específica.

8. BIBLIOGRAFÍA

1. Estimaciones de la incidencia del cáncer en España, 2023. Red Española de Registros de Cáncer (REDECAN), 2023. https://redecan.org/storage/documents/02d62122-9adb-4d35-b6d0-551435dbe4ae.pdf
2. Estadística de defunciones según causa de muerte. INE – España Eurostat. Diciembre 2023. www.ine.es.infografia/fallecidos_cancer
3. Siegel RL, Miller KD, Jemal A: Cancer statistics, 2018. CA Cancer J Clin 2018, 68(1):7-30.
4. Francini E, Gray KP, Xie W, et al. Time of metastatic disease presentation and volume of disease are prognostic for metastatic hormone sensitive prostate cancer (mHSPC). Prostate. 2018;78(12):889-895. doi:10.1002/pros.23645
5. J.M Cózar, B. Miñana, F. Gómez-Veiga et al. Registro nacional de cáncer de próstata 2010 en España. Act Urol Esp 2013; 37(1): 12-19
6. Wallis CJD, Saskin R, Choo R, et al. Surgery Versus Radiotherapy for Clinically-localized Prostate Cancer: A Systematic Review and Meta-analysis. Eur Urol. 2016;70(1):21-30. doi:10.1016/j.eururo.2015.11.010
7. Bergengren O, Pekala KR, Matsoukas K, et al. 2022 Update on Prostate Cancer Epidemiology and Risk Factors-A Systematic Review. Eur Urol. 2023;84(2):191-206. doi:10.1016/j.eururo.2023.04.021
8. Glass, T.R., et al. Metastatic carcinoma of the prostate: identifying prognostic groups using recursive partitioning. J Urol, 2003. 169: 164.
9. Gravis, G., et al. Prognostic Factors for Survival in Noncastrate Metastatic Prostate Cancer: Validation of the Glass Model and Development of a Novel Simplified Prognostic Model. Eur Urol, 2015. 68: 196.

10. Gravis, G., et al. Androgen Deprivation Therapy (ADT) Plus Docetaxel Versus ADT Alone in Metastatic Non castrate Prostate Cancer: Impact of Metastatic Burden and Long-term Survival Analysis of the Randomized Phase 3 GETUG-AFU15 Trial. Eur Urol, 2016. 70: 256.
11. Sweeney, C.J., et al. Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer. N Engl J Med, 2015. 373: 737.
12. Reese AC, Wessel SR, Fisher SG, Mydlo JH: Evidence of prostate cancer "reverse stage migration" toward more advanced disease at diagnosis: Data from the Pennsylvania Cancer Registry. Urologic oncology 2016.
13. Van Hemelrijck M, Folkvaljon Y, Adolfsson J, Akre O, Holmberg L, Garmo H, Stattin P: Causes of death in men with localized prostate cancer: a nationwide, population-based study. BJU international 2016, 117(3):507-514.
14. Abdollah F, Sood A, Sammon JD, Hsu L, Beyer B, Moschini M, Gandaglia G, Rogers CG, Haese A, Montorsi F et al: Long-term cancer control outcomes in patients with clinically high-risk prostate cancer treated with robot-assisted radical prostatectomy: results from a multi-institutional study of 1100 patients. European urology 2015, 68(3):497-505.
15. Gandaglia G, De Lorenzis E, Novara G, Fossati N, De Groote R, Dovey Z, Suardi N, Montorsi F, Briganti A, Rocco B et al: Robot-assisted Radical Prostatectomy and Extended Pelvic Lymph Node Dissection in Patients with Locally-advanced Prostate Cancer. European urology 2016.
16. Ramirez-Backhaus M, Mira Moreno A, Gomez Ferrer A, Calatrava Fons A, Casanova J, Solsona Narbon E, Ortiz Rodriguez IM, Rubio Briones J: Indocyanine Green guided pelvic lymph node dissection. An efficient technique to classify the lymph node status of patients with prostate cancer who underwent radical prostatectomy. The Journal of urology 2016.
17. Yuh B, Artibani W, Heidenreich A, Kimm S, Menon M, Novara G, Tewari A, Touijer K, Wilson T, Zorn KC et al: The role of robot-assisted radical prostatectomy and pelvic lymph node dissection in the management of high-risk prostate cancer: a systematic review. European urology 2014, 65(5):918-927.
18. EAU Guidelines. Edn. presented at the EAU Annual Congress Milan 2023. ISBN 978-94-92671-19-6.

19. Heesakkers RA, Hovels AM, Jager GJ, van den Bosch HC, Witjes JA, Raat HP, Severens JL, Adang EM, van der Kaa CH, Futterer JJ et al: MRI with a lymph-node-specific contrast agent as an alternative to CT scan and lymph-node dissection in patients with prostate cancer: a prospective multicohort study. The Lancet Oncology 2008, 9(9):850-856.
20. Hovels AM, Heesakkers RA, Adang EM, Jager GJ, Strum S, Hoogeveen YL, Severens JL, Barentsz JO: The diagnostic accuracy of CT and MRI in the staging of pelvic lymph nodes in patients with prostate cancer: a meta-analysis. Clin Radiol 2008, 63(4):387-395.
21. Maurer T, Eiber M, Schwaiger M, Gschwend JE: Current use of PSMA-PET in prostate cancer management. Nature reviews Urology 2016, 13(4):226-235.
22. Corfield J, Perera M, Bolton D, Lawrentschuk N: (68)Ga-prostate specific membrane antigen (PSMA) positron emission tomography (PET) for primary staging of high-risk prostate cancer: a systematic review. World journal of urology 2018, 36(4):519-527.
23. Gandaglia G, Ploussard G, Valerio M, Mattei A, Fiori C, Fossati N, Stabile A, Beauval JB, Malavaud B, Roumiguie M et al: A Novel Nomogram to Identify Candidates for Extended Pelvic Lymph Node Dissection Among Patients with Clinically Localized Prostate Cancer Diagnosed with Magnetic Resonance Imaging-targeted and Systematic Biopsies. European urology 2019, 75(3):506-514.
24. Briganti A, Larcher A, Abdollah F, Capitanio U, Gallina A, Suardi N, Bianchi M, Sun M, Freschi M, Salonia A et al: Updated nomogram predicting lymph node invasion in patients with prostate cancer undergoing extended pelvic lymph node dissection: the essential importance of percentage of positive cores. European urology 2012, 61(3):480- 487.
25. Briganti A, Chun FK, Salonia A, Zanni G, Scattoni V, Valiquette L, Rigatti P, Montorsi F, Karakiewicz PI: Validation of a nomogram predicting the probability of lymph node invasion among patients undergoing radical prostatectomy and an extended pelvic lymphadenectomy. European urology 2006, 49(6):1019-1026; discussion 1026-1017.
26. Cagiannos I, Karakiewicz P, Eastham JA, Ohori M, Rabbani F, Gerigk C, Reuter V, Graefen M, Hammerer PG, Erbersdobler A et al: A preoperative nomogram

identifying decreased risk of positive pelvic lymph nodes in patients with prostate cancer. The Journal of urology 2003, 170(5):1798-1803.

27. Touijer KA, Mazzola CR, Sjoberg DD, Scardino PT, Eastham JA: Long-term outcomes of patients with lymph node metastasis treated with radical prostatectomy without adjuvant androgen-deprivation therapy. European urology 2014, 65(1):20-25.
28. Briganti A, Karnes JR, Da Pozzo LF, Cozzarini C, Gallina A, Suardi N, Bianchi M, Freschi M, Doglioni C, Fazio F et al: Two positive nodes represent a significant cut-off value for cancer specific survival in patients with node positive prostate cancer. A new proposal based on a two-institution experience on 703 consecutive N+ patients treated with radical prostatectomy, extended pelvic lymph node dissection and adjuvant therapy. European urology 2009, 55(2):261-270.
29. Messing EM, Manola J, Yao J, Kiernan M, Crawford D, Wilding G, di'SantAgnese PA, Trump D, Eastern Cooperative Oncology Group study EST: Immediate versus deferred androgen deprivation treatment in patients with node-positive prostate cancer after radical prostatectomy and pelvic lymphadenectomy. The Lancet Oncology 2006, 7(6):472-479.
30. Joniau S, Van den Bergh L, Lerut E, Deroose CM, Haustermans K, Oyen R, Budiharto T, Ameye F, Bogaerts K, Van Poppel H: Mapping of pelvic lymph node metastases in prostate cancer. European urology 2013, 63(3):450-458.
31. Mattei A, Fuechsel FG, Bhatta Dhar N, Warncke SH, Thalmann GN, Krause T, Studer UE: The template of the primary lymphatic landing sites of the prostate should be revisited: results of a multimodality mapping study. European urology 2008, 53(1):118-125.
32. Touijer KA, Sjoberg DD, Benfante N, et al. Limited versus Extended Pelvic Lymph Node Dissection for Prostate Cancer: A Randomized Clinical Trial. Eur Urol Oncol. 2021;4(4):532-539. doi:10.1016/j.euo.2021.03.006
33. Wawroschek F, Vogt H, Weckermann D, Wagner T, Hamm M, Harzmann R: Radioisotope guided pelvic lymph node dissection for prostate cancer. The Journal of urology 2001, 166(5):1715-1719.
34. Algaba F, Montironi R: Impact of prostate cancer multifocality on its biology and treatment. Journal of endourology 2010, 24(5):799-804.

35. Winter A, Kneib T, Henke RP, Wawroschek F: Sentinel lymph node dissection in more than 1200 prostate cancer cases: rate and prediction of lymph node involvement depending on preoperative tumor characteristics. International journal of urology : official journal of the Japanese Urological Association 2014, 21(1):58-63.
36. Vermeeren L, Valdes Olmos RA, Meinhardt W, Bex A, van der Poel HG, Vogel WV, Sivro F, Hoefnagel CA, Horenblas S: Intraoperative radioguidance with a portable gamma camera: a novel technique for laparoscopic sentinel node localisation in urological malignancies. European journal of nuclear medicine and molecular imaging 2009, 36(7):1029-1036.
37. Motomura K, Inaji H, Komoike Y, Kasugai T, Noguchi S, Koyama H: Sentinel node biopsy guided by indocyanine green dye in breast cancer patients. Japanese journal of clinical oncology 1999, 29(12):604-607.
38. van Leeuwen AC, Buckle T, Bendle G, Vermeeren L, Valdes Olmos R, van de Poel HG, van Leeuwen FW: Tracer-cocktail injections for combined pre- and intraoperative multimodal imaging of lymph nodes in a spontaneous mouse prostate tumor model. Journal of biomedical optics 2011, 16(1):016004.
39. Ramirez-Backhaus M, Mira Moreno A, Gomez Ferrer A, Calatrava Fons A, Casanova J, Solsona Narbon E, Ortiz Rodriguez IM, Rubio Briones J: Indocyanine Green Guided Pelvic Lymph Node Dissection: An Efficient Technique to Classify the Lymph Node Status of Patients with Prostate Cancer Who Underwent Radical Prostatectomy. The Journal of urology 2016, 196(5):1429-1435.
40. Wilson, D.; Jackson, T.; Sapey, E.; Lord, J.M. Frailty and sarcopenia: The potential role of an aged immune system. Ageing Res. Rev. 2017, 36, 1–10.
41. Cruz-Jentoft, A.J.; Bahat, G.; Bauer, J.; Boirie, Y.; Bruyère, O.; Cederholm, T.; Cooper, C.; Landi, F.; Rolland, Y.; Sayer, A.A.; et al. Sarcopenia: Revised European consensus on definition and diagnosis. Age Ageing 2019, 48, 16–31.
42. Smith, M.R.; Saad, F.; Egerdie, B.; Sieber, P.R.; Tammela, T.L.; Ke, C.; Leder, B.Z.; Goessl, C. Sarcopenia During Androgen- Deprivation Therapy for Prostate Cancer. J. Clin. Oncol. 2012, 30, 3271–3276
43. Ubachs, J.; Ziemons, J.; Minis-Rutten, I.J.G.; Kruitwagen, R.F.P.M.; Kleijnen, J.; Lambrechts, S.; Olde Damink, S.W.M.; Rensen, S.S.; Van Gorp, T. Sarcopenia and

ovarian cancer survival: A systematic review and meta-analysis. J. Cachexia Sarcopenia Muscle 2019,

44. Zhang, X.-M.; Dou, Q.-L.; Zeng, Y.; Yang, Y.; Cheng, A.S.K.; Zhang, W.-W. Sarcopenia as a predictor of mortality in women with breast cancer: A meta-analysis and systematic review. BMC Cancer 2020, 20, 1–11.
45. Yang, M.; Shen, Y.; Tan, L.; Li, W. Prognostic Value of Sarcopenia in Lung Cancer. Chest 2019, 156, 101–111
46. Sun, G.; Li, Y.; Peng, Y.; Lu, D.; Zhang, F.; Cui, X.; Zhang, Q.; Li, Z. Can sarcopenia be a predictor of prognosis for patients with non-metastatic colorectal cancer? A systematic review and meta-analysis. Int. J. Color. Dis. 2018, 33, 1419–1427.
47. Pinart, M.; German Prostate Cancer Consortium (DPKK); Kunath, F.; Lieb, V.; Tsaur, I.; Wullich, B.; Schmidt, S. Prognostic models for predicting overall survival in metastatic castration-resistant prostate cancer: A systematic review. World J. Urol. 2020, 38, 613–635.
48. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, de Santibanes E, Pekolj J, Slankamenac K, Bassi C et al: The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg 2009, 250(2):187-196.
49. Olsen TW, Lim JI, Capone A, Jr., Myles RA, Gilman JP: Anaphylactic shock following indocyanine green angiography. Archives of ophthalmology 1996, 114(1):97.
50. Hope-Ross M, Yannuzzi LA, Gragoudas ES, Guyer DR, Slakter JS, Sorenson JA, Krupsky S, Orlock DA, Puliafito CA: Adverse reactions due to indocyanine green. Ophthalmology 1994, 101(3):529-533.
51. Kench JG, Delahunt B, Griffiths DF, Humphrey PA, McGowan T, Trpkov K, Varma M, Wheeler TM, Srigley JR: Dataset for reporting of prostate carcinoma in radical prostatectomy specimens: recommendations from the International Collaboration on Cancer Reporting. Histopathology 2013, 62(2):203-218.
52. Moons, K.G.; Hooft, L.; Williams, K.; Hayden, J.A.; Damen, J.A.; Riley, R.D. Implementing systematic reviews of prognosis studies in Cochrane. Cochrane Database Syst. Rev. 2018, 10, ED000129
53. Page, M.J.; McKenzie, J.E.; Bossuyt, P.M.; Boutron, I.; Hoffmann, T.C.; Mulrow, C.D.; Shamseer, L.; Tetzlaff, J.M.; Akl, E.A.; Brennan, S.E.; et al. The PRISMA 2020

Statement: An Updated Guideline for Reporting Systematic Reviews. BMJ 2021, 372, n71.

54. Hayden, J.A.; Van Der Windt, D.A.; Cartwright, J.L.; Côté, P.; Bombardier, C. Assessing Bias in Studies of Prognostic Factors. Ann. Intern. Med. 2013, 158, 280–286.
55. Grooten, W.J.A.; Tseli, E.; Äng, B.O.; Boersma, K.; Stålnacke, B.-M.; Gerdle, B.; Enthoven, P. Elaborating on the assessment of the risk of bias in prognostic studies in pain rehabilitation using QUIPS—Aspects of interrater agreement. Diagn. Progn. Res. 2019, 3, 1–11
56. Higgins, J.P.T.; Thomas, J.; Chandler, J.; Cumpston, M.; Li, T.; Page, M.J.; Welch, V.A. (Eds.) Cochrane Handbook for Systematic Reviews of Interventions, version 6.3 (updated February 2022); Cochrane: London, UK, 2022.
57. Antoun, S.; Bayar, A.; Ileana, E.; Laplanche, A.; Fizazi, K.; di Palma, M.; Escudier, B.; Albiges, L.; Massard, C.; Loriot, Y. High subcutaneous adipose tissue predicts the prognosis in metastatic castration-resistant prostate cancer patients in post chemotherapy setting. Eur. J. Cancer 2015, 51, 2570–2577
58. Fischer, S.; Clements, S.; McWilliam, A.; Green, A.; Descamps, T.; Oing, C.; Gillessen, S. Influence of abiraterone and enzalutamide on body composition in patients with metastatic castration resistant prostate cancer. Cancer Treat. Res. Commun. 2020, 25, 100256.
59. Ikeda, T.; Ishihara, H.; Iizuka, J.; Hashimoto, Y.; Yoshida, K.; Kakuta, Y.; Takagi, T.; Okumi, M.; Ishida, H.; Kondo, T.; et al. Prognostic impact of sarcopenia in patients with metastatic hormone-sensitive prostate cancer. Jpn. J. Clin. Oncol. 2020, 50, 933–939.
60. Lee, J.; Lee, H.S.; Ha, J.S.; Han, K.S.; Rha, K.H.; Hong, S.J.; Chung, B.H.; Koo, K.C. Subcutaneous Fat Distribution is a Prognostic Biomarker for Men with Castration Resistant Prostate Cancer. J. Urol. 2018, 200, 114–120.
61. Lee, J.; Park, J.S.; Heo, J.E.; Ahn, H.K.; Jang, W.S.; Ham, W.S.; Rha, K.H.; Choi, Y.D. Muscle Characteristics Obtained Using Computed Tomography as Prognosticators in Patients with Castration-Resistant Prostate Cancer. Cancers 2020, 12, 1864.
62. Muñoz-Rodríguez, J.; Domínguez, A.; Rosado, M.A.; Centeno, C.; Parejo, V.; Costa-Trachsel, I.; Gallardo, E.; Bonfill, T.; García-Rojo, D.; De Verdonces, L.; et al. Efecto de

la densidad muscular en pacientes con cáncer de próstata metastásico tratados con terapia de privación androgénica. Endocrinol. Diabet. Nutr. 2021, 68, 92–98.

63. Ohtaka, A.; Aoki, H.; Nagata, M.; Kanayama, M.; Shimizu, F.; Ide, H.; Tsujimura, A.; Horie, S. Sarcopenia is a poor prognostic factor of castration-resistant prostate cancer treated with docetaxel therapy. Prostate Int. 2019, 7, 9–14
64. Pak, S.; Kim, M.S.; Park, E.Y.; Kim, S.H.; Lee, K.H.; Joung, J.Y. Association of Body Composition With Survival and Treatment Efficacy in Castration-Resistant Prostate Cancer. Front. Oncol. 2020, 10, 558.
65. Stangl-Kremser, J.; Suarez-Ibarrola, R.; Andrea, D.D.; Korn, S.M.; Pones, M.; Kramer, G.; Marhold, M.; Krainer, M.; Enikeev, D.; Glybochko, P.; et al. Assessment of body composition in the advanced stage of castration-resistant prostate cancer: Special focus on sarcopenia. Prostate Cancer Prostatic Dis. 2020, 23, 309–315.
66. Musch M, Klevecka V, Roggenbuck U, Kroepfl D. Complications of pelvic lymphadenectomy in 1,380 patients undergoing radical retropubic prostatectomy between 1993 and 2006. J Urol 2008; 179: 923–9
67. Cacciamani GE, Maas M, Nassiri N et al. Impact of pelvic lymph node dissection and its extent on perioperative morbidity in patients undergoing radical prostatectomy for prostate cancer: a comprehensive systematic review and meta-analysis. Eur Urol Oncol 2021; 4: 134–49
68. Fossati N, Willemse PM, Van den Broeck T, et al. The Benefits and Harms of Different Extents of Lymph Node Dissection During Radical Prostatectomy for Prostate Cancer: A Systematic Review. Eur Urol. 2017;72(1):84-109. doi:10.1016/j.eururo.2016.12.003.
69. Lestingi J, Pontes JJ, Borges LL et al. Extended vs limited pelvic lymphadenectomy during radical prostatectomy for intermediate- and high-risk prostate cancer: a prospective randomized trial. J Urol 2015; 193 (Suppl): e983–4
70. Schwerfeld-Bohr J, Kaemper M, Krege S, Heidenreich A. Prospective randomized multicenter study comparing limited vs extended pelvic lymphadenectomy in intermediate and high risk prostate cancer- comparison of complications (SEAL, AUO AP 55/09). Eur Urol Suppl 2014; 13: e270

71. Clark T, Parekh DJ, Cookson MS et al. Randomized prospective evaluation of extended versus limited lymph node dissection in patients with clinically localized prostate cancer. J Urol 2003; 169: 145–8
72. Lestingi JFP, Guglielmetti GB, Trinh QD et al. Extended versus limited pelvic lymph node dissection during radical prostatectomy for intermediate- and high-risk prostate cancer: early oncological outcomes from a randomized phase 3 trial. Eur Urol 2021; 79: 595–604.
73. Claps F, de Pablos-Rodrıguez P, Gomez-Ferrer Aet al. Free-indocyanine green-guided pelvic lymph node dissection during radical prostatectomy. Urol Oncol 2022; 40: 489.e19–489.e26
74. Manny TB, Patel M, Hemal AK. Fluorescence-enhanced robotic radical prostatectomy using real-time lymphangiography and tissue marking with percutaneous injection of unconjugated indocyanine green: the initial clinical experience in 50 patients. Eur Urol 2014; 65: 1162–8
75. Hruby S, Englberger C, Lusuardi L et al. Fluorescence guided targeted pelvic lymph node dissection for intermediate and high risk prostate cancer. J Urol 2015; 194: 357–63
76. KleinJan GH, van den Berg NS, Brouwer OR et al. Optimisation of fluorescence guidance during robot-assisted laparoscopic sentinel node biopsy for prostate cancer. Eur Urol 2014; 66: 991–8
77. Nguyen DP, Huber PM, Metzger TA, Genitsch V, Schudel HH, Thalmann GN. A specific mapping study using fluorescence sentinel lymph node detection in patients with intermediate- and high-risk prostate cancer undergoing extended pelvic lymph node dissection. Eur Urol 2016; 70: 734–7
78. Wit EMK, van Beurden F, Kleinjan GH et al. The impact of drainage pathways on the detection of nodal metastases in prostate cancer: a phase II randomized comparison of intratumoral vs intraprostatic tracer injection for sentinel node detection. Eur J Nucl Med Mol Imaging 2022; 49: 1743–53
79. Gandaglia G, Mazzone E, Stabile A et al. Prostate-specific membrane antigen radioguided surgery to detect nodal metastases in primary prostate cancer patients undergoing robot-assisted radical prostatectomy and extended pelvic lymph node

dissection: results of a planned interim analysis of a prospective phase 2 study. Eur Urol 2022; 82: 411–8

80. Meyer, H.-J.; Wienke, A.; Surov, A. CT-defined low-skeletal muscle mass as a prognostic marker for survival in prostate cancer: A systematic review and meta-analysis. Urol. Oncol. Semin. Orig. Investig. 2022, 40, 103.e9–103.e16.
81. Jahrreiss, V.; Laukhtina, E.; D'Andrea, D.; Shariat, S.F. The prognostic value of sarcopenia in patients with prostate cancer: A systematic review. Curr. Opin. Urol. 2021, 31, 315–323.
82. Pamoukdjian, F.; Bouillet, T.; Lévy, V.; Soussan, M.; Zelek, L.; Paillaud, E. Prevalence and predictive value of pre-therapeutic sarcopenia in cancer patients: A systematic review. Clin. Nutr. 2018, 37, 1101–1113.
83. Del Fabbro, E.; Parsons, H.; Warneke, C.L.; Pulivarthi, K.; Litton, J.K.; Dev, R.; Palla, S.L.; Brewster, A.; Bruera, E. The Relationship Between Body Composition and Response to Neoadjuvant Chemotherapy in Women with Operable Breast Cancer. Oncologist 2012, 17, 1240–1245.
84. Martin, L.; Birdsell, L.; MacDonald, N.; Reiman, T.; Clandinin, M.T.; McCargar, L.J.; Murphy, R.; Ghosh, S.; Sawyer, M.B.; Baracos, V.E. Cancer Cachexia in the Age of Obesity: Skeletal Muscle Depletion Is a Powerful Prognostic Factor, Independent of Body Mass Index. J. Clin. Oncol. 2013, 31, 1539–1547
85. Shachar, S.S.; Williams, G.R.; Muss, H.B.; Nishijima, T.F. Prognostic value of sarcopenia in adults with solid tumours: A meta-analysis and systematic review. Eur. J. Cancer 2016, 57, 58–67.
86. Antoun, S.; Borget, I.; Lanoy, E. Impact of sarcopenia on the prognosis and treatment toxicities in patients diagnosed with cancer. Curr. Opin. Support. Palliat. Care 2013, 7, 383–389.
87. de Pablos-Rodríguez P, Suárez Novo JF, Castells Esteve M, et al. Preliminary results of the implementation of robotic radical prostatectomy in a major ambulatory surgery regimen. *Actas Urol Esp (Engl Ed)*. 2023;47(5):288-295. doi:10.1016/j.acuroe.2022.09.006
88. Kondrup, J. Incidence of nutritional risk and causes of inadequate nutritional care in hospitals. Clin. Nutr. 2002, 21, 461–468.

89. da Silva, F.C.; da Silva, F.M.C.; Gonçalves, F.; Santos, A.; Kliment, J.; Whelan, P.; Oliver, T.; Antoniou, N.; Pastidis, S.; Queimadelos, A.M.; et al. Locally Advanced and Metastatic Prostate Cancer Treated with Intermittent Androgen Monotherapy or Maximal Androgen Blockade: Results from a Randomised Phase 3 Study by the South European Uroncological Group. Eur. Urol. 2014, 66, 232–239.
90. Niraula, S.; Le, L.W.; Tannock, I.F. Treatment of Prostate Cancer with Intermittent Versus Continuous Androgen Deprivation: A Systematic Review of Randomized Trials. J. Clin. Oncol. 2013, 31, 2029–2036
91. Mottet, N.; Cornford, P.; van den Bergh, R.C.N.; Briers, E.; De Santis, M.; Gillessen, S.; Grummet, J.; Henry, A.M.; van der Kwast, T.H.; Lam, T.B.; et al. EAU-EANM-ESTRO-ESUR-ISUP_SIOG Guidelines on Prostate Cancer; European Association of Urology: Arnhem, The Netherlands, 2022.
92. Higano, C.; Shields, A.; Wood, N.; Brown, J.; Tangen, C. Bone mineral density in patients with prostate cancer without bone metastases treated with intermittent androgen suppression. Urology 2004, 64, 1182–1186.
93. Dawson, J.K.; Dorff, T.B.; Schroeder, E.T.; Lane, C.J.; Gross, M.E.; Dieli-Conwright, C.M. Impact of resistance training on body composition and metabolic syndrome variables during androgen deprivation therapy for prostate cancer: A pilot randomized controlled trial. BMC Cancer 2018, 18, 368
94. Hanson, E.D.; Sheaff, A.K.; Sood, S.; Ma, L.; Francis, J.D.; Goldberg, A.P.; Hurley, B.F. Strength Training Induces Muscle Hypertrophy and Functional Gains in Black Prostate Cancer Patients Despite Androgen Deprivation Therapy. J. Gerontol. Ser. A 2013, 68, 490–498.
95. Inglis, J.E.; Culakova, E.; Dunne, R.F.; Janelsins, M.C.; Lin, P.-J.; Mustian, K.M.; Peppone, L.J. Impact of high-dose vitamin d supplementation on short physical performance battery and bioelectrical impedance analysis in older patients with prostate cancer on ADT. J. Clin. Oncol. 2019, 37, e23106.
96. Inglis, J.E.; Fernandez, I.D.; van Wijngaarden, E.; Culakova, E.; Reschke, J.E.; Kleckner, A.S.; Lin, P.-J.; Mustian, K.M.; Peppone, L.J. Effects of High-Dose Vitamin D Supplementation on Phase Angle and Physical Function in Patients with Prostate Cancer on ADT. Nutr. Cancer 2021, 73, 1882–1889.

97. Kiwata, J.L.; Dorff, T.B.; Schroeder, E.T.; Salem, G.J.; Lane, C.J.; Rice, J.C.; Gross, M.E.; Dieli-Conwright, C.M. A pilot randomised controlled trial of a periodised resistance training and protein supplementation intervention in prostate cancer survivors on androgen deprivation therapy. BMJ Open 2017, 7, e016910.

98. Fairman, C.M.; Kendall, K.L.; Newton, R.U.; Hart, N.H.; Taaffe, D.R.; Chee, R.; Tang, C.I.; Galvão, D.A. Examining the effects of creatine supplementation in augmenting adaptations to resistance training in patients with prostate cancer undergoing androgen deprivation therapy: A randomised, double-blind, placebo-controlled trial. BMJ Open 2019, 9, e030080.

99. Yamamoto, D.; Maki, T.; Herningtyas, E.H.; Ms, N.I.; Ms, H.S.; Sugiyama, Y.; Bs, S.N.; Iida, K.; Iguchi, G.; Takahashi, Y.; et al. Branched-chain amino acids protect against dexamethasone-induced soleus muscle atrophy in rats. Muscle Nerve 2010, 41, 819–827.

100. Liu, C.-J.; Latham, N.K. Progressive resistance strength training for improving physical function in older adults. Cochrane Database Syst. Rev. 2009, 2009, CD002759.

101. Bozzetti, F. Forcing the vicious circle: Sarcopenia increases toxicity, decreases response to chemotherapy and worsens with chemotherapy. Ann. Oncol. 2017, 28, 2107–2118.

102. Cushen, S.J.; Power, D.G.; Murphy, K.P.; McDermott, R.; Griffin, B.T.; Lim, M.; Daly, L.; MacEneaney, P.; Sullivan, K.O.; Prado, C.M.; et al. Impact of body composition parameters on clinical outcomes in patients with metastatic castrate-resistant prostate cancer treated with docetaxel. Clin. Nutr. ESPEN 2016, 13, e39–e45.

103. Attard, G.; Merseburger, A.S.; Arlt, W.; Sternberg, C.N.; Feyerabend, S.; Berruti, A.; Joniau, S.; Géczi, L.; Lefresne, F.; Lahaye, M.; et al. Assessment of the Safety of Glucocorticoid Regimens in Combination With Abiraterone Acetate for Metastatic Castration-Resistant Prostate Cancer. JAMA Oncol. 2019, 5, 1159

104. Tombal, B.; Borre, M.; Rathenborg, P.; Werbrouck, P.; Van Poppel, H.; Heidenreich, A.; Iversen, P.; Braeckman, J.; Heracek, J.; Baron, B.; et al. Long-Term Antitumor Activity and Safety of Enzalutamide Monotherapy in Hormone Naïve Prostate Cancer: 3-Year Open Label Followup Results. J. Urol. 2018, 199, 459–464.

9. ACTIVIDAD CIENTÍFICA

Publicaciones

- **de Pablos-Rodríguez P,** Suárez Novo JF, Castells Esteve M, et al. Preliminary results of the implementation of robotic radical prostatectomy in a major ambulatory surgery regimen. *Actas Urol Esp (Engl Ed)*. 2023;47(5):288-295. doi:10.1016/j.acuroe.2022.09.006.
- Sopeña Sutil R, Vázquez-Martul D, **De Pablos-Rodríguez P,** et al. European Association of Urology biochemical recurrence risk groups after radical prostatectomy: External validation and identification of independent risk factors for progression and death. *Actas Urol Esp (Engl Ed)*. 2023;47(7):422-429. doi:10.1016/j.acuroe.2023.02.001.
- **de Pablos-Rodríguez P**, Claps F, Rebez G, et al. Personalised indocyanine-guided lymphadenectomy for prostate cancer: a randomised clinical trial. *BJU Int*. 2023;132(5):591-599. doi:10.1111/bju.16117
- **de Pablos-Rodríguez P,** Del Pino-Sedeño T, Infante-Ventura D, et al. Prognostic Impact of Sarcopenia in Patients with Advanced Prostate Carcinoma: A Systematic Review. *J Clin Med*. 2022;12(1):57. Published 2022 Dec 21. doi:10.3390/jcm12010057
- López-Abad A, Backhaus MR, Gómez GS, Avellaneda EC, Alarcón CM, Cubillana PL, Giménez PY, **de Pablos Rodríguez P**, Juan Fita MJ, Climent Durán MÁ, Ruiz IG, Crespo NV, Artés MA, Chinchilla RM, Avilés JM, Guzmán Martínez-Valls PL, López González PÁ, Real-World Prostate-Specific Antigen (PSA) reduction and survival outcomes of metastatic hormone-sensitive prostate cancer patients treated with Apalutamide: an observational, retrospective and multicentre study Optimizing Treatment Strategies for Metastatic Hormone-Sensitive Prostate Cancer Patients: Insights from a Real-world Study, *Prostate International*, https://doi.org/10.1016/j.prnil.2023.10.003.
- Rossin G, Zorzi F, **De Pablos-Rodríguez P**, et al. Sentinel Lymph Node Biopsy in Prostate Cancer: An Overview of Diagnostic Performance, Oncological Outcomes, Safety, and Feasibility. *Diagnostics (Basel)*. 2023;13(15):2543. Published 2023 Jul 31. doi:10.3390/diagnostics13152543.

- Nakdali Kassab B**, De Pablos-Rodríguez P**, Gómez-Ferrer A, et al. Is unilateral Lymphadenectomy an option in selected prostate cancer patients? Arch. EsP. Urol 2024; 77 (2): 119-123.

Comunicaciones

- Aldaz Acin A, **De Pablos-Rodríguez P,** Claps F, Gómez-Ferrer, A, Boronat Catalá J, Calatrava Fons A, Coy García A, Casanova Ramón Borja, J, Ramírez Backhaus M. Prostate cancer patients with lymphatic node involvement detected by immunohistochemistry. Is the effort worthwhile? 39th EAU Annual Congress.
- **De Pablos-Rodríguez, Pedro**; Claps Francesco; Rebez Giacomo; Gómez-Ferrer, Álvaro; Casanova Ramón Borja, Juan; Ramírez Backhaus, Miguel. Linfadenectomía guiada por indocianina frente a linfadenectomía extendida. 28 congreso Sociedad Canaria de Urología. Premio a la mejor comunicación oral.
- **De Pablos-Rodríguez, Pedro**; Boronat Catalá, Juan; Gómez-Ferrer, Álvaro; ; Ramírez Backhaus, Miguel, Casanova Ramón Borja, Juan. Resultados oncológicos de la crioterapia focal en cáncer de próstata localizado. LVII Congreso de la AUCV. Premiado como comunicación oral.
- Gómez Díez, Nidia, **De Pablos-Rodríguez, Pedro**; Boronat Catalá, Juan; Gómez-Ferrer, Álvaro; ; Ramírez Backhaus, Miguel, Casanova Ramón Borja, Juan. Fiabilidad de la RMN en el cáncer de próstata: Análisis retrospectivo de cinco años de experiencia con biopsia transperineal. LVII Congreso de la AUCV. Premiado como comunicación oral.

BJU Int 2023 doi:10.1111/bju.16117

BJUI
BJU International

Original Article

Personalised indocyanine-guided lymphadenectomy for prostate cancer: a randomised clinical trial

Pedro de Pablos-Rodríguez[1], Francesco Claps[2,4], Giacomo Rebez[4], Natalia Vidal Crespo[5], Álvaro Gómez-Ferrer[2], Juan Manuel Mascarós[2], Argimiro Collado Serra[2], Ana Caltrava Fons[3], José Rubio-Briones[2], Juan Casanova Ramon Borja[2] and Miguel Ramírez Backhaus[2]

[1]*Department of Urology, Research Institute of Biomedical and Health Sciences, Doctoral School of University of Las Palmas de Gran Canaria,* [2]*Department of Urology,* [3]*Department of Pathology, Instituto Valenciano de Oncología (IVO), Valencia, Spain,* [4]*Urology Clinic, Department of Medicine, Surgery and Health Sciences, University of Trieste, Trieste, and* [5]*Department of Urology, Hospital General Universitario Santa Lucía, Murcia, Italy*

Objectives

To study the safety and efficacy of a personalised indocyanine-guided pelvic lymph node dissection (PLND) against extended PLND (ePLND) during radical prostatectomy (RP).

Patients and Methods

Patients who were candidates for RP and lymphadenectomy, with intermediate- or high-risk prostate cancer (PCa) according to the National Comprehensive Cancer Network guidelines, were enrolled in this randomised clinical trial. Randomisation was made 1:1 to indocyanine green (ICG)-PLND (only ICG-stained LNs) or ePLND (obturator fossa, external, internal, and common iliac and presacral LNs). The primary endpoint was the complication rate within 3 months after RP. Secondary endpoints included: rate of major complications (Clavien–Dindo Grade III-IV), time to drainage removal, length of stay, percentage of patients classified as pN1, number of LNs removed, number of metastatic LNs, rate of patients with undetectable prostate-specific antigen (PSA), biochemical recurrence (BCR)-free survival, and rate of patients with androgen-deprivation therapy at 24 months.

Results

A total of 108 patients were included with a median follow-up of 16 months. In all, 54 were randomised to ICG-PLND and 54 to ePLND. The postoperative complication rate was higher in the ePLND (70%) vs the ICG-PLND group (32%) ($P < 0.001$). Differences between major complications in both groups were not statically significant ($P = 0.7$). The pN1 detection rate was higher in the ICG-PLND group (28%) vs the ePLND group (22%); however, this difference was not statistically significant ($P = 0.7$). The rate of undetectable PSA at 12 months was 83% in the ICG-PLND vs 76% in the ePLND group, which was not statistically significant. Additionally, there were no statistically significant differences in BCR-free survival between groups at the end of the analysis.

Conclusions

Personalised ICG-guided PLND is a promising technique to stage patients with intermediate- and high-risk PCa properly. It has shown a lower complication rate than ePLND with similar oncological outcomes at short-term follow-up.

Keywords

indocyanine green (ICG), personalised, complication, lymphadenectomy, prostate cancer

Introduction

The risk of death from prostate cancer (PCa) is markedly increased in patients with metastatic lymph nodes (LNs) and is estimated to be around 22%–30% [1]. The European Association of Urology (EAU) Guidelines recommend extended pelvic lymph node dissection (ePLND) in patients with high- and intermediate-risk PCa with an estimated risk of pN1 of >5% [2]. The prediction of LN involvement is based on several parameters, including PSA, multiparametric MRI, percentage of positive cores and histological characteristics [3]. Unfortunately, preoperative staging and prediction of the anatomical site of positive LNs are still unsatisfactory, even though imaging for PCa continues to

improve with the introduction of prostate-specific membrane antigen (PSMA) positron emission tomography [4]. Therefore, removing the primary PCa lymphatic landing sites within the extended template dissection remains the most accurate technique for nodal staging.

There are no randomised clinical trials (RCTs) supporting the oncological benefit of ePLND in this scenario; however, a meta-analysis showed no benefit with the low-quality of data available [5]. Indeed, the rationale for ePLND stands between the most accurate staging technique and a controversial therapeutic role [6,7]. Additionally, two recent RCTs have failed to demonstrate an oncological benefit of conventional ePLND against limited PLND (lPLND) [8,9].

Complication rates related to PLND vary among the different series, most of them being lymphoceles, thromboembolic events, and bleeding [10]. The extent of the dissection template seems to correlate with the risk of developing intra- and postoperative complications [10]; however, some studies have not endorsed this [8,11,12].

Indocyanine green (ICG) with near-infrared fluorescence absorption at 780 nm and emission at 820 nm, is one of the few imaging agents approved by the United States Food and Drug Administration [13] and enables in vivo visualisation of an organ's lymphatic drainage. Our previous experience with ICG-guided PLND (ICG-PLND) have supported this technique with a negative predictive value of ~97% [14,15].

As diminishing the extension of the lymphadenectomy is being explored as an alternative to ePLND with presumably non-inferior oncological outcomes and less toxicity, we decided to evaluate the safety and efficacy of a personalised ICG-PLND vs the recommended ePLND.

Patients and Methods

Study Design

In this RCT, patients with intermediate- or high-risk PCa who were candidates for radical prostatectomy (RP) were enrolled between March 2019 and March 2022 at Fundación Instituto Valenciano de Oncología. Recruited patients were randomised to ICG-PLND or ePLND (Fig. 1).

Study Participants

The inclusion criteria were as follows: (i) patients with PCa who were candidates for RP; (ii) National Comprehensive Cancer Network (NCCN) intermediate- and high-risk PCa; (iii) Eastern Cooperative Oncology Group performance status of 0; (iv) American Society of Anesthesiologists score below IV.

The exclusion criteria were as follows: (i) androgen-deprivation therapy (ADT) prior to surgery. Use of finasteride or dutasteride was allowed; (ii) body mass index of >40 kg/m^2; (iii) other active tumour, excluding basal or squamous cell tumours of the dermis; (iv) history of major surgery of the rectum or sigmoid; (v) active diverticulitis; (vi) psychological alterations, or family, socio-cultural or geographical conditions that, according to the investigator's judgement, may affect the patient's consent or completion of the study; and (vii) previous treatment with pelvic radiotherapy (RT) or brachytherapy. Focal treatment was allowed.

The study was approved by the local research ethics committee and was registered in European Union Drug Regulating Authorities Clinical Trials Database number 2019-003483-43. All patients signed the informed consent.

A complication rate of 10% in the ICG-PLND group and 35% in the ePLND was considered. These rates were calculated using our prospectively registered database. Assuming an alpha error of 0.05 and a statistical power of 80%, 100 patients was stablished as the minimum sample size to detect differences.

Study Randomisation

For allocation of the participants, a random allocation rule generator was created using the package 'ramdomizeR' from R (R Foundation for Statistical Computing, Vienna, Austria). The random allocation sequence was created by the statistician. Enrolment was made by the Principal Investigator. The same day before RP, the Principal Investigator was informed about the procedure he had to perform.

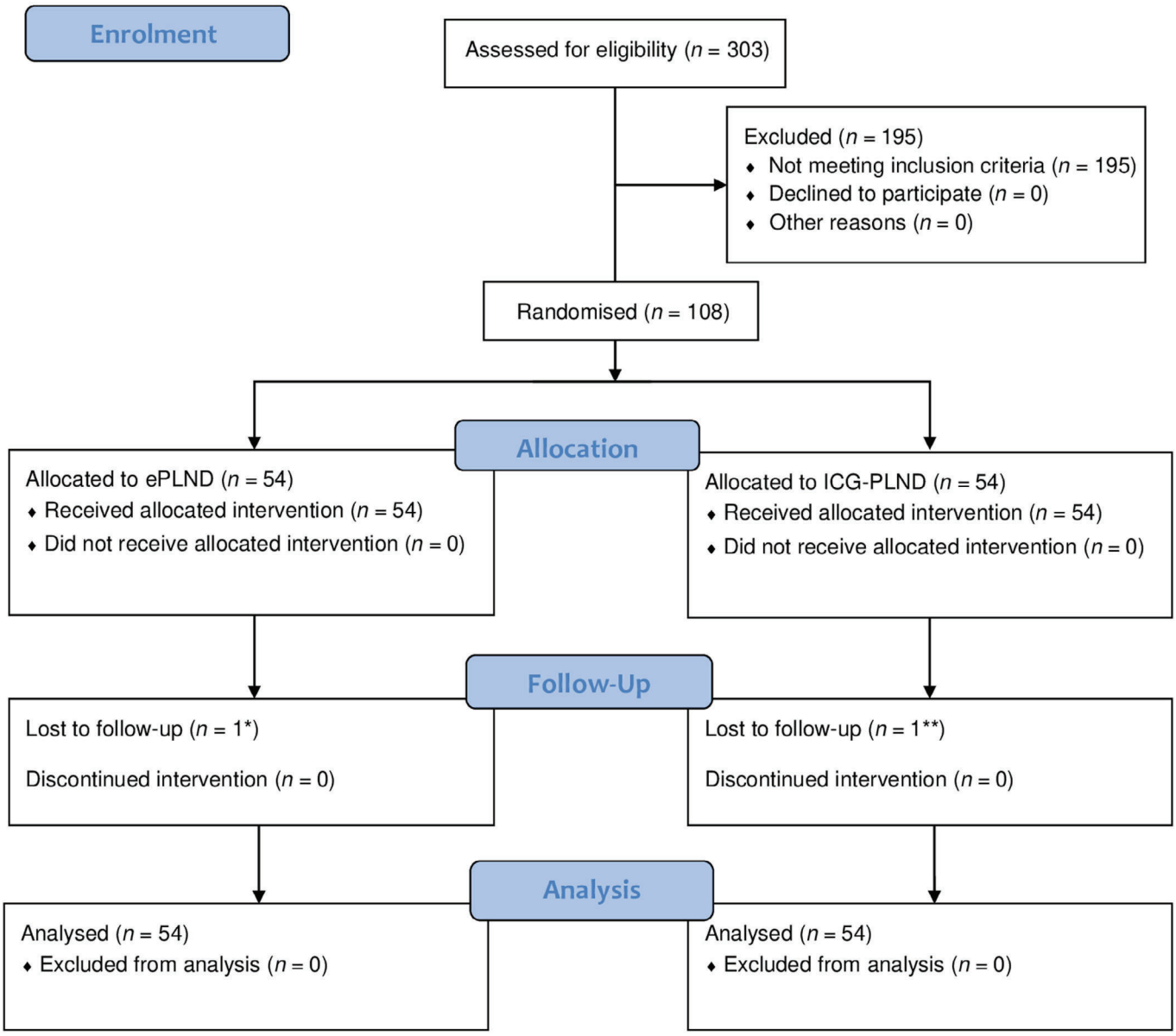
Perioperative Management and Surgical Technique

All patients underwent abdominopelvic CT and bone scan for preoperative staging.

Patients in the ePLND group underwent PLND in the first place and RP last. The extended template included the obturator, external, internal, and common iliac and presacral nodes.

Patients randomised to ICG-PLND were placed in a dorsal lithotomy position, and a BK UltraView 800® ultrasound was used. A dose of 25 mg ICG was diluted in a 5 mL sterile water solution, which was used for injection; 2.5 mL of the dilution was injected transperineally in the middle of the transitional zone of each prostatic lobe. Later, the patient was re-positioned for surgery. Only ICG-stained LNs were resected and carefully sampled individually. Nodal tissue was assessed ex vivo and labelled according to a previously designed scheme. When a LN vessel was observed driving fluorescence to a LN above the common iliac artery, it was sealed with a Hem-o-Lok®, and cranial dissection was

Fig. 1 Consolidated Standards of Reporting Trials (CONSORT) flow diagram. *, change of residency; **, lost contact.



interrupted. After ICG-PLND, RP was performed. Figure 2 summarises the PLND protocol in both groups.

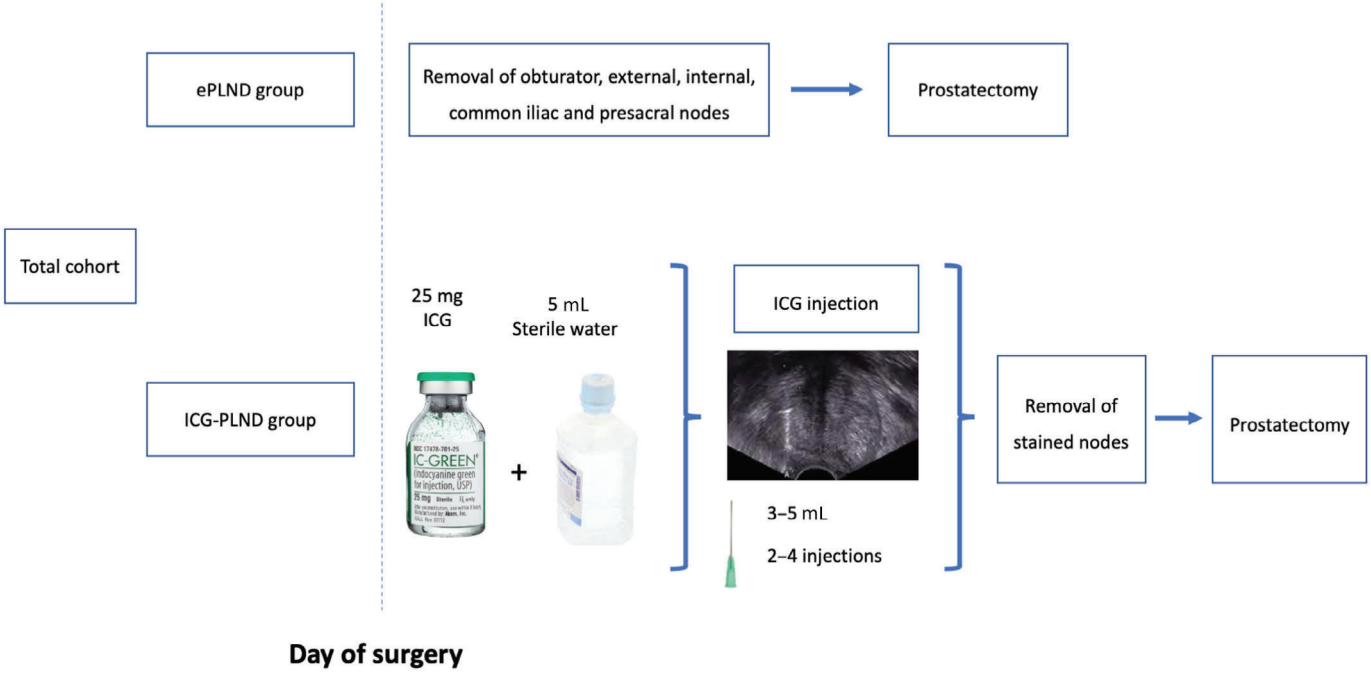
All procedures were performed by the same urologist using the laparoscopic fluorescence imaging IMAGE1 S™ RUBINA from Karl Storz 3D and 4 K technology with near-infrared ICG fluorescence, (Karl Storz, Tuttlingen, Germany). Intraoperative complications were recorded according to the EAU Intraoperative Adverse Incident Classification [16].

Prostate specimens and LNs were submitted for pathological evaluation according to the College of American Pathologists protocol and evaluated according to the International Society of Urological Pathology recommendations.

Postoperative complications were recorded in compliance with the suggestions from the EAU Panel Ad Hoc recommendations [17,18]. A checklist of the recommendation's adherence is given in Table S1.

Every patient had low-molecular-weight heparin administered for 1 month postoperatively for venous thromboembolism prophylaxis [19]. Regular postoperative course was considered if all the following items were accomplished: opioids administration and onset of ambulation in the first 24 h, intravenous NSAIDs up to the second day, length of hospitalisation stay between 4 and 6 days if the patient lived <50 or >50 km away from our centre, respectively. Any

Fig. 2 Flowchart of patient's intervention.



deviation from an ordinary postoperative course was defined as a complication. If a patient developed more than one complication, the most severe was considered. The definition of each complication is given in the Table S2.

Outpatient appointments were scheduled at 6 weeks and at 3 months. The following visits were planned according to the LN status and PSA value. The use of ADT or adjuvant RT was decided in a multidisciplinary genitourinary tumour board. The scheme of these treatments and the dose and anatomical areas of RT were registered. The use of stereotactic body RT for treating oligorecurrent disease was permitted. Imaging techniques at follow-up were based on multidisciplinary internal consensus meeting.

Endpoints

The primary endpoint was the complication rate registered according to the Clavien–Dindo classification within 3 months after RP. Major complications were defined as Clavien–Dindo Grade III–IV. Complications were also distributed according to the likeliness of PLND relation, based on a recent meta-analysis [10]. Secondary endpoints included the rate of major complications, median time to drain removal, median length of stay (LOS), percentage of patients classified with pN1 disease, number of LNs removed, number of metastatic LNs, rate of patients with ADT at 24 months, rate of patients with undetectable PSA (PSA level of ≤0.01 ng/mL), and biochemical recurrence (BCR)-free survival at 3, 12 and 24 months.

This study constitutes the first analysis of data that was planned 3 months after the last patient's intervention.

Statistical Analysis

Descriptive analysis included frequencies and proportions for categorical variables. Pearson's chi-squared test was used to compare categorical variables including: Clavien–Dindo grades, positive LNs, pN1 disease, Gleason score, R1 status, and locally advance disease. Median and interquartile range (IQR) were reported for continuous coded variables. Regarding continuous data, the *t*-test was used to assess differences between groups in complications per patient and dissected LNs. The Kaplan–Meier was used to estimate undetectable PSA level, BCR-free survival, and the rate of patients with ADT at 24 months. The log-rank test was used for group comparison. All tests were two-sided with a level of significance set at 5%. Statistical analysis was performed using R statistical software, version 3.6.3.

Results

A total of 108 patients were enrolled in this RCT with a median (IQR) follow-up of 16 (10–24) months; 54 of them were included in the ICG-PLND arm and 54 were included in the ePLND arm. The median age was 65 years, the median preoperative PSA level was 8 ng/mL, and 46% of patients had intermediate-risk PCa. Baseline characteristics of the cohort are presented in Table 1.

Table 1 Baseline characteristics.

Variable	Total	ePLND	ICG-PLND
Patients, *n*	108	54	54
Age, years, median (IQR)	65 (60–69)	65 (61–68)	65 (60–69)
PSA, ng/mL, median (IQR)	8 (6–12)	8 (5–11)	9 (6–12)
Gleason score, *n* (%)			
6	5 (4.6)	2 (3.7)	3 (5.6)
3 + 4	30 (28)	15 (28)	15 (28)
4 + 3	35 (32)	15 (28)	20 (37)
8	28 (26)	18 (33)	10 (19)
9–10	10 (9.3)	4 (7.4)	6 (11)
Clinical T stage, *n* (%)			
cT1	64 (60)	31 (57)	33 (61)
cT2	22 (20)	13 (24)	9 (17)
cT3	22 (20)	10 (19)	12 (22)
NCCN risk group, *n* (%)			
Intermediate	50 (46)	24 (44)	26 (48)
High	58 (54)	30 (56)	28 (52)

In all, 55 patients out of the total cohort (51%) presented at least one postoperative complication. Regarding the primary endpoint, the postoperative complication rate was significantly higher in the ePLND (70%) vs the ICG-PLND group (32%) ($P < 0.001$).

Four patients (11%) from the ePLND group presented a major complication vs two patients (12%) from the ICG-PLND group. This difference was not statistically significant ($P = 0.7$). Strongly PLND-related complications were more frequent in the ePLND group (relative risk [RR] 4.00, 95% CI 1.62–9.88; $P < 0.05$). This association was statically significant but weaker in the likely and unlikely PLND-related groups. These findings are summarised in Tables 2 and 3.

The most frequent complications were lymphoedema (29%), sensory disturbances (15%), and bleeding (10%). Lymphoedema was the only complication significantly higher in the ePLND group (RR 4.75, 95% CI 1.73–13.04; $P < 0.05$). Sensory disturbances and bleeding failed to reach significance (RR 3.00, 95% CI 0.86–10.48, $P = 0.1$; and RR 7.00, 95% CI 0.89–54.98, $P = 0.06$, respectively).

One patient in the ePLND group had an iliac vein injury that was considered the only intraoperative complication in the overall cohort.

The operative time was longer in the ePLND group, at a median (IQR) of 270 (243–300) vs 240 (210–252) min in the ICG-PLND group, which was statistically significant ($P < 0.001$). There were no differences in the median (IQR) LOS, at 3 (3–4) days in both groups ($P = 0.9$). Two patients in the ICG-PLND group had a drain placed after surgery vs one in the ePLND group. No patient carried the drain for longer than 14 days.

Histopathological Findings

The median (IQR) number of LNs dissected was 7 (4–9) in the ICG-PLND group and 24 (18–27) in the ePLND group ($P < 0.001$). The pN1 detection rate was higher in the ICG-PLND group (28%; $n = 15$) than in the ePLND group (22%; $n = 12$), although this difference was not statistically significant ($P = 0.7$). As shown in Table 4, prostate specimens' analysis had comparable findings between both groups.

The distribution of the ICG-dyed LNs resected and the metastatic LNs found is detailed in the Figure S1.

Oncological Outcomes

At 3, 12 and 24 months, 98% (95% CI 88%–99%), 83% (95% CI 68%–91%), and 64% (95% CI 45%–78%) of patients, respectively had undetectable PSA in the ICG-PLND group. Similarly, in the ePLND group, the rate of undetectable PSA were 94% (95% CI 84%–98%), 76% (95% CI 62%–86%), and 56% (95% CI 38%–71%), respectively. No statistically significant differences were observed between the groups ($P = 0.5$).

The rate of patients with ADT at 24 months was 8% (95% CI 3%–20%) in the ICG-PLND group and 4% (95% CI 1%–4%) in the ePLND group ($P = 0.2$). In all, 87% (95% CI

Table 2 Complication rates according to Clavien–Dindo classification.

Variable	Total	ePLND	ICG-PLND	*P*
Clavien–Dindo, *n* (%)				
0	53 (49)	16 (30)	37 (69)	<0.001
I	33 (31)	22 (41)	11 (20)	
II	16 (15)	12 (22)	4 (7.4)	
IIIb	5 (4.6)	4 (7.4)	1 (1.9)	
IVa	1 (0.9)	0 (0)	1 (1.9)	
Clavien–Dindo Grade, *n* (%)				
0	53 (49)	16 (30)	37 (69)	<0.001
>0	55 (51)	38 (70)	17 (31)	
Clavien–Dindo Grade, *n* (%)				
I–II	49 (89)	34 (89)	15 (88)	1
III–IV	6 (1.9)	4 (10)	2 (12)	
Complications for patient, *n*, mean (SD)	0.76 (0.91)	1.2 (1)	0.35 (0.55)	<0.001

Table 3 Type and severity of complications.

	Clavien–Dindo Grade I		Clavien–Dindo Grade II		Clavien–Dindo Grade IIIa		Clavien–Dindo Grade IIIb		Clavien–Dindo Grade IVa		Total
	ePLND	ICG-PLND	ePLND	ICG-PLND	ePLND	ICG-PLND	ePLND	ICG-PLND	ePLND	ICG-PLND	
Strongly PLND related (RR 4.00, 95% CI 1.62–9.88) $P < 0.05$											
Lymphoedema	19	4	–	–	–	–	–	–	–	–	23
Lymphocele	1	1	–	–	–	–	–	–	–	–	2
Likely PLND related (RR 2.57, 95% CI 1.17–5.65) $P = 0.021$											
Sensory disturbances	7	3	2	–	–	–	–	–	–	–	12
Bleeding	5	–	–	–	–	–	2	1	–	–	8
Motor dysfunction	2	2	1	–	–	–	–	–	–	–	5
Ureteric injury	–	–	–	–	–	–	1	–	–	–	1
Pulmonary embolism	–	–	–	–	–	–	–	–	–	1	1
Unlikely PLND related (RR 2.22, 95% CI 1.11–4.43) $P = 0.017$											
UTI	–	–	3	2	–	–	–	–	–	–	5
Haematuria	3	1	1	–	–	–	–	–	–	–	5
Urinary leak	1	–	1	2	–	–	–	–	–	–	4
Fever	2	–	1	–	–	–	–	–	–	–	3
Pain	1	1	1	–	–	–	–	–	–	–	3
Diarrhoea	1	–	1	–	–	–	–	–	–	–	2
Evisceration	–	–	–	–	–	–	1	–	–	–	1
Renal function impairment	1	–	–	–	–	–	–	–	–	–	1
Seroma	–	1	–	–	–	–	–	–	–	–	1
Ileus	–	–	–	1	–	–	–	–	–	–	1
Pneumonia	–	–	–	1	–	–	–	–	–	–	1
Haemorrhoids	–	–	1	–	–	–	–	–	–	–	1
Allergic reaction	1	–	–	–	–	–	–	–	–	–	1
Total	**57**		**18**		**0**		**5**		**1**		**81**

Table 4 Histopathological findings.

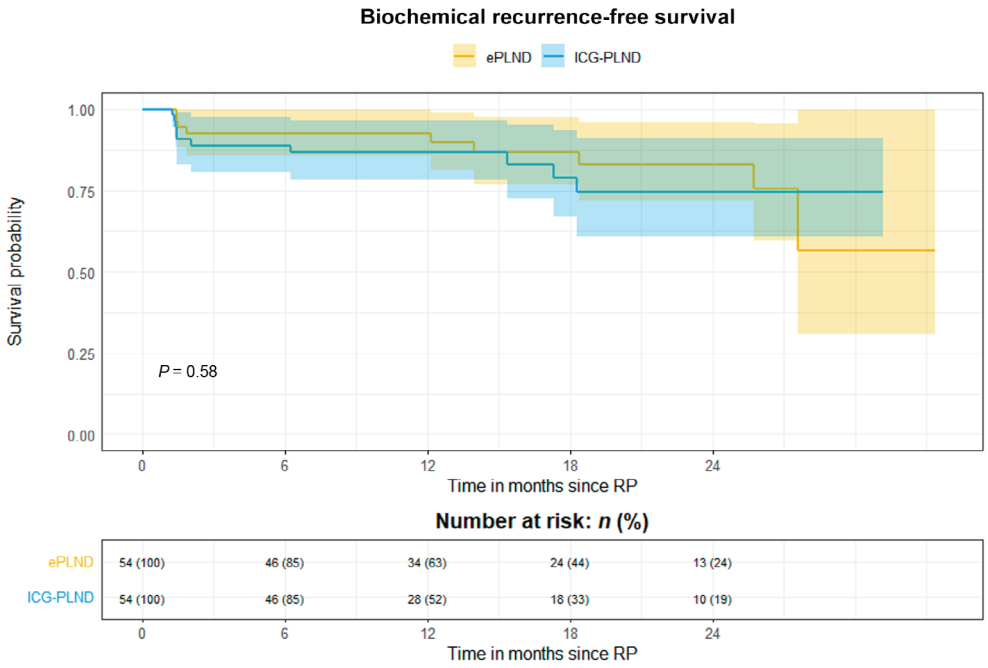
Variable	Total	ePLND	ICG-PLND	*P*
Dissected nodes, median (IQR)	14 (7–23)	23 (18–27)	7 (4–9)	<0.001
Positive LNs, *n* (%)				
0	81 (75)	42 (78)	39 (72)	0.733
1	17 (16)	6 (11)	11 (20)	
2	4 (3.7)	2 (3.7)	2 (3.7)	
3	2 (1.9)	1 (1.9)	1 (1.9)	
4	2 (1.9)	1 (1.9)	1 (1.9)	
5	1 (0.9)	1 (1.9)	0 (0)	
17	1 (0.9)	1 (1.9)	0 (0)	
pN1, *n* (%)	27 (25)	12 (22)	15 (28)	0.657
Gleason score, *n* (%)				
6	2 (1.9)	1 (1.9)	1 (1.9)	0.28
3 + 4	35 (32)	15 (28)	20 (37)	
4 + 3	38 (35)	24 (44)	14 (26)	
8	11 (10)	6 (11)	5 (9.3)	
9–10	22 (20)	8 (15)	14 (26)	
R1 status, *n* (%)	34 (32)	17 (31)	17 (31)	1
Locally advanced disease, *n* (%)	75 (70)	39 (72)	36 (67)	0.676

78%–96%) and 75% (95% CI 61%–91%) of patients in the ICG-PLND group experienced BCR, against 93% (95% CI 86–99%) and 83% (95% CI 71–96%) of patients in the ePLND group at 12 and 24 months after surgery, respectively. As noted in Fig. 3, no statistically significant differences were seen in terms of BCR-free survival between groups. At the time of the analysis, two patients were lost to follow-up, and one death was registered due to other causes rather than PCa.

Discussion

We present the first RCT that evaluates the safety and efficacy of a personalised ICG-guided PLND in contrast with

Fig. 3 Biochemical recurrence-free survival.



conventional ePLND. Our initial experience shows promising results regarding its lesser toxicity with similar oncological outcomes at short-term follow-up.

Major complications related to PLND are rare, and mortality is almost anecdotal [20]. However, considering all complications, up to 14% of patients may experience at least one after surgery [10]. The fact that we considered a complication any deviation from the established regular postoperative course could explain the high prevalence (51%) of patients who experienced one or more complications in this study.

A systematic review by Fossati et al. [5] assessing the safety and oncological benefits of PLND highlighted the scarcity of high-quality evidence published (only three RCTs out of 66 studies). One of them, Lestingi et al. [11], found no difference in the postoperative complication rate, and the other two agreed that lymphoceles were more likely to happen in ePLND than in lPLND, with little differences between groups (2% and 9%) [12,21]. Lymphoedema was found, in one RCT, to be another complication statistically different between groups. However, this difference was only 1%, so it may not be clinically relevant [20]. In our study, lymphoedema was the only complication that was significantly higher in the ePLND group. Lymphocele formation seems to be related to the extent of the PLND (RR 0.52, 95% CI 0.37–0.74; $P < 0.001$) [22]; however, we found no differences between groups with an exceptionally low rate of development.

Another interesting approach is the analysis of complications according to the likeliness of being related to the PLND. In this way, Cacciamani et al. [10] revealed a marked difference in complications strongly related to PLND, favouring lPLND (RR 0.46; 95% CI 0.34–0.61; $P = 0.01$), whereas no differences were found in the likely and the unlikely PLND-related groups. We found statistically significant differences in the three groups in favour of the ICG-PLND group. The RR of each group higher, as it was the likeliness of relation to the lymphadenectomy.

Regarding anatomopathological outcomes, pN1 disease was found in 28% of patients in the ICG-PLND group, in contrast with the 22% detected in the ePLND group. This finding is remarkable if we consider that there was a difference of 17 LNs dissected between the two groups (seven vs 24). Although this research was not designed to prove the oncological non-inferiority outcomes of ICG-PLND, these results are promising.

Two RCTs have shown comparable oncological outcomes between ePLND and lPLND. Touijer et al. [8], with a large cohort of patients, described similar rates of BCR between ePLND and lPLND. The main critique of that study was that there was little difference in the LN count between both groups. On the other hand, Lestingi et al. [9] reported a larger difference in the number of LNs removed between both groups, three vs 17. However, they also did not find differences in BCR with a follow-up of 53.9 months. The large proportion of patients with a favourable cancer profile (one third of patients with preoperative Gleason 6) might have underestimated the oncological benefit of ePLND, and a longer follow-up may be needed to assess oncological results.

Interestingly, if we analyse the number of LNs dissected and the rate of pN1 disease in these trials, a similar pattern can be appreciated. In the Touijer et al. [8], they found 14% pN1 disease in the ePLND group with a median of 14 LNs removed. In the lPLND group, they found 12% pN1 disease with a median dissection of 12 LNs. The same finding was detected in the Lestingi et al. [9] trial, where they dissected 17 nodes and found 17% of pN1 patients in the ePLND group. In the lPLND, the median number of nodes dissected was three, and the rate of pN1 was precisely 3.4%. In the present study, we detected pN1 disease in 28% of patients in the ICG-PLND group, with a median LN removal of only seven. This finding suggests the oncological feasibility of an ICG-guided dissection by increasing the likelihood of removing the LNs with the highest chance of being affected. Our previous experience with ICG showed a negative predictive value (NPV) of 97% [15]. Only five of 219 patients (2%) were staged incorrectly. We decided to perform the present clinical trial to assess complication rates and to evaluate the clinical relevance of missing positive LNs in adequately staged patients, as this question remains unclear.

Sensitivity stands as the main goal of PCa lymphadenectomy, and in the setting of ICG-guided PLND, a high variability of 50%–100% is reported in the literature [23–26]. Several reasons have been proposed for these discordant results. First, sensitivity has been calculated either based on the number of removed LNs or the staging of the patients. The nature of the present clinical trial hinders the analysis of sensitivity or NPV. Secondly, different techniques, vision systems, and dosages have been described. Manny et al. [23] performed a percutaneous robot-guided 0.4 mL injection of a 2.5 mg/mL ICG solution. They describe a sensitivity of 100% in this pilot study with 50 patients. Hruby et al. [24] performed the same approach as we used but with a lower concentration of the solution (0.25 mg ICG dissolved in 2.5 mL water). The highest sensitivity was obtained in the ICG group, followed by the super-ePLND and ePLND, 97.7%, 87.8% and 80.5%, respectively.

Lastly, combinations of ICG with radioactive colloids, such as ^{99m}Tc, have also been validated. [25,27]. Van der Poel's group [25] describes three modifications of their technique concerning the particle concentration and the imaging system, with an increased sensitivity in every modification. Although the best sensitivity, 93.5%, was achieved with the Image 1 HUB HD with D-Light P system KARL STORZ GmbH & Co.KG, results should be taken with caution given the small cohort of patients. This group has recently published a phase II RCT where they describe a better performance with the intratumoral injection of the marker rather than the systematic prostatic injection [27], opening an interesting new research idea.

Recently, PSMA-guided lymphadenectomy is also being explored as an alternative to substitute ePLND in the primary PCa setting; however, scientific evidence is still scarce [28]. Until new imaging techniques emerge to properly stage the LN status of patients with PCa, less invasive approaches, such as ICG-guided PLND, should continue to be investigated.

Indocyanine green is a safe and economical substance affordable for most centres. It is easily injected inside the prostrate assisted by a conventional ultrasound. A personalised ICG-guided PLND has shown to be less aggressive (in terms of complication rates), less time-consuming, and has identified a similar rate of pN1 patients compared to ePLND. The short follow-up and the sample size are the main limitations of the study, especially when reporting oncological outcomes. External validation of these outcomes is mandatory.

Conclusions

An ePLND for patients with intermediate- and high-risk PCa is being reconsidered as the best staging method. In this clinical trial, we suggest ICG-guided PLND as an alternative to conventional ePLND, with lower complication rates and similar oncological findings at short-term follow-up.

Disclosure of Interests

None of the authors have any conflicts of interest related to the development of the study in question.

Trial Registry Name

Phase II Safety and Efficacy of personalized lymphadenectomy or guided by indocyanine green (ICG) vs extended pelvic lymph node dissection in patients diagnosed with prostate cancer subsidiaries of radical prostatectomy and lymphadenectomy.

Trial Identification Number

European Union Drug Regulating Authorities Clinical Trials Database no. 2019-003483-43.

Trial Uniform Resource Locator (URL)

https://www.clinicaltrialsregister.eu/ctr-search/search?query=2019-003483-43

References

1 **Eggener SE, Scardino PT, Walsh PC et al.** Predicting 15-year prostate cancer specific mortality after radical prostatectomy. *J Urol* 2011; 185: 869–75

2 **Briganti A, Larcher A, Abdollah F et al.** Updated nomogram predicting lymph node invasion in patients with prostate cancer undergoing extended pelvic lymph node dissection: the essential importance of percentage of positive cores. *Eur Urol* 2012; 61: 480–7

3 **Gandaglia G, Ploussard G, Valerio M et al.** A novel nomogram to identify candidates for extended pelvic lymph node dissection among patients with clinically localized prostate cancer diagnosed with magnetic resonance imaging-targeted and systematic biopsies. *Eur Urol* 2019; 75: 506–14

4 **Maurer T**, **Gschwend JE**, **Rauscher I et al.** Diagnostic efficacy of (68) gallium-PSMA positron emission tomography compared to conventional imaging for lymph node staging of 130 consecutive patients with intermediate to high risk prostate cancer. *J Urol* 2016; 195: 1436–43

5 **Fossati N**, **Willemse PM**, **Van den Broeck T et al.** The benefits and harms of different extents of lymph node dissection during radical prostatectomy for prostate cancer: a systematic review. *Eur Urol* 2017; 72: 84–109

6 **Briganti A**, **Blute ML**, **Eastham JH et al.** Pelvic lymph node dissection in prostate cancer. *Eur Urol* 2009; 55: 1251–65

7 **Bader P**, **Burkhard FC**, **Markwalder R**, **Studer UE**. Disease progression and survival of patients with positive lymph nodes after radical prostatectomy. Is there a chance of cure? *J Urol* 2003; 169: 849–54

8 **Touijer KA**, **Sjoberg DD**, **Benfante N et al.** Limited versus extended pelvic lymph node dissection for prostate cancer: a randomized clinical trial. *Eur Urol Oncol* 2021; 4: 532–9

9 **Lestingi JFP**, **Guglielmetti GB**, **Trinh QD et al.** Extended versus limited pelvic lymph node dissection during radical prostatectomy for intermediate- and high-risk prostate cancer: early oncological outcomes from a randomized phase 3 trial. *Eur Urol* 2021; 79: 595–604

10 **Cacciamani GE**, **Maas M**, **Nassiri N et al.** Impact of pelvic lymph node dissection and its extent on perioperative morbidity in patients undergoing radical prostatectomy for prostate cancer: a comprehensive systematic review and meta-analysis. *Eur Urol Oncol* 2021; 4: 134–49

11 **Lestingi J**, **Pontes JJ**, **Borges LL et al.** Extended vs limited pelvic lymphadenectomy during radical prostatectomy for intermediate- and high-risk prostate cancer: a prospective randomized trial. *J Urol* 2015; 193 (Suppl): e983–4

12 **Schwerfeld-Bohr J**, **Kaemper M**, **Krege S**, **Heidenreich A**. Prospective randomized multicenter study comparing limited vs extended pelvic lymphadenectomy in intermediate and high risk prostate cancer-comparison of complications (SEAL, AUO AP 55/09). *Eur Urol Suppl* 2014; 13: e270

13 **Leung K**. Quenched indocyanine green-anti-prostate-specific membrane antigen antibody J591. In *Molecular Imaging and Contrast Agent Database (MICAD)*. Bethesda: National Center for Biotechnology Information (US), 2011

14 **Ramírez-Backhaus M**, **Mira Moreno A**, **Gómez Ferrer A et al.** Indocyanine green guided pelvic lymph node dissection: an efficient technique to classify the lymph node status of patients with prostate cancer who underwent radical prostatectomy. *J Urol* 2016; 196: 1429–35

15 **Claps F**, **de Pablos-Rodríguez P**, **Gómez-Ferrer Á et al.** Free-indocyanine green-guided pelvic lymph node dissection during radical prostatectomy. *Urol Oncol* 2022; 40: 489.e19–489.e26

16 **Biyani CS**, **Pecanka J**, **Rouprêt M**, **Jensen JB**, **Mitropoulos D**. Intraoperative Adverse Incident Classification (EAUiaiC) by the European Association of Urology ad hoc Complications Guidelines Panel. *Eur Urol* 2020; 77: 601–10

17 **Mitropoulos D**, **Artibani W**, **Graefen M et al.** Reporting and grading of complications after urologic surgical procedures: an ad hoc EAU guidelines panel assessment and recommendations. *Eur Urol* 2012; 61: 341–9

18 **Vetterlein MW**, **Klemm J**, **Gild P et al.** Improving estimates of perioperative morbidity after radical cystectomy using the European Association of Urology Quality Criteria for standardized reporting and introducing the comprehensive complication index. *Eur Urol* 2020; 77: 55–65

19 **Naik R**, **Mandal I**, **Hampson A et al.** The role of extended venous thromboembolism prophylaxis for major urological cancer operations. *BJU Int* 2019; 124: 935–44

20 **Musch M**, **Klevecka V**, **Roggenbuck U**, **Kroepfl D**. Complications of pelvic lymphadenectomy in 1,380 patients undergoing radical retropubic prostatectomy between 1993 and 2006. *J Urol* 2008; 179: 923–9

21 **Clark T**, **Parekh DJ**, **Cookson MS et al.** Randomized prospective evaluation of extended versus limited lymph node dissection in patients with clinically localized prostate cancer. *J Urol* 2003; 169: 145–8

22 **Briganti A**, **Chun FK**, **Salonia A et al.** Complications and other surgical outcomes associated with extended pelvic lymphadenectomy in men with localized prostate cancer. *Eur Urol* 2006; 50: 1006–13

23 **Manny TB**, **Patel M**, **Hemal AK**. Fluorescence-enhanced robotic radical prostatectomy using real-time lymphangiography and tissue marking with percutaneous injection of unconjugated indocyanine green: the initial clinical experience in 50 patients. *Eur Urol* 2014; 65: 1162–8

24 **Hruby S**, **Englberger C**, **Lusuardi L et al.** Fluorescence guided targeted pelvic lymph node dissection for intermediate and high risk prostate cancer. *J Urol* 2015; 194: 357–63

25 **KleinJan GH**, **van den Berg NS**, **Brouwer OR et al.** Optimisation of fluorescence guidance during robot-assisted laparoscopic sentinel node biopsy for prostate cancer. *Eur Urol* 2014; 66: 991–8

26 **Nguyen DP**, **Huber PM**, **Metzger TA**, **Genitsch V**, **Schudel HH**, **Thalmann GN**. A specific mapping study using fluorescence sentinel lymph node detection in patients with intermediate- and high-risk prostate cancer undergoing extended pelvic lymph node dissection. *Eur Urol* 2016; 70: 734–7

27 **Wit EMK**, **van Beurden F**, **Kleinjan GH et al.** The impact of drainage pathways on the detection of nodal metastases in prostate cancer: a phase II randomized comparison of intratumoral vs intraprostatic tracer injection for sentinel node detection. *Eur J Nucl Med Mol Imaging* 2022; 49: 1743–53

28 **Gandaglia G**, **Mazzone E**, **Stabile A et al.** Prostate-specific membrane antigen radioguided surgery to detect nodal metastases in primary prostate cancer patients undergoing robot-assisted radical prostatectomy and extended pelvic lymph node dissection: results of a planned interim analysis of a prospective phase 2 study. *Eur Urol* 2022; 82: 411–8

Correspondence: Miguel Ramírez Backhaus, Jefe Clínico, Servicio de Urología, Fundación IVO, Valencia, Spain; Profesor Asociado, Facultad de Medicina, UCHCEU, Alfara del Patriarca, Spain.

e-mail: ramirezfivo@gmail.com; www.ivo.es

Abbreviations: ADT, androgen-deprivation therapy; BCR, biochemical recurrence; EAU, European Association of Urology; ICG, indocyanine green; IQR, interquartile range; LOS, length of stay; LN, lymph node; NCCN, National Comprehensive Cancer Network; PCa, prostate cancer; (e)(l)PLND, (extended) (limited) pelvic lymph node dissection; PSMA, prostate-specific membrane antigen; RCT, randomised clinical trial; RP, radical prostatectomy; RR, relative risk; RT, radiotherapy.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Fig. S1 (A) The LN distribution scheme; (B) Number and location of the ICG LNs resected; (C) Number and location of the metastatic ICG LNs resected.

Table S1 Checklist on recommendations given by the EAU guidelines on reporting complications after urological surgical procedures.

Table S2 Definition of each complication.

Journal of
Clinical Medicine

MDPI

Review

Prognostic Impact of Sarcopenia in Patients with Advanced Prostate Carcinoma: A Systematic Review

Pedro de Pablos-Rodríguez [1,2], Tasmania del Pino-Sedeño [3,4,5], Diego Infante-Ventura [3,4], Aythami de Armas-Castellano [3,4], Miguel Ramírez Backhaus [1], Juan Francisco Loro Ferrer [6], Pedro de Pablos-Velasco [7,8,*], Antonio Rueda-Domínguez [5,9,10] and María M. Trujillo-Martín [3,4,5,10]

1 Department of Urology, Instituto Valenciano de Oncología (IVO), 46009 Valencia, Spain
2 Doctoral School of University of Las Palmas de Gran Canaria (ULPGC), 35001 Las Palmas de Gran Canaria, Spain
3 Canary Islands Health Research Institute Foundation (FIISC), 38320 Santa Cruz de Tenerife, Spain
4 Evaluation Unit of the Canary Islands Health Service (SESCS), 38109 Santa Cruz de Tenerife, Spain
5 Network for Research on Chronicity, Primary Care, and Health Promotion (RICAPPS), 38109 Santa Cruz de Tenerife, Spain
6 Department of Clinical Sciences, University of Las Palmas de Gran Canaria (ULPGC), 35001 Las Palmas de Gran Canaria, Spain
7 Department of Endocrinology and Nutrition, University Hospital of Gran Canaria Doctor Negrín, 35012 Las Palmas de Gran Canaria, Spain
8 Research Institute of Biomedical and Health Sciences (IUIBS), University of Las Palmas de Gran Canaria (ULPGC), 35001 Las Palmas de Gran Canaria, Spain
9 Medical Oncology Intercenter Unit, Regional and Virgen de la Victoria University Hospitals, IBIMA, 29590 Malaga, Spain
10 Research Network on Health Services in Chronic Diseases (REDISSEC), Carlos III Health Institute, 28029 Madrid, Spain
* Correspondence: pablos.velasco@gmail.com; Tel.: +34-928-450-491

Abstract: Prostate cancer (PCa) is the second most common cancer in men and the fifth leading cause of death from cancer. The possibility of sarcopenia being a prognostic factor in advanced PCa patients has recently become a subject of interest. The aim of the present study was to evaluate the prognostic value of sarcopenia in advanced prostate carcinoma. A systematic review was conducted in Medline, EMBASE, and Web of Science (March, 2021). The quality of studies was assessed using the Quality in Prognosis Studies tool. Meta-analyses for overall, cancer-specific, and progression-free survival were performed. Nine studies (n = 1659) were included. Sarcopenia was borderline associated with a shorter overall survival (HR = 1.20, 95% CI: 1.01, 1.44, P = 0.04, I^2 = 43%) but was significantly associated with progression-free survival (HR = 1.61, 95% CI: 1.26, 2.06, P < 0.01; k = 3; n = 588). Available evidence supports sarcopenia as an important prognostic factor of progression-free survival in patients with advanced PCa. However, sarcopenia has a weak association with a shorter overall survival. The evidence on the role of sarcopenia in prostate-cancer-specific survival is insufficient and supports the need for further research. Patient summary: The literature was reviewed to determine whether the loss of muscle mass (sarcopenia) affects the survival in patients with advanced PCa. Patients with advanced PCa and sarcopenia were found to have a shorter progression-free survival (the length of time during and after treatment of a cancer that the patient lives with the disease but it does not get worse), but sarcopenia did not have much influence on the overall survival and cancer-specific survival (the length of time from either the date of diagnosis or the start of treatment to the date of death due to the cancer).

Keywords: prostatic neoplasms; sarcopenia; prognosis; survival; systematic review; meta-analysis

Citation: de Pablos-Rodríguez, P.; del Pino-Sedeño, T.; Infante-Ventura, D.; de Armas-Castellano, A.; Ramírez Backhaus, M.; Ferrer, J.F.L.; de Pablos-Velasco, P.; Rueda-Domínguez, A.; Trujillo-Martín, M.M. Prognostic Impact of Sarcopenia in Patients with Advanced Prostate Carcinoma: A Systematic Review. *J. Clin. Med.* **2023**, *12*, 57. https://doi.org/10.3390/jcm12010057

Academic Editor: Giacomo Novara

Received: 30 October 2022
Revised: 1 December 2022
Accepted: 15 December 2022
Published: 21 December 2022

1. Introduction

Prostate cancer (PCa) is a global health problem, with approximately 1.4 million cases diagnosed worldwide each year [1]. It is the second most common type of cancer in men, after lung cancer [2], and the fifth leading cause of death from cancer [3]. The mean age of PCa onset is sixty-five and the majority of cases are diagnosed from that age onward [3].

There is an inherent decrease in serum testosterone concentrations as age increases, directly affecting the development of muscle mass and fat mass. Consequently, the ageing process accelerates the development of sarcopenia [4]. Sarcopenia is a progressive and musculoskeletal disease linked to the chronological age of the person [5], characterized by the loss of muscle mass and its associated function, which is associated with an increased likelihood of adverse outcomes including falls, fractures, physical disability, and mortality [5]. Specifically, sarcopenia is probable when low muscle strength is detected. A sarcopenia diagnosis is confirmed by the presence of low muscle quantity or quality. When low muscle strength, low muscle quantity/quality, and low physical performance are all detected, sarcopenia is considered severe [5].

Furthermore, one of the therapeutic approaches in the different PCa scenarios may involve androgen deprivation therapy (ADT), which produces adverse effects such as changes in body composition and physical function [6]. Therefore, the age-related loss of muscle and fat mass and, therefore, sarcopenia is accentuated in these patients by the effect of the therapy [6].

To date, sarcopenia has been identified as a poor prognostic factor for disease progression and mortality in patients with ovarian cancer [7], breast cancer [8], lung cancer [9], or colorectal cancer [10], among others. In the case of PCa, although different prognostic factors for disease progression and mortality have been established including Gleason score, clinical stage, prostate-specific antigen (PSA), presence of visceral or liver metastases, and number of metastatic sites [11], there is a lack of a clear conclusion or consensus about the prognosis role of sarcopenia. Determining this association may potentially inform the design of specific and tailored strategies to improve the prognosis of PCa patients and the effectiveness of the first-line treatments.

Therefore, the aims of the study were to identify, critically assess, and synthesize the available scientific evidence on the impact of sarcopenia on disease progression and mortality in patients with advanced PCa.

2. Evidence Acquisition

A systematic review was developed following the Cochrane Prognosis Methods Group [12] and the reporting followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [13]. The protocol is registered in the PROSPERO database (reference number CRD42021248645).

2.1. Information Sources and Search Strategy

Medline (using the Ovid platform), EMBASE, and Web of Science (WOS) databases were searched (26 March 2021). The search strategy was initially developed in Medline including both controlled vocabulary and text-word terms related to sarcopenia and prostate neoplasms and then adapted for each of the other databases. Searches were restricted to the English and Spanish languages and no time limits were imposed. The search strategy is available in Supplementary Material (Supplementary Table S1). The reference lists of all relevant papers were examined to identify possible additional studies meeting selection criteria.

2.2. Study Selection Process

Studies were eligible for inclusion if they fulfilled the following criteria:

(a) Type of study: Any longitudinal observational study (e.g., cohort studies, case–control studies, or database linkage studies) and secondary analyses of experimental studies (randomized or non-randomized) investigating the prognosis significance of sarcopenia in

patients with PCa for predicting mortality or disease progression were included. For an experimental study to be eligible, it must have used either the control group alone or the entire study sample adjusted for the intervention. Cross-sectional studies, case series, or case studies and systematic or narrative reviews were excluded.

(b) Population: Studies that evaluated men aged sixty and older diagnosed with advanced PCa were included. Patients were considered advanced if they had metastatic, hormone-sensitive, or castration-resistant PCa (nodal, bone, and/or visceral) defined as cTxNxM1.

Studies including only a subset of the participants relevant to the review question, such as studies including patients with other types of cancer in addition to patients with PCa, were included as long as the results for patients meeting the inclusion criteria were reported separately or they accounted for more than 80% of the target population.

Studies conducted with healthy volunteers or animals were excluded.

(c) Index prognostic factor: the presence of sarcopenia defined as progressive and the generalized loss of skeletal muscle mass and function assessed by magnetic resonance imaging (MRI), computed tomography scan (muscle area or muscle volume or skeletal muscle index—SMI), dual-energy X-ray absorptiometry (SMI), or bioelectrical impedance analysis—BIA (SMI).

(d) Comparator: absence of sarcopenia.

(e) Outcome measures: studies had to report on overall survival (OS), cancer-specific survival, overall response rate to cancer treatment, progression-free survival (PFS), complications of cancer, or health-related quality of life (HRQL).

(f) Timing: sarcopenia measurement had to be performed during or after diagnosis.

No study based on the duration of follow-up was excluded.

(g) Setting: studies conducted in primary or secondary healthcare were included.

(h) Language: only studies published in English or Spanish were included.

2.3. Study Selection Process

The study selection process was conducted by two reviewers as follows: first, the reviewers screened independently and in duplicate the titles and abstracts of all the retrieved citations; secondly, the reviewers, again independently and in duplicate, read and evaluated for inclusion the full text articles that appeared to fulfil the pre-determined selection criteria. The reviewers compared and discussed results in both phases and consulted a third reviewer in case of doubt and discrepancy.

2.4. Data Collection Process

A data extraction form (in Excel format) was prepared by the authors, pilot-tested on three studies before the start of the data extraction process, and refined accordingly. Two reviewers independently and in duplicate extracted the following data from the included studies: identification of the article (author, year of publication, country, and funding), design and methodology (objective, number of centers, and duration of follow-up), population and their demographics (e.g., sample size, age, cancer grade/stage, and metastases), sarcopenia (definition, measurement method, timing, and cut-off point), and outcomes and the results of the study (means, event counts, hazard ratio—HR, or odds ratio—OR, with special attention to the variability in the results presented (standard deviation, variance, *p*-values, etc.)). HRs and ORs were extracted from univariate and multivariate analyses. A third reviewer subsequently verified the extracted data.

2.5. Risk of Bias Assessment

Again, two reviewers independently and in duplicate assessed the potential risk of bias in the studies included using the Quality in Prognosis Studies (QUIPS) tool [14]. Each of the six domains used by QUIPS includes multiple items that are judged separately. Based on the ratings of the items, a conclusive judgment of the risk of bias within each domain was made and expressed on a three-grade scale (low, moderate, or high risk of bias). In the

systematic review here, the overall risk of bias was considered low if up to one domain was rated as at moderate risk of bias. If one or more study domains were rated as at high risk or if three or more were rated as at moderate risk, the study was then classified as at high risk of bias. All studies in between were classified as having moderate risk of bias [15].

The inter-rater agreement using the weighted Kappa and percent agreement was assessed. Discrepancies of judgments between the reviewers were discussed and, in case no consensus could be achieved, a third reviewer was consulted. The QUIPS-files are available upon request from the authors.

2.6. Assessment of Publication Bias

According to the recommendations of the Cochrane Collaboration [16], publication bias was examined by constructing a funnel plot and computing the Egger test, with the significance level set at 0.05, using metafunnel and metabias commands in STATA version 16 (StataCorp LLC, College Station, TX, USA).

2.7. Analysis and Synthesis of Results

A meta-analysis was performed for outcomes reported by two or more studies. The meta-analysis and forest plot for the sarcopenia rate were calculated using the metaprop command in STATA version 16. The hazard ratio (HR) and the corresponding 95% CI for OS, cancer-specific survival, and PFS were pooled with an indirect variance estimation in meta-analyses using the statistical program Review Manager (RevMan, version 5.4.1. Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2020), and results were displayed in forest plots. Heterogeneity was assessed using the I^2 statistic. When there was heterogeneity ($I^2 \geq 50\%$ or $P < 0.1$), meta-analyses were performed using a random-effects model. A sensitivity analysis was conducted by omitting each study individually to determine the stability of the overall estimate of the effect. The effects of disease stage (castration-sensitive or castration-resistant PCa) and treatment type (androgen deprivation therapy plus chemotherapy or alone; or chemotherapy) were explored using subgroup analyses. The nature of the data reported for age, presence of metastases, and sarcopenia stage did not allow them to be grouped for the analysis. Meta-regression was also not possible, due to the small number of studies evaluated.

2.8. Certainty of Evidence Assessment

An assessment of the certainty of evidence per outcome was performed based on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach. Certainty could be rated down considering five domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias; or rated up considering three domains: large effect, dose−response gradient, and plausible confounding [17]. Evidence profiles were built and the overall certainty of evidence was rated from very low (little confidence in the estimate; the true prognosis is likely to be substantially different from the estimate) to high (very confident that the true prognosis is close to that of the estimate).

3. Evidence Synthesis

The results of the literature search and study selection process are shown in Figure 1. Out of a total of 861 initially identified references after eliminating duplicates, 164 potentially relevant articles were selected for full text assessment. Nine studies were finally eligible for inclusion according to the pre-established selection criteria [18–26], and eight of them were selected for quantitative synthesis [18–22,24–26]. All selected studies were published in English between 2015 and 2021. The list of studies excluded at the full-text level and the reasons for exclusion are provided in Supplementary Table S2.

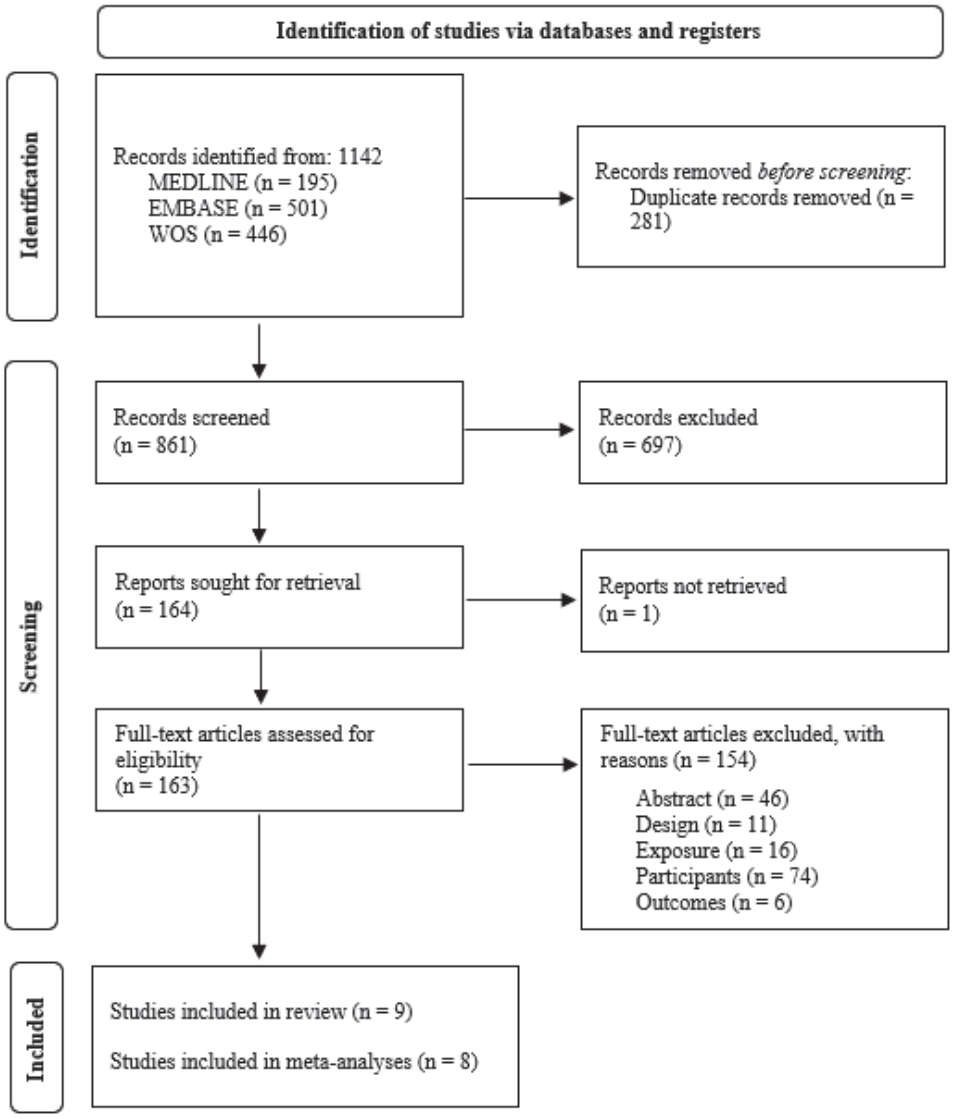


Figure 1. PRISMA flow chart detailing the screening process.

3.1. Description of Included Studies

The main characteristics of the selected studies are summarized in Table 1. Seven studies were retrospective medical record reviews [18,21–26] and two were retrospective cohorts [19,20]; studies were conducted in South Korea [20–22], Japan [20,24], the United Kingdom [19], France [18], Spain [23], and Austria [26].

Table 1. Characteristics of included studies.

First Author, Year (Country)	Design	N	Patient					Sarcopenia			Outcomes	Follow-Up Time (Months)
			Age [a]	Inclusion Criteria	Exclusion Criteria	Metastases (N)	Cancer Treatment (%)	Definition	Prevalence (%)	Diagnosis Method		
Antoun, 2015 [18] (France)	RRR	127	69 (63–74) *	Metastatic CRPCa	NR	Visceral: 15	1. Enzalutamide + prednisolone: 62 2. Abiraterone + prednisolone: 24	SMI < 43 cm^2/m^2 (BMI < 25 kg/m^2) SMI < 53 cm^2/m^2 (BMI > 25 kg/m^2)	66.14	At L3 by CT scan	OS	16 (95% CI: 12–19)
											PFS	Sarcopenia: 4 (95% CI: 3–6) Non-sarcopenia: 5 (95% CI: 3–6)
Fischer, 2020 [19] (UK)	RCS	90	69 (NR) *	Starting treatment (enzalutamide or abiraterone) for metastatic CRPCa	No imaging data	Bone: 15 Bone and lymph node: 17 Lymph node: 10 Visceral: 1	Previous ADT: 100% 1. Enzalutamide + prednisolone: 69% 2. Abiraterone + prednisolone: 31%	SMI < 52.4 cm^2/m^2	NR	At L3 by CT scan	OS	NR
Ikeda, 2020 [20] (Japan)	RCS	197	73 (66.0–78.0) *	1. Metastatic hormone-sensitive PCa 2. No previous treatments	Missing clinical or imaging data at diagnosis	Bone: 127 Distant lymph node: 29 Other locations: 9	Previous ADT:100% 1. Docetaxel: 39.6% 2. Cabazitaxel: 6.7% 3. Enzalutamide: 30.6% 4. Abiraterone: 34.3% 5. Other treatment: 17.1%	SMI < 33 cm^2/m^2 (BMI < 25 kg/m^2) SMI < 53 cm^2/m^2 (BMI >25 kg/m^2)	82,74	At L3 by CT scan	OS	Sarcopenia: 72 (IQR: 50–84) Non-sarcopenia: NR (IQR: 52-NR)
											CSS	Sarcopenia: 77 (IQR: 62-NR) Non-sarcopenia: NR (IQR: 75-NR)
Lee, 2018 [21] (Republic of Korea)	RRR	282	67.0 (61.0–72.0) *	CRPCa progression	1. Incomplete clinical data 2. Loss to follow-up 3. Unknown cause of death	Bone: 155 Lymph node: 118 Visceral: 10	Previous ADT: 100% 1. Docetaxel + prednisolone: NR 2. Enzalutamide + prednisolone: NR 3. Abiraterone + prednisolone: NR	SMI < 52.4	NR	At L3 by CT scan)	CSS	15
											PFS	3.7
Lee, 2020 [22] (Republic of Korea)	RRR	411	70 (65–76) *	CRPCa progression	1. Insufficient imaging data 2. Lost to follow-up 3. Unknown cause of death	Bone: 344 Lymph node: 199 Visceral:70	Previous ADT:100% 1. Docetaxel + prednisolone: NR 2. Cabazitaxel + prednisolone: NR 3. Enzalutamide + prednisolone: NR 4. Abiraterone + prednisolone: NR	SMI < 45.2 cm^2/m^2 SMA < 32.4 HU	50.36	At L3 by CT scan	OS	Sarcopenia: 19 Non-sarcopenia: 24
Muñoz-Rodríguez, 2021 [23] (Spain)	RRR	59	72.74 (12.25)	Metastatic onset PCa + first-line ADT	No imaging data	Bone: 52 Retroperitoneal lymphadenopathy: 30 Visceral: 6	1. ADT: 100%	European Working Group on Sarcopenia in Older People criteria [5]	NR	CT scan	OS	32.3 (95% CI: 17.1–47.16)

Table 1. *Cont.*

First Author, Year (Country)	Design	N	Patient					Sarcopenia			Outcomes	Follow-Up Time (Months)
			Age [a]	Inclusion Criteria	Exclusion Criteria	Metastases (N)	Cancer Treatment (%)	Definition	Prevalence (%)	Diagnosis Method		
Ohtaka, 2019 [24] (Japan)	RRR	77	70 (65–76) *	CRPCa + docetaxel chemotherapy	NR	Bone: 55 Lymph node: 34 Visceral: 12	1. Previous ADT + docetaxel+ prednisolone: 100%	Psoas muscle index < 5.7 cm^2/m^2	33.77	At L3-psoas muscle by CT scan	OS	16.41 (IQR: 10.85–25.97)
Pak, 2020 [25] (Republic of Korea)	RRR	230	68.3 (9.1)	CRPCa + first-line therapy	1. Insufficient imaging data before starting first-line treatment 2. Patients treated for <2 months 3. Patients followed-up for <6 months	Bone: 196 Lymph node: 122 Solid organ: 28	Previous ADT: 100% 1. Docetaxel + prednisolone: 7.0% 2. Cabazitaxel + prednisolone: 24.3% 3. Enzalutamide + prednisolone: 10.0% 4. Abiraterone + prednisolone: 13.0% 5. Other treatment + prednisolone: 2.1%	SMI < 50 cm^2/m^2	51.30	At L3 by CT scan	OS	Sarcopenia: 16.9 Non-sarcopenia: 24.1
											PFS	Sarcopenia: 9.1 Non-sarcopenia: 14.9
Stangl-Kremser, 2019 [26] (Austria)	RRR	186	68,8 (64.6–75.0) *	CRPCa + chemo hormonal therapy	1. Insufficient imaging data 2. Lost to follow-up	Bone: 146 Distant lymph node: 65 Liver: 16 Visceral (No liver): 19	1. Docetaxel + prednisolone: 100	SMI < 55 cm^2/m^2 (men)	82.80	At L3 by CT scan	OS	26.2 (IQR 13.7–42.4)
											PFS	7.8 (IQR: 4.4–16.3)

[a] Mean (SD) or median (IQR); * as reported. ADT: androgen deprivation therapy; BMI: body mass index; CRPCa: Castration-resistant prostate cancer; CSS: Cancer-specific survival; CT: Computerized Tomography; DSF: Progression-free survival; HU: Hounsfield Units; CI: confidence interval; IQR: interquartile range; NR: not reported; OS: Overall survival; PCa: Prostate cancer; RCS: Retrospective cohort study; RRR: Retrospective record review; SD: standard deviation; SMA: Skeletal Muscle Attenuation; SMI: Skeletal muscle index; UK: United Kingdom.

Across the nine studies, 1659 men were recruited. The largest study consisted of 411 men [22], whereas the smallest study had only 59 men [23].

The mean age of the patients was 69.77 years (SD: 1.85) ranging from 61 to 78 years of age. Five studies focused on patients with castration-resistant PCa [21,22,24–26], two studies on patients with metastatic castration-resistant PCa [18,19], and two others on patients with metastatic PCa [20,23]. The overall prevalence of sarcopenia was 61% (95% CI: 46– 76%; I^2 = 97.07%, $P > 0.01$) (Supplementary Figure S1). However, three of the included studies did not report the number of participants with sarcopenia; the data of these studies could not be included in the analysis [19,21,23].

The most commonly used method for sarcopenia screening of participants was measuring SMI using a CT scan at L3 [18–22,25,26]. Nonetheless, one study used the L3-psoas muscle index [24] and another study [23] used the European Working Group on Sarcopenia in Older People criteria [5]. The criteria used to define sarcopenia are shown in Table 1. Finally, sarcopenia measurement was performed at the time of disease diagnosis, PCa diagnosis [23,26], or castration-resistant PCa diagnosis [21,22] in four studies; before starting treatments in three studies [19,20,25]; at tumor assessment in one study [18]. One study did not report on the time point of the sarcopenia measurement [24].

Seven studies considered OS as the clinical outcome [18–20,22–26], two considered cancer-specific survival [20,21], and four considered PFS [18,21,25,26]. None reported data on overall response rates, complications of cancer, or HRQL. The mean duration of the reported follow-up was twenty-nine weeks [18,20–23,26].

3.2. Risk of Bias in Included Studies

Risk of bias was considered high in two of the nine included studies [19,26] and moderate in one study [20]. Study attrition and prognostic factor measurement bias were suspected in one study due to the failure to account for confounding concerns in the exclusion criteria [26]. A probable study-confounding bias was identified in three studies due to the partial information on the measurement and analysis of all important confounders [19] or the method and setting of confounding measurement [20,26]. In general, in the domain of statistical analyses and reporting bias, analysis intentions were not available, or not reported in sufficient detail to enable an assessment. The detailed judgements for each of the risk of bias domain criteria are shown in Table 2.

Table 2. Risk of bias assessment.

Study	Study Participation	Study Attrition	Prognostic Factor Measurement	Outcome Measurement	Study Confounding	Statistical Analysis and Reporting	Overall Risk of Bias
Antoun [18]	Low	Low	Low	Low	Low	Moderate	Low
Fischer [19]	Low	Low	Low	Low	High	High	High
Ikeda [20]	Low	Low	Low	Low	Moderate	Moderate	Moderate
Lee [21]	Low	Low	Low	Low	Low	Moderate	Low
Lee [22]	Low	Low	Low	Low	Low	Moderate	Low
Muñoz-Rodríguez [23]	Low	Low	Low	Low	Low	Moderate	Low
Ohtaka [24]	Low	Low	Low	Low	Low	Moderate	Low
Pak [25]	Low	Low	Low	Low	Low	Moderate	Low
Stangl-Kremser [26]	Low	High	High	Low	Moderate	Moderate	High

Low: low risk of bias; Moderate: moderate risk of bias; High: high risk of bias.

The percent agreement was 82% and the inter-rater agreement was moderate (Kappa = 0.56).

3.3. Synthesis of Results

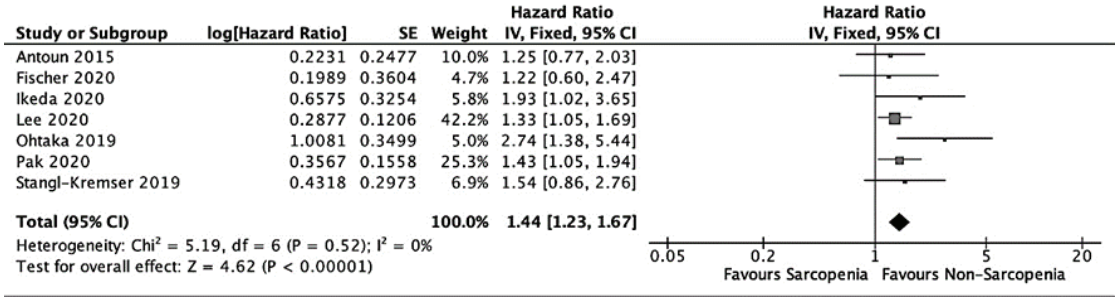
Out of the nine included studies, eight that included 1600 patients remained for quantitative analysis [18–22,24–26]. The study excluded from quantitative analyses did not determine a cut-off for defining sarcopenia but instead analyzed muscle mass as a continuous variable [23]. Results of all meta-analyses and subgroup and sensitivity analysis are available in Supplementary Table S3.

The quality of evidence ranged from high to very low. Supplementary Table S4 provides the evidence profile for sarcopenia-related outcomes.

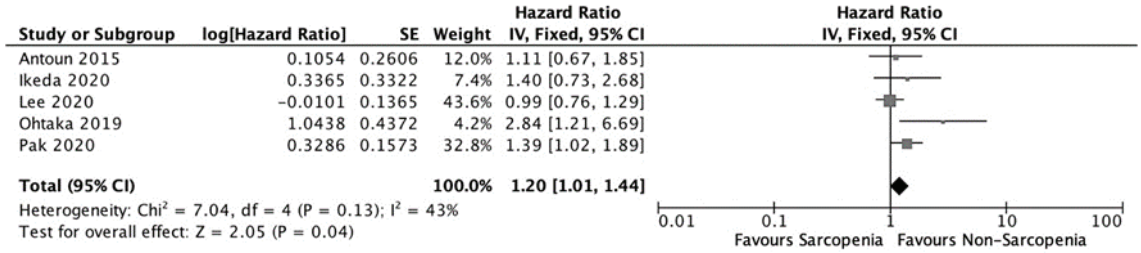
No evidence of publication bias was detected through visual assessment (Supplementary Figures S2–S6) or from the result of Egger's regression test for each pooled outcome, except in univariate analysis of PFS (P = 0.02) (see Supplementary Table S3).

3.3.1. Overall Survival

The meta-analyses of the univariate [18–20,22,24–26] and multivariable data [19,20,22,24,25] on the influence of sarcopenia on OS is shown in Figure 2. The pooled results of univariate data showed that PCa patients with sarcopenia had a significantly higher risk of all-cause mortality (fixed effects, HR = 1.44, 95% CI: 1.23, 1.67, P < 0.01, I^2 = 0%; k = 7; n = 1081) versus participants without sarcopenia. In the multivariate data meta-analysis (fixed effects), there was a borderline significant association between sarcopenia and OS (fixed effects, HR = 1.20, 95% CI: 1.01, 1.44, P = 0.04, I^2 = 43%; k = 5; n = 831).



(**A**) Univariate Analysis.



(**B**) Multivariate Analysis.

Figure 2. Forest plots for overall survival [10–20,22,24–26].

The subgroup and sensitivity analysis showed no statistically significant changes in the overall outcome estimate, as shown in Supplementary Table S3.

3.3.2. Cancer-Specific Survival

Only two studies [20,21] reported on cancer-specific survival. In the meta-analysis of the univariate data, there was no significant association between sarcopenia and cancer-specific survival (random effects, HR = 1.98, 95% CI: 0.80, 4.90, P = 0.14; I^2 = 74%; k = 2; n = 479) (Figure 3). However, the only study that reported a multivariate model [20]

showed that sarcopenia was significantly associated with shorter cancer-specific survival (HR = 2.18, 95% CI: 1.07, 7.32, P = 0.04; n = 197).

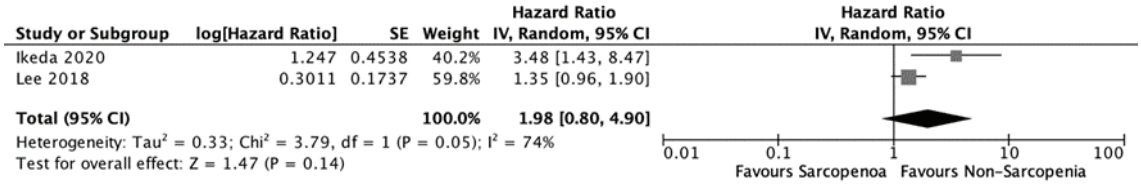
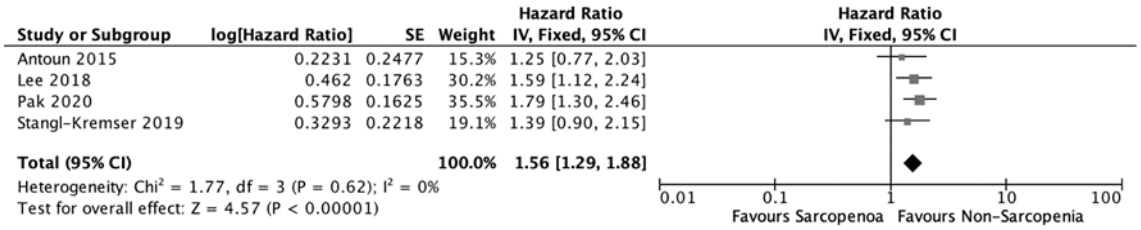


Figure 3. Forest plot for cancer-specific survival—Univariate Analysis [20,21].

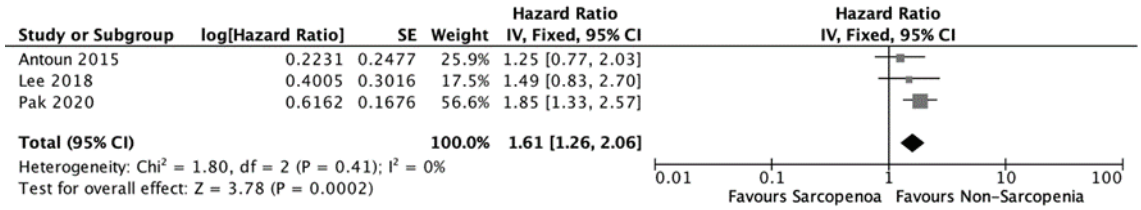
Subgroup analysis of univariate data indicated a statistically significant association in patients with hormone-sensitive PCa (HR = 3.48, 95% CI: 1.43, 8.47, P = 0.05; n = 197).

3.3.3. Progression-Free Survival

Four studies provided data on PFS [18,21,25,26]. The pooled analysis demonstrated an association between sarcopenia and shorter PFS, and this association existed in both univariate (HR = 1.56, 95% CI: 1.29, 1.88, P < 0.01; I^2 = 0%; k = 4; n = 818) and multivariate analyses (HR = 1.61, 95% CI: 1.26, 2.06, P < 0.01; k = 3; n = 588) (Figure 4).



(**A**) Univariate Analysis.



(**B**) Multivariate Analysis.

Figure 4. Forest plots for progression-free survival [18,21,25,26].

The subgroup analysis of univariate data suggested no significant effect of treatment on the association between sarcopenia and PFS.

4. Discussion

The findings reported here support sarcopenia as being an important prognostic factor of PFS in patients with advanced PCa. Additionally, a less clear association between sarcopenia and cancer-specific survival or OS was also found.

As PFS is a surrogate outcome of cancer-specific survival and OS, the fact that the results of the present review have been conclusive only for this variable and not for cancer-specific survival and OS may be related to the short duration of follow-up in the included studies (mean: 29 weeks). It is likely that a longer follow-up could demonstrate a clearer positive association between sarcopenia and survival/mortality variables.

As with the results obtained for other types of cancer [7–10], two recent meta-analyses identified sarcopenia as a poor prognostic factor for disease progression in PCa [27,28]; however, none have focused on sarcopenia as a prognostic factor for advanced PCa. In addition, the effect of sarcopenia on overall survival was assessed in both studies but not

on cancer-specific survival and PFS. Finally, our subgroup analyses and the assessment of the certainty of evidence were not performed in these previous studies.

Sarcopenia prevalence in patients with PCa estimated by SMI in the included studies ranged widely from 50.36 [22] to 82.80% [26]. This may be due to the use of different cut-offs for sarcopenia diagnosis (45.2–55 cm^2/m^2), including the use of an obesity-specific SMI cut-off. As the cut-off used to define sarcopenia directly influences the outcome of associations made between SMI and prognosis in cancer patients, it is necessary for a consensus to be reached on this.

The prevalence of sarcopenia in patients with PCa is markedly high (61%) as compared to patients affected by other types of cancer (38.6%) [29]. This higher prevalence can be explained by two factors: first, the advanced mean age of the sample (69.77 years), and secondly, because a significant percentage of the patients were under ADT.

The main result obtained in the present review is the association between sarcopenia and PFS, which could be explained by the worse treatment response that patients with sarcopenia experience [29].

It is easier to explain the relationship obtained between sarcopenia and OS (weak association but statistically significant on multivariate analysis). This association has been shown in other solid tumors [30–33]. Sarcopenia assumed decreased functional reserves. The poor functional reserves are associated with the frailty phenotype. The close relationship between sarcopenia and frailty functional syndrome is probably the main reason behind the findings here concerning OS.

Moreover, in patients requiring surgery, surgical procedures that minimize the risk of worsening sarcopenia should be prioritized. In this sense, it is widely known that outpatient surgery or minimally invasive surgery involving fewer days of hospitalization compared to conventional surgery can help reduce the risk of malnutrition and, consequently, the worsening of sarcopenia that hospitalization entails [34].

When ADT is required, intermittent ADT may be an alternative to reduce the impact of hypogonadism on muscle. From the oncological point of view, this strategy has shown non-inferiority with respect to continuous ADT [35,36]. In fact, the European urology guidelines endorse intermittence as an ADT treatment option in a selected profile of patients [37]. In the same way that intermittence can attenuate the impact on bone mass [38], it could perhaps attenuate its effect on muscle mass.

Current European Urology Guidelines only mention sarcopenia as a consequence of androgenic treatment. However, as sarcopenia could be an unfavorable prognostic factor that can be worsened by PCa treatment, it should be systematically screened and, if detected, patients should receive personalized treatment [6,37]. On the other hand, the diagnosis of sarcopenia should be accompanied by other measures to reduce the impact of hypogonadism on the muscle. Thus, preliminary studies have shown that physical exercise programs can improve sarcopenia in patients with PCa [39], even in the absence of testosterone [40]. Improvements in sarcopenia have also been obtained in patients with PCa supplemented with high doses of vitamin D [41,42]. In addition, different studies are currently being conducted to assess the effect of protein and creatinine supplementation, but the results have not been published yet [43,44].

The main limitation of the present review is that the evidence comes exclusively from retrospective studies, a design characterized by poor control over the exposure factor, covariates, and potential confounders and bias. In addition to the short follow-up periods in the studies included in our review, another important limitation is, due to the lack of consensus on the definition of sarcopenia, the diversity of cut-off points used by the considered studies for assessing sarcopenia. Moreover, subgroup and meta-regression analyses to explore the effect of important variables such as age, presence of metastases, and sarcopenia stage on the magnitude of association could not be performed. Finally, another potential limitation of this review is the possibility that some studies have not been included, because they are not written in English or Spanish or because they are not indexed in the consulted databases. Despite all these limitations, the present study

benefits from rigorous methods following the fundamental principles of transparency and replicability, a comprehensive search, a peer selection, data extraction and risk of bias assessment, a quantitative synthesis of results with the exploration of important potential sources of heterogeneity, and an assessment of the certainty of evidence on the basis of a structured and explicit approach.

For sarcopenia diagnosis, the following cut-off points are arbitrary at this time; the development of validated cut-off points depends on normative data and their predictive value for hard endpoints, which is a high priority for research studies.

In addition to new studies with a longer-term follow-up on the effects of sarcopenia on advanced PCa progression, future lines of research should be related to the analysis of the impact of different measures aimed at eliminating or attenuating sarcopenia and their effect on the evolution of advanced PCa, such as nutrition [45], physical exercise [46], or whether intermittence is an ADT treatment option in patients with advanced PCa. Other aspects in which the evaluation of the role of sarcopenia could be relevant are related to the decision to start treatment or not, or whether or not to combine treatment, as well as the decision on the type of treatment that best suits a muscle state. In this respect, several studies, some of which are included in the meta-analysis here, support the view that patients with sarcopenia suffer greater toxicity and have worse tolerance to chemotherapy [24,25,47,48]. The proposal of these studies is to use sarcopenia as a factor to decide to treat patients with a new generation of antiandrogens rather than with chemotherapy. The fact that the new antiandrogens also lead to a reduction in lean body mass is known [49,50], but whether or not this is related to decreased survival or disease-free time has not been established [25].

In conclusion, the available evidence supports the view that sarcopenia is an important prognostic factor of PFS in patients with advanced prostate carcinoma. However, sarcopenia has a weak association with a shorter OS. Finally, the available evidence on the role of sarcopenia in cancer-specific survival is insufficient and, as such, precludes drawing definitive conclusions and, furthermore, supports the need for further research efforts.

5. Take Home Message

Sarcopenia is an important prognostic factor of PFS in patients with advanced PCa.
Sarcopenia has a weak association with a shorter overall survival.
There is a lack of evidence on the role of sarcopenia in cancer-specific survival.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm12010057/s1, Figure S1: Forest plot for sarcopenia prevalence; Figure S2: Funnel plot—publication bias: Univariate analysis of overall survival; Figure S3: Funnel plot—publication bias: multivariate analysis of overall survival; Figure S4: Funnel plot—publication bias: univariate analysis of cancer-specific survival; Figure S5: Funnel plot—publication bias: univariate analysis of disease-free survival; Figure S6: Funnel plot—publication bias: multivariate analysis of disease-free survival; Table S1: Search strategy; Table S2: Results of meta-analysis, subgroup analysis and publication bias; Table S3: Results of meta-analysis, subgroup analysis and publication bias.

Author Contributions: Conceptualization, P.d.P.-R. and T.d.P.-S.; methodology, T.d.P.-S. and M.M.T.-M.; literature review process, D.I.-V., A.d.A.-C. and M.R.B.; formal analysis, P.d.P.-R. and T.d.P.-S.; writing—original draft preparation, P.d.P.-R., T.d.P.-S., D.I.-V., A.d.A.-C. and M.R.B.; writing—review and editing, J.F.L.F., P.d.P.-V., A.R.-D. and M.M.T.-M.; project supervision, J.F.L.F., P.d.P.-V., A.R.-D. and M.M.T.-M.; project coordination, M.M.T.-M.; funding acquisition, P.d.P.-V. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The data presented in this study is available in the supplementary material.

Acknowledgments: We would like to thank Leticia Rodríguez for developing the search strategy and running the study search and Daniel Estaña Malaret for his help in the first steps of this study, in

the selection of studies, and the elaboration of the protocol. We are also grateful to Patrick Dennis for English language editing support with the final manuscript.

Conflicts of Interest: The authors have no conflict of interest with the subject matter or materials discussed in the manuscript.

References

1. Sung, H.; Ferlay, J.; Siegel, R.L.; Laversanne, M.; Soerjomataram, I.; Jemal, A.; Bray, F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J. Clin.* **2021**, *71*, 209–249. [CrossRef]
2. Torre, L.A.; Siegel, R.L.; Ward, E.M.; Jemal, A. Global Cancer Incidence and Mortality Rates and Trends—An Update. *Cancer Epidemiol. Biomark. Prev.* **2016**, *25*, 16–27. [CrossRef] [PubMed]
3. Ferlay, J.; Ervik, M.; Lam, F.; Colombet, M.; Mery, L.; Piñeros, M.; Znaor, A.; Soerjomataram, I.; Bray, F. *Global Cancer Observatory: Cancer Today*; International Agency for Research on Cancer: Lyon, France, 2020.
4. Wilson, D.; Jackson, T.; Sapey, E.; Lord, J.M. Frailty and sarcopenia: The potential role of an aged immune system. *Ageing Res. Rev.* **2017**, *36*, 1–10. [CrossRef] [PubMed]
5. Cruz-Jentoft, A.J.; Bahat, G.; Bauer, J.; Boirie, Y.; Bruyère, O.; Cederholm, T.; Cooper, C.; Landi, F.; Rolland, Y.; Sayer, A.A.; et al. Sarcopenia: Revised European consensus on definition and diagnosis. *Age Ageing* **2019**, *48*, 16–31. [CrossRef] [PubMed]
6. Smith, M.R.; Saad, F.; Egerdie, B.; Sieber, P.R.; Tammela, T.L.; Ke, C.; Leder, B.Z.; Goessl, C. Sarcopenia During Androgen-Deprivation Therapy for Prostate Cancer. *J. Clin. Oncol.* **2012**, *30*, 3271–3276. [CrossRef]
7. Ubachs, J.; Ziemons, J.; Minis-Rutten, I.J.G.; Kruitwagen, R.F.P.M.; Kleijnen, J.; Lambrechts, S.; Olde Damink, S.W.M.; Rensen, S.S.; Van Gorp, T. Sarcopenia and ovarian cancer survival: A systematic review and meta-analysis. *J. Cachexia Sarcopenia Muscle* **2019**, *10*, 1165–1174. [CrossRef]
8. Zhang, X.-M.; Dou, Q.-L.; Zeng, Y.; Yang, Y.; Cheng, A.S.K.; Zhang, W.-W. Sarcopenia as a predictor of mortality in women with breast cancer: A meta-analysis and systematic review. *BMC Cancer* **2020**, *20*, 1–11. [CrossRef]
9. Yang, M.; Shen, Y.; Tan, L.; Li, W. Prognostic Value of Sarcopenia in Lung Cancer. *Chest* **2019**, *156*, 101–111. [CrossRef]
10. Sun, G.; Li, Y.; Peng, Y.; Lu, D.; Zhang, F.; Cui, X.; Zhang, Q.; Li, Z. Can sarcopenia be a predictor of prognosis for patients with non-metastatic colorectal cancer? A systematic review and meta-analysis. *Int. J. Color. Dis.* **2018**, *33*, 1419–1427. [CrossRef]
11. Pinart, M.; German Prostate Cancer Consortium (DPKK); Kunath, F.; Lieb, V.; Tsaur, I.; Wullich, B.; Schmidt, S. Prognostic models for predicting overall survival in metastatic castration-resistant prostate cancer: A systematic review. *World J. Urol.* **2020**, *38*, 613–635. [CrossRef]
12. Moons, K.G.; Hooft, L.; Williams, K.; Hayden, J.A.; Damen, J.A.; Riley, R.D. Implementing systematic reviews of prognosis studies in Cochrane. *Cochrane Database Syst. Rev.* **2018**, *10*, ED000129. [CrossRef]
13. Page, M.J.; McKenzie, J.E.; Bossuyt, P.M.; Boutron, I.; Hoffmann, T.C.; Mulrow, C.D.; Shamseer, L.; Tetzlaff, J.M.; Akl, E.A.; Brennan, S.E.; et al. The PRISMA 2020 Statement: An Updated Guideline for Reporting Systematic Reviews. *BMJ* **2021**, *372*, n71. [CrossRef]
14. Hayden, J.A.; Van Der Windt, D.A.; Cartwright, J.L.; Côté, P.; Bombardier, C. Assessing Bias in Studies of Prognostic Factors. *Ann. Intern. Med.* **2013**, *158*, 280–286. [CrossRef]
15. Grooten, W.J.A.; Tseli, E.; Äng, B.O.; Boersma, K.; Stålnacke, B.-M.; Gerdle, B.; Enthoven, P. Elaborating on the assessment of the risk of bias in prognostic studies in pain rehabilitation using QUIPS—Aspects of interrater agreement. *Diagn. Progn. Res.* **2019**, *3*, 1–11. [CrossRef]
16. Higgins, J.P.T.; Thomas, J.; Chandler, J.; Cumpston, M.; Li, T.; Page, M.J.; Welch, V.A. (Eds.) *Cochrane Handbook for Systematic Reviews of Interventions*, version 6.3 (updated February 2022); Cochrane: London, UK, 2022.
17. Foroutan, F.; Guyatt, G.; Zuk, V.; Vandvik, P.O.; Alba, A.C.; Mustafa, R.; Vernooij, R.; Arevalo-Rodriguez, I.; Munn, Z.; Roshanov, P.; et al. GRADE Guidelines 28: Use of GRADE for the assessment of evidence about prognostic factors: Rating certainty in identification of groups of patients with different absolute risks. *J. Clin. Epidemiology* **2020**, *121*, 62–70. [CrossRef]
18. Antoun, S.; Bayar, A.; Ileana, E.; Laplanche, A.; Fizazi, K.; di Palma, M.; Escudier, B.; Albiges, L.; Massard, C.; Loriot, Y. High subcutaneous adipose tissue predicts the prognosis in metastatic castration-resistant prostate cancer patients in post chemotherapy setting. *Eur. J. Cancer* **2015**, *51*, 2570–2577. [CrossRef]
19. Fischer, S.; Clements, S.; McWilliam, A.; Green, A.; Descamps, T.; Oing, C.; Gillessen, S. Influence of abiraterone and enzalutamide on body composition in patients with metastatic castration resistant prostate cancer. *Cancer Treat. Res. Commun.* **2020**, *25*, 100256. [CrossRef]
20. Ikeda, T.; Ishihara, H.; Iizuka, J.; Hashimoto, Y.; Yoshida, K.; Kakuta, Y.; Takagi, T.; Okumi, M.; Ishida, H.; Kondo, T.; et al. Prognostic impact of sarcopenia in patients with metastatic hormone-sensitive prostate cancer. *Jpn. J. Clin. Oncol.* **2020**, *50*, 933–939. [CrossRef]
21. Lee, J.; Lee, H.S.; Ha, J.S.; Han, K.S.; Rha, K.H.; Hong, S.J.; Chung, B.H.; Koo, K.C. Subcutaneous Fat Distribution is a Prognostic Biomarker for Men with Castration Resistant Prostate Cancer. *J. Urol.* **2018**, *200*, 114–120. [CrossRef]
22. Lee, J.; Park, J.S.; Heo, J.E.; Ahn, H.K.; Jang, W.S.; Ham, W.S.; Rha, K.H.; Choi, Y.D. Muscle Characteristics Obtained Using Computed Tomography as Prognosticators in Patients with Castration-Resistant Prostate Cancer. *Cancers* **2020**, *12*, 1864. [CrossRef]

23. Muñoz-Rodríguez, J.; Domínguez, A.; Rosado, M.A.; Centeno, C.; Parejo, V.; Costa-Trachsel, I.; Gallardo, E.; Bonfill, T.; García-Rojo, D.; De Verdonces, L.; et al. Efecto de la densidad muscular en pacientes con cáncer de próstata metastásico tratados con terapia de privación androgénica. *Endocrinol. Diabet. Nutr.* **2021**, *68*, 92–98. [CrossRef] [PubMed]
24. Ohtaka, A.; Aoki, H.; Nagata, M.; Kanayama, M.; Shimizu, F.; Ide, H.; Tsujimura, A.; Horie, S. Sarcopenia is a poor prognostic factor of castration-resistant prostate cancer treated with docetaxel therapy. *Prostate Int.* **2019**, *7*, 9–14. [CrossRef] [PubMed]
25. Pak, S.; Kim, M.S.; Park, E.Y.; Kim, S.H.; Lee, K.H.; Joung, J.Y. Association of Body Composition With Survival and Treatment Efficacy in Castration-Resistant Prostate Cancer. *Front. Oncol.* **2020**, *10*, 558. [CrossRef] [PubMed]
26. Stangl-Kremser, J.; Suarez-Ibarrola, R.; Andrea, D.D.; Korn, S.M.; Pones, M.; Kramer, G.; Marhold, M.; Krainer, M.; Enikeev, D.; Glybochko, P.; et al. Assessment of body composition in the advanced stage of castration-resistant prostate cancer: Special focus on sarcopenia. *Prostate Cancer Prostatic Dis.* **2020**, *23*, 309–315. [CrossRef] [PubMed]
27. Meyer, H.-J.; Wienke, A.; Surov, A. CT-defined low-skeletal muscle mass as a prognostic marker for survival in prostate cancer: A systematic review and meta-analysis. *Urol. Oncol. Semin. Orig. Investig.* **2022**, *40*, 103.e9–103.e16. [CrossRef]
28. Jahrreiss, V.; Laukhtina, E.; D'Andrea, D.; Shariat, S.F. The prognostic value of sarcopenia in patients with prostate cancer: A systematic review. *Curr. Opin. Urol.* **2021**, *31*, 315–323. [CrossRef]
29. Pamoukdjian, F.; Bouillet, T.; Lévy, V.; Soussan, M.; Zelek, L.; Paillaud, E. Prevalence and predictive value of pre-therapeutic sarcopenia in cancer patients: A systematic review. *Clin. Nutr.* **2018**, *37*, 1101–1113. [CrossRef]
30. Del Fabbro, E.; Parsons, H.; Warneke, C.L.; Pulivarthi, K.; Litton, J.K.; Dev, R.; Palla, S.L.; Brewster, A.; Bruera, E. The Relationship Between Body Composition and Response to Neoadjuvant Chemotherapy in Women with Operable Breast Cancer. *Oncologist* **2012**, *17*, 1240–1245. [CrossRef]
31. Martin, L.; Birdsell, L.; MacDonald, N.; Reiman, T.; Clandinin, M.T.; McCargar, L.J.; Murphy, R.; Ghosh, S.; Sawyer, M.B.; Baracos, V.E. Cancer Cachexia in the Age of Obesity: Skeletal Muscle Depletion Is a Powerful Prognostic Factor, Independent of Body Mass Index. *J. Clin. Oncol.* **2013**, *31*, 1539–1547. [CrossRef]
32. Shachar, S.S.; Williams, G.R.; Muss, H.B.; Nishijima, T.F. Prognostic value of sarcopenia in adults with solid tumours: A meta-analysis and systematic review. *Eur. J. Cancer* **2016**, *57*, 58–67. [CrossRef]
33. Antoun, S.; Borget, I.; Lanoy, E. Impact of sarcopenia on the prognosis and treatment toxicities in patients diagnosed with cancer. *Curr. Opin. Support. Palliat. Care* **2013**, *7*, 383–389. [CrossRef]
34. Kondrup, J. Incidence of nutritional risk and causes of inadequate nutritional care in hospitals. *Clin. Nutr.* **2002**, *21*, 461–468. [CrossRef]
35. da Silva, F.C.; da Silva, F.M.C.; Gonçalves, F.; Santos, A.; Kliment, J.; Whelan, P.; Oliver, T.; Antoniou, N.; Pastidis, S.; Queimadelos, A.M.; et al. Locally Advanced and Metastatic Prostate Cancer Treated with Intermittent Androgen Monotherapy or Maximal Androgen Blockade: Results from a Randomised Phase 3 Study by the South European Uroncological Group. *Eur. Urol.* **2014**, *66*, 232–239. [CrossRef]
36. Niraula, S.; Le, L.W.; Tannock, I.F. Treatment of Prostate Cancer with Intermittent Versus Continuous Androgen Deprivation: A Systematic Review of Randomized Trials. *J. Clin. Oncol.* **2013**, *31*, 2029–2036. [CrossRef]
37. Mottet, N.; Cornford, P.; van den Bergh, R.C.N.; Briers, E.; De Santis, M.; Gillessen, S.; Grummet, J.; Henry, A.M.; van der Kwast, T.H.; Lam, T.B.; et al. *EAU-EANM-ESTRO-ESUR-ISUP_SIOG Guidelines on Prostate Cancer*; European Association of Urology: Arnhem, The Netherlands, 2022.
38. Higano, C.; Shields, A.; Wood, N.; Brown, J.; Tangen, C. Bone mineral density in patients with prostate cancer without bone metastases treated with intermittent androgen suppression. *Urology* **2004**, *64*, 1182–1186. [CrossRef]
39. Dawson, J.K.; Dorff, T.B.; Schroeder, E.T.; Lane, C.J.; Gross, M.E.; Dieli-Conwright, C.M. Impact of resistance training on body composition and metabolic syndrome variables during androgen deprivation therapy for prostate cancer: A pilot randomized controlled trial. *BMC Cancer* **2018**, *18*, 368. [CrossRef]
40. Hanson, E.D.; Sheaff, A.K.; Sood, S.; Ma, L.; Francis, J.D.; Goldberg, A.P.; Hurley, B.F. Strength Training Induces Muscle Hypertrophy and Functional Gains in Black Prostate Cancer Patients Despite Androgen Deprivation Therapy. *J. Gerontol. Ser. A* **2013**, *68*, 490–498. [CrossRef]
41. Inglis, J.E.; Culakova, E.; Dunne, R.F.; Janelsins, M.C.; Lin, P.-J.; Mustian, K.M.; Peppone, L.J. Impact of high-dose vitamin d supplementation on short physical performance battery and bioelectrical impedance analysis in older patients with prostate cancer on ADT. *J. Clin. Oncol.* **2019**, *37*, e23106. [CrossRef]
42. Inglis, J.E.; Fernandez, I.D.; van Wijngaarden, E.; Culakova, E.; Reschke, J.E.; Kleckner, A.S.; Lin, P.-J.; Mustian, K.M.; Peppone, L.J. Effects of High-Dose Vitamin D Supplementation on Phase Angle and Physical Function in Patients with Prostate Cancer on ADT. *Nutr. Cancer* **2021**, *73*, 1882–1889. [CrossRef]
43. Kiwata, J.L.; Dorff, T.B.; Schroeder, E.T.; Salem, G.J.; Lane, C.J.; Rice, J.C.; Gross, M.E.; Dieli-Conwright, C.M. A pilot randomised controlled trial of a periodised resistance training and protein supplementation intervention in prostate cancer survivors on androgen deprivation therapy. *BMJ Open* **2017**, *7*, e016910. [CrossRef]
44. Fairman, C.M.; Kendall, K.L.; Newton, R.U.; Hart, N.H.; Taaffe, D.R.; Chee, R.; Tang, C.I.; Galvão, D.A. Examining the effects of creatine supplementation in augmenting adaptations to resistance training in patients with prostate cancer undergoing androgen deprivation therapy: A randomised, double-blind, placebo-controlled trial. *BMJ Open* **2019**, *9*, e030080. [CrossRef] [PubMed]

45. Yamamoto, D.; Maki, T.; Herningtyas, E.H.; Ms, N.I.; Ms, H.S.; Sugiyama, Y.; Bs, S.N.; Iida, K.; Iguchi, G.; Takahashi, Y.; et al. Branched-chain amino acids protect against dexamethasone-induced soleus muscle atrophy in rats. *Muscle Nerve* **2010**, *41*, 819–827. [CrossRef] [PubMed]
46. Liu, C.-J.; Latham, N.K. Progressive resistance strength training for improving physical function in older adults. *Cochrane Database Syst. Rev.* **2009**, *2009*, CD002759. [CrossRef] [PubMed]
47. Bozzetti, F. Forcing the vicious circle: Sarcopenia increases toxicity, decreases response to chemotherapy and worsens with chemotherapy. *Ann. Oncol.* **2017**, *28*, 2107–2118. [CrossRef]
48. Cushen, S.J.; Power, D.G.; Murphy, K.P.; McDermott, R.; Griffin, B.T.; Lim, M.; Daly, L.; MacEneaney, P.; Sullivan, K.O.; Prado, C.M.; et al. Impact of body composition parameters on clinical outcomes in patients with metastatic castrate-resistant prostate cancer treated with docetaxel. *Clin. Nutr. ESPEN* **2016**, *13*, e39–e45. [CrossRef]
49. Attard, G.; Merseburger, A.S.; Arlt, W.; Sternberg, C.N.; Feyerabend, S.; Berruti, A.; Joniau, S.; Géczi, L.; Lefresne, F.; Lahaye, M.; et al. Assessment of the Safety of Glucocorticoid Regimens in Combination With Abiraterone Acetate for Metastatic Castration-Resistant Prostate Cancer. *JAMA Oncol.* **2019**, *5*, 1159. [CrossRef]
50. Tombal, B.; Borre, M.; Rathenborg, P.; Werbrouck, P.; Van Poppel, H.; Heidenreich, A.; Iversen, P.; Braeckman, J.; Heracek, J.; Baron, B.; et al. Long-Term Antitumor Activity and Safety of Enzalutamide Monotherapy in Hormone Naïve Prostate Cancer: 3-Year Open Label Followup Results. *J. Urol.* **2018**, *199*, 459–464. [CrossRef]

Actas Urológicas Españolas xxx (xxxx) xxx–xxx

Actas Urológicas Españolas

www.elsevier.es/actasuro

ORIGINAL ARTICLE

Preliminary results of the implementation of robotic radical prostatectomy in a major ambulatory surgery regimen

P. de Pablos-Rodríguez[a,c,*], J.F. Suárez Novo[a], M. Castells Esteve[a], X. Bonet Puntí[a], N. Picola Brau[a], A. Abella Serra[a], E. López Picazo[a], A. Cabrera Coma[b], A. Sánchez Allueva[b], F. Vigués Julià[a]

[a] *Servicio de Urología, Hospital Universitari de Bellvitge, Barcelona, Spain*
[b] *Servicio de Anestesiología y Reanimación, Hospital Universitari de Bellvitge, Barcelona, Spain*
[c] *Escuela de Doctorado de la Universidad de Las Palmas de Gran Canaria (ULPGC), Las Palmas de Gran Canaria, Spain*

Received 15 February 2022; accepted 19 July 2022

KEYWORDS
Robotic radical prostatectomy;
Major outpatient surgery;
Ambulatory basis;
Outpatient surgery

Abstract
Objective: To report our initial experience with robotic radical prostatectomy as an outpatient procedure.
Material and Methods: Retrospective analysis of patients who underwent RRP as MAS (Major Ambulatory Surgery) at our center between March 2021 and May 2022. We collected baseline patient characteristics, intraoperative outcomes and postoperative data (need for unplanned medical care and complications at one month after surgery). Oncologic characteristics at disease diagnosis (PSA, staging, ISUP, MRI) and postoperative pathologic outcomes were collected.
Results: We identified a total of 35 patients with an average age of 60,8 ± 6,88 years and a BMI of 27 ± 2,9 Kg/m^2. All patients had a low anesthetic risk and 25.71% had undergone previous abdominal surgery. The surgical time was 151,66 ± 42,15 min and the average blood loss was 301,2 ± 184,38 mL. Two patients (5.7%) were admitted for one night and 7 patients (20%) consulted the emergency department in the following month, of which 3 (8.57%) were readmitted. We recorded one intraoperative complication, seven mild postoperative complications (Clavien I-II) and one severe complication (Clavien IIIb). The severe complication occurred on the eighth postoperative day and was not related to the procedure being ambulatory.
Conclusion: The absence of serious complications in the immediate postoperative period supports RRP in MAS as a safe technique for selected patients.

* Corresponding author.
E-mail address: pablos.rodriguez92@gmail.com (P. de Pablos-Rodríguez).

https://doi.org/10.1016/j.acuroe.2022.09.006
2173-5786/

Please cite this article as: P. de Pablos-Rodríguez, J.F. Suárez Novo, M. Castells Esteve et al., Preliminary results of the implementation of robotic radical prostatectomy in a major ambulatory surgery regimen, Actas Urológicas Españolas, https://doi.org/10.1016/j.acuroe.2022.09.006

PALABRAS CLAVE
Prostatectomía radical robótica;
Cirugía mayor ambulatoria;
Régimen ambulatorio;
Cirugía sin ingreso

Resultados preliminares de la implementación de la prostatectomía radical robótica en régimen de cirugía mayor ambulatoria

Resume

Objetivo: Reportar nuestra experiencia inicial de prostatectomía radical robótica en régimen ambulatorio.

Material y métodos: Análisis retrospectivo de los pacientes intervenidos de PRR en CMA en nuestro centro entre marzo de 2021 y mayo de 2022. Recopilamos las características basales de los pacientes, resultados intraoperatorios y datos del postoperatorio (necesidad de asistencia médica no planificada y complicaciones al mes de la cirugía). Se recogieron las características oncológicas al diagnóstico de la enfermedad (PSA, estadificación, ISUP, RMN) y el resultado anatomopatológico tras la intervención.

Resultados: Identificamos un total de 35 pacientes con una edad promedio de 60,8 ± 6,88 años y un IMC de 27 ± 2,9 Kg/m^2. Todos presentaban un riesgo anestésico bajo y un 25,71% tenía alguna cirugía abdominal previa. El tiempo quirúrgico fue de 151,66 ± 42,15 minutos y el sangrado promedio fue de 301,2 ± 184,38 mililitros. Dos pacientes (5,7%) ingresaron la primera noche de la cirugía y 7 pacientes (20%) consultaron en urgencias en el mes siguiente, de los cuales 3 (8,57%), reingresaron. Registramos una complicación intraoperatoria, siete complicaciones postoperatorias leves (Clavien I-II) y una complicación grave (Clavien IIIb). La complicación grave transcurrió al octavo día postoperatorio y no tuvo relación con la ambulatorización del procedimiento.

Conclusión: La ausencia de complicaciones graves en el postoperatorio inmediato avala la PRR en régimen de CMA como una técnica segura dirigida a pacientes seleccionados.

Introduction

Radical prostatectomy is considered one of the treatments of choice for organ-confined prostate cancer (PCa). The robotic approach has become the standard technique due to its minimally invasive nature, although there is controversy about its superiority in functional outcomes compared to the open or laparoscopic approach.[1–3] The complication and readmission rates after robotic radical prostatectomy (RRP) are below 5% with a conventional hospital stay of 24–48 hours.[4]

Advances in minimally invasive surgery and anesthetic techniques have allowed the performance of multiple surgeries on an outpatient setting. Major ambulatory surgery (MAS) has demonstrated benefits for the patient (reduced risk of nosocomial infection and thrombotic events, improved health perception) as well as for the health system (reduced costs and optimization of hospital resources).[5–7] These advantages are particularly important in the current COVID-19 pandemic.

Recently, several centers in the United States and France have published their experience with outpatient RRP, obtaining good results in terms of safety.[8–10] In the present study we show and evaluate the results of the first RRP program as MAS in our country and one of the first in Europe.

Material and methods

We retrospectively analyzed the first cases of outpatient robotic radical prostatectomy performed between March 2021 and May 2022 at our center. The protocol of RRP as MAS was designed by the urology and anesthesia departments and approved by the center's management. All the patients who were proposed to undergo surgery under MAS signed the consent for surgery and therefore approval by the ethics and clinical research committee was not required.

We collected baseline patient characteristics (age, BMI, anesthetic risk according to the ASA classification, previous abdominal surgery), intraoperative results (operative time, blood loss volume, preservation of neurovascular bundles, need for drainage) and postoperative data (time to bladder catheter removal, need for unplanned medical care, and complications one month after surgery). Oncologic characteristics at disease diagnosis (PSA, staging, ISUP, MRI) and pathologic outcome after surgery were collected.

Inclusion criteria included: age less than 70 years, BMI < 30 kg/m^2, ability to understand the MAS pathway instructions, need for a companion after surgery, availability of a cell phone, home without architectural barriers, home <100 km from the hospital, ASA < III, start of surgery before 10:00 am, low or intermediate risk PCa and prostate size <70 cubic centimeters.

Patients who were candidates for lymphadenectomy, allergic to NSAIDs or latex, with a history of COPD, epilepsy or coronary artery disease, addicted to parenteral drugs, congenital or acquired coagulation disorders, previous thrombosis or who did not meet any of the described inclusion criteria were excluded.

In previous visits, patients were offered the possibility of undergoing outpatient surgery or with conventional hospital admission. After accepting the outpatient care, signing the consent form and complying with its requirements, they were visited by a nurse from the Prostate Cancer Functional Unit (UFCaP are its initials in Spanish) who gave them instructions on the MAS process.

The surgery consisted of a transperitoneal robotic radical prostatectomy through an anterior approach using the Da Vinci X® or Xi® system, according to availability. It was performed by two surgeons with experience of more than 100 RRP, assisted by residents in training. Airway control was performed by orotracheal intubation, and intraoperative analgesia was performed with intravenous medication and local anesthesia (in the abdominal wall and in the pouch of Douglas). Pneumoperitoneum pressures were to range between 10 and 15 mmHg maximum during the entire surgery.

Table 1 Oncological characteristics of the patients.

Preoperative variables	N (%)	Mean ± SD
cT		
T1c	31 (88,6)	
T2a	4 (11,4)	
Baseline PSA, ng/dl		7,59 ± 3,09
MRI	34 (97,1)	
1 lesion	20 (57,1)	
> 1 lesion	10 (28,6)	
Size of lesion, cm*		1,34 ± 0,66
PIRADS 3	5 (14,3)	
PIRADS 4	19 (54,3)	
PIRADS 5	6 (17,1)	
Transperineal biopsy	25 (71,4)	
Fusion biopsy	25 (71,4)	
ISUP		
No. of positive cores		5,89 ± 3,52
Total cores		16,17 ± 3,4
1	2 (5,7)	
2	24 (68,6)	
3	8 (22,9)	
4	1 (2,8)	
Pathological anatomy results		
Specimen weight, grams		55,89 ± 23,43
pT		
T2	27 (77,1)	
T3	8 (22,9)	
ISUP		
1	1 (2,8)	
2	24 (68,6)	
3	10 (28,6)	

Table 2 Preoperative and intraoperative variables.

Variable	N	Mean ± SD
Age, years		60,8 ± 6,88
BMI, Kg/m^2		27 ± 2,9
ASA		
I	1 (2,8)	
II	34 (97,2)	
Previous abdominal surgery		
Yes	9 (25,7)	
No	26 (74,3)	
Prostate size, cc		47,48 ± 23,84
Surgical time, minutes		151,66 ± 42,15
Average blood loss, milliliters		301,2 ± 184,38
Preservation of neurovascular bundles*		
Left		
≥4	27 (77,1)	
<4	8 (22,9)	
Right		
≥4	30 (85,7)	
<4	5 (14,3)	
Drainage placement	1 (2,8)	
Time at the MAS recovery unit, median (range)		7 h 27 min (6 h 22 min - 10 h 20 min)

Two of the 35 patients (5.71%) remained hospitalized after surgery. One patient felt unwell due to a sense of instability at the beginning of ambulation, and was discharged the following day. On the other hand, the patient who underwent incidental bladder opening remained hospitalized at the surgeon's discretion. He presented a self-limited urinary fistula 72 h after surgery and was discharged on the fifth day without drainage.

* The preservation of the neurovascular bundles was decided by the main surgeon using a Likert-type scale in which 0 corresponds to no preservation and 5 to complete preservation.

After an observation period of less than 8 h in the MAS recovery unit, the patient's clinical stability, good pain management, absence of nausea/vomiting, tolerance of diet, ability to ambulate, and understanding of instructions and rules for further consultations were assessed. Even though they met all the criteria for hospital discharge, they were offered an overnight stay if they did not feel ready to go home. In the absence of alarm signs, no laboratory tests were performed.

The morning after hospital discharge, the UFCaP nurse contacted the patients by telephone to check their health condition and resolve any doubts they might have. In addition, they had a 24-h telephone number available in case of need. The first in-person visit was after 7 days for the removal of the catheter and wound exploration. The medical visit took place one month after surgery. Fig. 1 summarizes the information described of the perioperative process.

Results

A total of 35 patients underwent robotic radical prostatectomy as MAS. The mean age was 60,8 ± 6,88 years, the mean BMI was 27 2.9 kg/m^2, all had a low anesthetic risk (ASA I or II) and 25.71% had undergone previous abdominal surgery. Tables 1 and 2 show the oncologic and non-oncologic features of the patients, respectively.

The operative time was 151,66 ± 42,15 min, the average blood loss was 301,2 ± 184,38 mL, and all patients underwent unilateral or bilateral preservation of neurovascular bundles, at the surgeon's discretion. In one patient there was an incidental bladder opening during dissection of the posterior prostatic plane, which was identified and repaired intraoperatively. This was the only intraoperative complication in the series and was also the only patient in whom drainage was left.

Seven of the 35 patients (20%) consulted the emergency department in the month following surgery. Fig. 2 summarizes the data on unplanned medical care. Two patients attended within the first 24 postoperative hours for urine leakage around the catheter; they were discharged after verifying its proper function. One patient consulted on the 4th postoperative day for paraphimosis, which was resolved in the emergency room. One patient presented a febrile urinary tract infection after removal of the bladder catheter on the 7th postoperative day, requiring hospital admission. Two patients attended the emergency department for episodes of hematuria. The first, on the 4th day, was discharged without requiring specific treatment. The second, on the 14th postoperative day, required bladder irrigation and hospital admission. Finally, one patient was treated on the 8th postoperative day for evisceration requiring urgent surgery. No patient required blood transfusion and the evolution after complications was satisfactory in all cases. Table 3 describes the complications of the study according to the Clavien–Dindo classification and the time to their appearance.

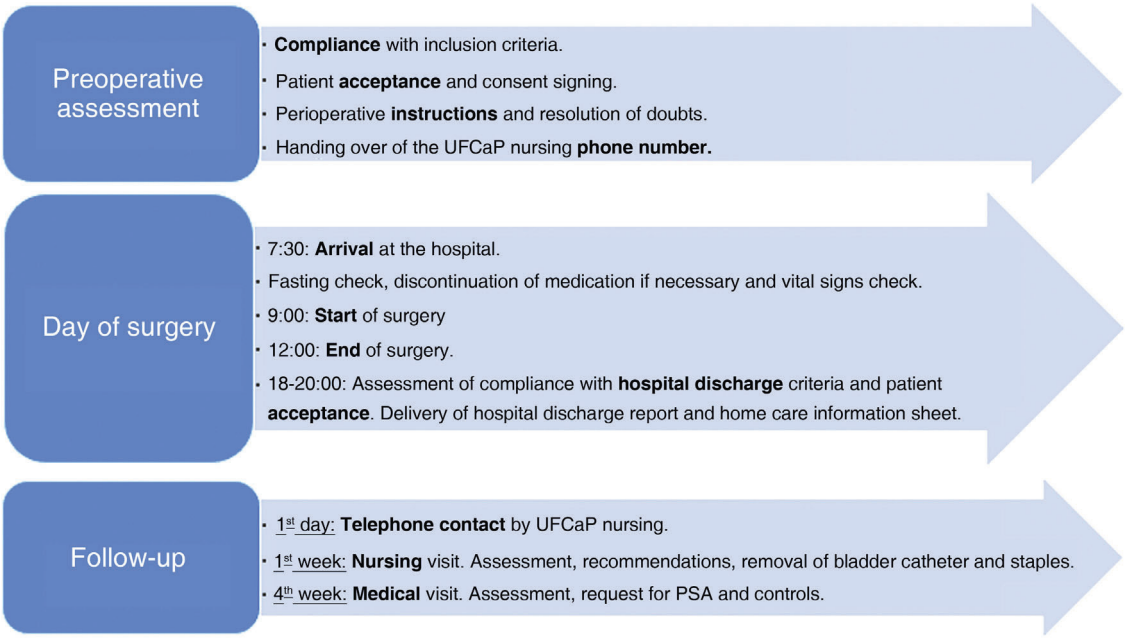


Figure 1 MAS pathway diagram.

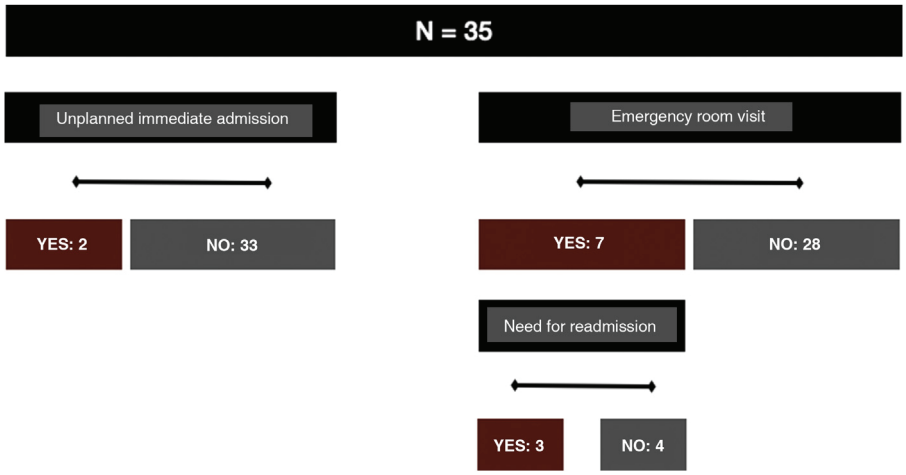


Figure 2 Unplanned medical care.

Table 3 Postoperative complications according to the Clavien-Dindo classification.

Grade	No. of patients	Description of complication	Time to complication, days
Absence of complications	27	–	–
Clavien I	5	Sense of instability	0
		Urine leakage around the catheter*	0
		Self-limited hematuria	4
		Paraphimosis	4
Clavien II	2	Hematuria requiring admission	14
		Febrile urinary tract infection	7
Clavien III	1	Evisceration	8
Clavien IV	0	–	–

Discussion

Robotic radical prostatectomy has usually required a minimum hospital stay of 24–48 h. Following the publication in 2010 of the first series of RRP as MAS,[11] several working groups have incorporated this modality into their clinical practice, showing good results in terms of safety.[8–10] Although in our series there was a serious complication on the eighth postoperative day, there was no relationship between this and the patient's outpatient status, and therefore the application of the outpatient regimen did not have a negative impact on the safety of any patient.

The incorporation of laparoscopy in prostatectomy has made it possible to integrate the proven perioperative benefits (intraoperative blood loss and postoperative recovery),[12] with the achievement of similar oncologic outcomes to open surgery[13]; there is controversy about the superiority of the technique in the functional field.[2,14] Subsequently, the globalization of robot-assisted surgery has been the second most important milestone in the development of prostatectomy. Robotic prostatectomy versus the open approach has also demonstrated a clear decrease in intraoperative blood loss and better postoperative pain management.[15] These advantages have made it possible to halve the number of days of hospital admission once the learning curve has been overcome.[16] On the other hand, the implementation of robotic surgery has led to an increase in the costs related to the surgical procedure. The MAS setting allows decreasing costs, increasing the availability of beds and human resources, and reducing the costs associated with robotic surgery. A cost analysis performed in France compared the costs of outpatient versus conventional admission procedures.[10] Although the inpatient group had a short hospital stay, with an average of 1.6 days, the authors described a 10.8% reduction in costs per ambulatory patient, €2,550 versus €2,860. If we extrapolate these data to the average of 100 RRPs performed annually in our center, we would obtain an annual saving of €31,000. In addition, the accelerated recovery of the patient at home allows his or her early return to work, thus producing indirect, hardly tangible economic benefits.

In our series we decided to exclude patients who were candidates for lymphadenectomy (LND) because of their potentially longer operative time and higher postoperative risk. In the literature we have both groups that have followed this precaution,[6,17] and others that have incorporated it. Abaza et al., with 246 patients, have the longest single-center series of RRP as MAS to date.[8] In their work they performed LND on all their patients with a mean of eight nodes removed and describe a complication rate of 4.4% and unscheduled medical care of 4.9%. Although these results support the safety of including LND in the MAS setting, a recent systematic review associated the extent of LND with worsening intraoperative and postoperative outcomes, including hospital stay.[18] Other groups have also associated the performance of LND as a predictor of ambulatory surgery failure.[19] For this reason, we obviated patients who were candidates for LND at the start of this protocol.

The inclusion of new surgeries, such as prostatectomy, to the MAS regimen should not affect patient safety. Collection, analysis and publication of results are required to ensure compatibility of both processes. In our initial experience, no serious complication that compromised patient safety occurred in the first 48 postoperative hours. We believe that the monitoring and recovery time established in the outpatient regimen is sufficient to predict or act in cases of life-threatening emergencies. In a retrospective study of 7,126 radical prostatectomies, a percentage of medical-surgical complications requiring immediate care was less than 1%. However, the time to onset of the complication was not specified.[20]

Among the main quality indicators of MAS are the need for unplanned immediate admission (the same night of surgery), the need for emergency department consultation and hospital readmission in the month following surgery.[21] In our experience, there was 5.71% of unplanned overnight stay, 20% of emergency room visits and 8.57% of hospital readmission in the month following surgery. In Table 4 we contrast these results with those obtained by the main series published in the literature.

The need for immediate unplanned admission paradoxically produces what the outpatient regimen tries to avoid. It involves the unforeseen search for beds and health personnel and has a negative impact on patient satisfaction. The literature reveals percentages below 5%.[23,24] Among the most frequent causes of admission are due to social/logistic, surgical and, to a lesser extent, anesthesia-related factors. In our series, two patients (5.7%) required immediate admission. One patient declined discharge due to sense of instability and a second was admitted at the surgeon's discretion.

Seven of the 35 patients visited the emergency department in the month following surgery. Table 3 shows the postoperative complications and the time to their appearance. Two of the seven visits to the emergency department occurred on the first postoperative day and, in both cases, the reason for the visit was urine leakage around the bladder catheter. The Ministry of Health, in its guide of standards and recommendations for MAS, subdivides postoperative visits to the emergency department into two groups: those occurring within the first 24 h and those occurring between 24 h and 28 days.[21] In our results, we consider that the visits that most penalize the MAS regimen were those produced in the first 24 h, due to their direct relationship with the ambulatory procedure, even in the case of mild complications (Clavien I). The rest of the complications that occurred after the first postoperative day are related to the surgical procedure and would probably have occurred in the same way in the inpatient setting.

The correct training of the patient and accompanying persons is also considered an important indicator of the quality of the ambulatory procedure[25] and could possibly have avoided the visit to the emergency department of patients with urine leakage around the catheter. The incorporation of technological advances in information systems will improve understanding of the perioperative process and increase patient satisfaction.[26,27]

One of the criticisms of MAS is the belief that the economic benefits it produces are detrimental to patient satisfaction. In this regard, Ploussard et al. describe a 100% satisfaction rate and 92% pain management prior to being discharged home.[10] In another study, satisfaction information was collected from 214 questionnaires of patients who underwent RRP surgery with conventional hospital admission.[28] Early mobilization and early return to work were the two main priorities requested by the patients. In addition, 97.6% of patients reported adequate postoperative pain control.

On the contrary, Dobbs et al., in a cohort of prostatectomies with hospital admission, distributed a questionnaire in the postoperative period asking if they wanted a same-day discharge, obtaining a negative response in 68.4% of the cases.[29] The most frequent reasons for not considering themselves ready for discharge were pain (55.9%) and discomfort from the catheter (44.7%). In this center, five prostatectomies are performed daily and, as previously discussed,[8] late surgery and discharge are factors that have a negative impact on the outpatient regimen, which is why we considered excluding those prostatectomies that begin after 10:00 am.

Among the limitations of the study is the absence of a control group. This characteristic prevents the comparison of complications and unforeseen medical care in the present study. On the other hand, we did not collect information on patient satisfaction. We have begun to collect this variable prospectively with a control group and hope that it can elucidate the patient's perception of outpatient prostatectomy.

This is the publication of the first series of cases of robotic radical prostatectomy under the MAS regimen in our country and one of the first in Europe. We describe an unplanned immediate admission rate of 5.71%, and emergency department visits and 30-day hospital readmission rates of 20% and 8.57%, respectively.

Table 4 Comparison of results between different series.

Year of publication, Main author	Country	No	Age, mean, years	Average BMI, Kg/m^2	ERAS, %	Average surgical time, minutes	Average intraoperative bleeding, ml	Drainage, %	Average prostate weight, grams	Lymphadenectomy, %	Unplanned medical care, %		Complication, %	
											Unforeseen immediate admission	Unforeseen medical visit	Mild (Clavien I-II)	Severe (III-IV)
2019, Bajpai* [6]	USA	100	63,3	25,6	100	75,6 (console)	68	NA	50,7	0	8	4	4	0
2019, Abaza** [8]	USA	246	61,2	28,8	0	159	131	0	NA	100	0,4	4,5	3,6	0,8
2019, Thomas[22]	France	32	65	25,7	0	120 (console)	200	87,5	NA	72	6,25	30	26,7	3,3
2020, Ploussard[19]	France	358	64,7	25,6	100	147,5	228	NA	48	43	4,2	2,8	15,4	1,5
2022, Suárez	Spain	35	60,8	27	0	151,7	301	2,8	55,9	0	5,71	20	20	2,9

NA, Not available.
* The percentages of unplanned visits and complications are in a 7-day period.
** The percentages of unplanned visits and complications are in a 90-day period.

Experience in surgical technique, an adequate outpatient surgery pathway and the nursing support of the UFCaP were essential elements in a setting as presumably demanding as RRP in MAS.

Conclusion

The absence of serious complications in the immediate postoperative period supports RRP in the MAS regimen as a safe technique aimed at selected patients. The collection of a larger number of cases, the addition of a control group and the analysis of satisfaction data will allow us to detect the patient profile that most benefits from this regimen.

Conflict of interest

The authors declare that they have no conflict of interest

References

1. Coughlin GD, Yaxley JW, Chambers SK, Occhipinti S, Samaratunga H, Zajdlewicz L, et al. Robot-assisted laparoscopic prostatectomy versus open radical retropubic prostatectomy: 24-month outcomes from a randomised controlled study. Lancet Oncol. 2018;19(8):1051–60.
2. Ilic D, Evans SM, Allan CA, Jung JH, Murphy D, Frydenberg M. Laparoscopic and robotic-assisted versus open radical prostatectomy for the treatment of localised prostate cancer. Cochrane Database Sys Rev. 2017;9(9):CD009625.
3. Du Y, Long Q, Guan B, Mu L, Tian J, Jiang Y, et al. Robot-assisted radical prostatectomy is more beneficial for prostate cancer patients: a system review and meta-analysis. Med Sci Monit. 2018;24:272–87.
4. Xia L, Taylor BL, Pulido JE, Mucksavage P, Lee DI, Guzzo TJ. Predischarge predictors of readmissions and postdischarge complications in robot-assisted radical prostatectomy. J Endourol. 2017;31(9):864–71.
5. Wang L, Baser O, Wells P, Peacock WF, Coleman CI, Fermann GJ, et al. Benefit of early discharge among patients with low-risk pulmonary embolism. PloS One. 2017;12(10):e0185022.
6. Bajpai RR, Razdan S, Barack J, Sanchez MA, Razdan S. Ambulatory robot-assisted laparoscopic prostatectomy: is it ready for prime time? A quality-of-life analysis. J Endourol. 2019;33(10):814–22.
7. Vergara F, Freitas Ramírez A, Gispert R, Coll J, Saltó E, Trilla A. Evolución de la cirugía mayor ambulatoria en Cataluña, 2001-2011. Gaceta Sanitaria. 2015;29(6):451–3.
8. Abaza R, Martinez O, Ferroni MC, Bsatee A, Gerhard RS. Same day discharge after robotic radical prostatectomy. J Urol. 2019;202(5):959–63.
9. Khalil MI, Bhandari NR, Payakachat N, Davis R, Raheem OA, Kamel MH. Perioperative mortality and morbidity of outpatient versus inpatient robot-assisted radical prostatectomy: a propensity matched analysis. Urol Oncol. 2020;38:3, e1-6.
10. Ploussard G, Almeras C, Beauval JB, Gautier JR, Loison G, Salin A, et al. Same-day discharge surgery for robot-assisted radical prostatectomy in the era of ERAS and prehabilitation pathways: a contemporary, comparative, feasibility study. World J Urol. 2020;40:1359–65, http://dx.doi.org/10.1007/s00345-020-03119-w.
11. Martin AD, Nunez RN, Andrews JR, Martin GL, Andrews PE, Castle EP. Outpatient prostatectomy: too much too soon or just what the patient ordered. Urology. 2010;75:421–4.
12. Guazzoni G, Cestari A, Naspro R, Riva M, Centemero A, Zanoni M, et al. Intra- and peri-operative outcomes comparing radical retropubic and laparoscopic

radical prostatectomy: results from a prospective, randomised, single-surgeon study. Eur Urol. 2006;50(1):98–104, http://dx.doi.org/10.1016/j.eururo.2006.02.051.
13. Martínez-Holguín E, Herranz-Amo F, Mayor de Castro J, Polanco-Pujol L, Hernández-Cavieres J, Subirá-Ríos D, et al. Comparison between laparoscopic and open prostatectomy: Oncological progression analysis. Actas Urol Esp (Engl Ed). 2021;45:139–45, http://dx.doi.org/10.1016/j.acuro.2020.09.008. PMID: 33160757.
14. Martínez-Holguín E, Herranz-Amo F, Lledó-García E, Ruiz-Bel J, Esteban-Labrador L, Subirá-Ríos D, et al. Comparison between laparoscopic and open prostatectomy: Postoperative urinary continence analysis. Actas Urol Esp (Engl Ed). 2020;44(8):535–41, http://dx.doi.org/10.1016/j.acuro.2019.10.002. PMID: 32151470.
15. Coughlin GD, Yaxley JW, Chambers SK, Occhipinti S, Samaratunga H, Zajdlewicz L, et al. Robot-assisted laparoscopic prostatectomy versus open radical retropubic prostatectomy: 24-month outcomes from a randomised controlled study. Lancet Oncol. 2018;19(8):1051–60.
16. Carlo FD, Celestino F, Verri C, Masedu F, Liberati E, Stasi SMD. Retropubic, laparoscopic, and robot-assisted radical prostatectomy: surgical, oncological, and functional outcomes: a systematic review. Urol Int. 2014;93:373–83.
17. Banapour P, Elliott P, Jabaji R, Parekh A, Pathak A, Merchant M, et al. Safety and feasibility of outpatient robot-assisted radical prostatectomy. J Robot Surg. 2019;13:261–5.
18. Fossati N, Willemse PM, Van den Broeck T, van den Bergh RCN, Yuan CY, Briers E, et al. The benefits and harms of different extents of lymph node dissection during radical prostatectomy for prostate cancer: a systematic review. Eur Urol. 2017;72(1):84–109.
19. Ploussard G, Dumonceau O, Thomas L, Benamran D, Parra J, Vaessen C, et al. Multi-institutional assessment of routine same day discharge surgery for robot-assisted radical prostatectomy. J Urol. 2020;204(5):956–61.
20. Pierorazio PM, Mullins JK, Ross AE, Hyams ES, Partin AW, Han M, et al. Trends in immediate perioperative morbidity and delay in discharge after open and minimally invasive radical prostatectomy (RP): a 20-year institutional experience. BJU Int. 2013;112:45.
21. Ministerio de Sanidad y Consumo. Estándares y recomendaciones. Unidad de Cirugía Mayor Ambulatoria. Madrid: Ministerio de Sanidad y Consumo; 2008.
22. Thomas L, Lacarriere E, Martinache G, Martinache PR. Expérience de la prostatectomie totale robot-assistée ambulatoire. À propos de 32 cas [Experience of day case robotic prostatectomy. About thirty-two patients]. Prog Urol. 2019;29(12):619–26.
23. Van Caelenberg E, De Regge M, Eeckloo K, Coppens M. Analysis of failed discharge after ambulatory surgery: unanticipated admission. Acta Chir Belg. 2019;119(3):139–45.
24. Whippey A, Kostandoff G, Paul J, Ma J, Thabane L, Ma HK. Predictors of unanticipated admission following ambulatory surgery: a retrospective case-control study. Can J Anaesth. 2013;60(7):675–83.
25. Nunes JS, Gomes R, Povo A, Alves EC. Quality indicators in ambulatory surgery: a literature review comparing portuguese and international systems. Acta Med Port. 2018;31(7–8):425–30.
26. Huber J, Ihrig A, Yass M, Bruckner T, Peters T, Huber CG, et al. Multimedia support for improving preoperative patient education: a randomized controlled trial using the example of radical prostatectomy. Ann Surg Oncol. 2013;20(1):15–23.
27. Heller L, Parker PA, Youssef A, Miller MJ. Interactive digital education aid in breast reconstruction. Plast Reconstr Surg. 2008;122(3):717–24.
28. Reynolds BR, Bulsara C, Zeps N, Codde J, Lawrentschuk N, Bolton D, et al. Exploring pathways towards improving patient experience of robot-assisted radical prostatectomy (RARP): assessing patient satisfaction and attitudes. BJU Int. 2018;121:33–9.
29. Dobbs RW, Nguyen TT, Shahait M, Lee DJ, Kim JL, El-Fahmawi A, et al. Outpatient robot-assisted radical prostatectomy: are patients ready for same-day discharge? J Endourol. 2020;34(4):450–5.