UNIWERSYTET MEDYCZNY
IM. PIASTÓW ŚLĄSKICH WE WROCŁAWIU

Rozprawa doktorska

Ocena wartości klinicznej limfoangioinwazji w raku gruczołu krokowego u chorych poddanych radykalnej prostatektomii

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SPIS TREŚCI:

1. Wykaz publikacji stanowiących rozprawę doktorską

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2. Wykaz stosowanych skrótów

AJCC	Amerykański Wspólny Komitet ds. Raka (ang. *the American Joint Committee on Cancer*)
AS	aktywny nadzór (ang. *active surveillance*)
BCR	wznowa biochemiczna (ang. *biochemical recurrence*)
BMI	wskaźnik masy ciała (ang. *body mass index*)
CI	przedział ufności (ang. *confidence interval*)
cT	kliniczne stadium zaawansowania (ang. *clinical tumor stage*)
DRE	badanie *per rectum* (ang. *digital rectal examination*)
EAU	Europejskie Towarzystwo Urologiczne (ang. *The European Association of Urology*)
ECE	naciek pozatorebkowy (ang. *extracapsular extension*)
EGFR	receptor nabłonkowego czynnika wzrostu (ang. *epidermal growth factor receptor*)
ePLND	rozszerzona limfadenektomia w obrębie miednicy mniejszej (ang. *extended pelvic lymph node dissection*)
GGG	grupa złośliwości histologicznej Gleasona (ang. *Gleason grading group*)
GS	stopień zaawansowania patomorfologicznego w skali Gleasona (ang. *Gleason score*)
H&E	barwienie hematoksyliną i eozyną (ang. *hematoxylin-eosin stain*)
IQR	zakres międzykwartylowy (ang. *interquartile range*)
ISUP	Międzynarodowe Towarzystwo Patologii Urologicznej (ang. *The International Society of Urological Pathology*)
LNI	przerzuty do węzłów chłonnych (ang. *lymph node invasion*)
LVI	limfoangioinwazja (ang. *lymphovascular invasion*)
MD	różnica średnich (ang. *mean difference*)
mpMRI	wieloparametryczny rezonans magnetyczny (ang. *multiparametric magnetic resonance imaging*)
NOS	skala Newcastle–Ottawa (ang. *Newcastle–Ottawa scale*)
OR	iloraz szans (ang. *odds ratio*)
PCa	rak prostaty (ang. *prostate cancer*)
PDPN	podoplanina (ang. *podoplanin*)
PET	pozytonowa tomografia emisyjna (ang. *positron emission tomography*)

PIRADS	system raportowania i danych obrazowania prostaty (ang. *Prostate Imaging Reporting and Data System*)
pN	przerzuty do węzłów chłonnych (ang. *pathologic nodal stage*)
PNI	naciekanie okołonerwowe (ang. *perineural invasion*)
PPBC	odsetek pozytywnych bioptatów (ang. *percent of positive biopsy cores*)
PRISMA	deklaracja zawierająca zestaw elementów niezbędnych do prawidłowego raportowania przeglądów systematycznych i meta-analiz (ang. *Preferred Reporting Items for Systematic Reviews and Meta-Analyses*)
PSA	swoisty antygen sterczowy (ang. *prostate-specific antigen*)
PSAD	gęstość PSA (ang. *prostate-specific antigen density*)
PSCA	antygen komórek macierzystych stercza (ang. *prostate stem cell antigen*)
PSM	dodatni margines chirurgiczny (ang. *positive surgical margin*)
PSMA	antygen błony komórek stercza (ang. *prostate-specific membrane antigen*)
pT	patologiczne stadium zaawansowania (ang. *pathologic tumor stage*)
RDW-SD	rozpiętość rozkładu objętości czerwonych krwinek (ang. *red blood cell distribution width-standard deviation*)
RP	prostatektomia radykalna (ang. *radical prostatectomy*)
SD	odchylenie standardowe (ang. *standard deviation*)

3. Streszczenie w języku polskim

Rak prostaty (*prostate cancer*, PCa) jest jednym z najczęściej występujących nowotworów u mężczyzn na świecie, diagnozowanym u ponad miliona pacjentów rocznie. Mimo że rozwój choroby bywa powolny, a pacjenci często są diagnozowani w późnym wieku, PCa może mieć zróżnicowany przebieg. Limfoangioinwazja (*lymphovascular invasion*, LVI), definiowana jako jednoznaczna (ang. *unequivocal*) obecność komórek nowotworowych w wyścielonych nabłonkiem przestrzeniach naczyniowych, stanowi istotny czynnik prognostyczny wskazujący na agresywniejszy przebieg choroby i zwiększone ryzyko wznowy biochemicznej oraz przerzutów. Może to istotnie wpływać na skuteczność kliniczną dostępnych opcji terapeutycznych. W ramach rozprawy doktorskiej obejmującej cykl trzech publikacji przeanalizowano wartość kliniczną LVI u pacjentów poddanych radykalnej prostatektomii (*radical prostatectomy*, RP), w celu wykrycia przedoperacyjnych czynników ryzyka wystąpienia LVI w pooperacyjnym badaniu histopatologicznym, ewaluacji powiązanych pooperacyjnych czynników ryzyka oraz oceny zjawiska lateralizacji LVI w kontekście przerzutów do węzłów chłonnych.

W badaniach wykorzystano retrospektywne dane pacjentów poddanych RP, w tym informacje demograficzne, wyniki badań laboratoryjnych i obrazowych, a także biopsji gruczołu krokowego. Wieloletnia obserwacja pacjentów (ang. *follow-up*) pozwoliła na zgromadzenie informacji dotyczących pooperacyjnego przebiegu choroby. Preparaty histopatologiczne utrwalano w buforowanej formalinie i zatapiano w parafinie. Za pomocą mikrotomu wykonywano przekroje tkanek, które następnie barwiono hematoksyliną i eozyną (H&E). Materiał histopatologiczny był oceniany przez doświadczonych uropatologów, którzy stosowali wystandaryzowany system raportowania. Ocena obejmowała również analizę obecności oraz lateralizacji LVI. W przypadkach wątpliwości diagnostycznych przeprowadzano barwienie podoplaniną. Analizy statystyczne umożliwiły ustalenie istotnych predyktorów oraz pooperacyjnych następstw związanych z LVI. Ponadto, przegląd systematyczny z metaanalizą pozwolił zidentyfikować dostępne w literaturze czynniki przedoperacyjne predysponujące do wystąpienia LVI w ostatecznym badaniu histopatologicznym.

Badania potwierdzają kluczową rolę LVI w ocenie ryzyka i agresywności PCa. Przegląd systematyczny z metaanalizą potwierdził, że poziom swoistego antygenu sterczowego (*prostate-specific antigen*, PSA), kliniczne stadium T oraz wynik w skali Gleasona z biopsji stercza stanowią najsilniejsze przedoperacyjne predyktory LVI u pacjentów z PCa.

W przeciwieństwie do nich objętość gruczołu krokowego, wskaźnik masy ciała i wiek nie wykazały istotnej korelacji z LVI. Wiele czynników przedoperacyjnych wykrytych za pomocą systematycznego przeglądu literatury korelowało z LVI w końcowym badaniu histopatologicznym, potwierdzając ich istotność w prognozowaniu ryzyka. W drugiej publikacji wykazano, że jednostronna LVI koreluje z jednostronnym zajęciem węzłów chłonnych u pacjentów z PCa z przerzutami do węzłów chłonnych (pN+), zwłaszcza w przypadku LVI po prawej stronie. Z kolei LVI po lewej stronie jest związana z wyższymi stadiami klinicznymi pT i wyższym odsetkiem przypadków obustronnego zajęcia węzłów chłonnych. Ostatnia publikacja podkreśla kluczową rolę LVI w prognozowaniu raka prostaty. Badanie to po raz pierwszy, według najlepszej wiedzy autorów, wykazało związek między LVI a liczbą zajętych węzłów chłonnych u pacjentów pN+. Wyższy wynik w skali Gleasona, stadium kliniczne T3-4 określone za pomocą rezonansu magnetycznego, wyższy przedoperacyjny poziom PSA i odsetek zajętych bioptatów przekraczający 50% to najsilniejsze predyktory wystąpienia LVI. Wyniki badań podkreślają znaczenie uwzględniania LVI w ocenie ryzyka u pacjentów z PCa oraz mogą przyczynić się do reewaluacji strategii terapeutycznych, mając na celu optymalizację leczenia i wydłużenie przeżycia pacjentów z PCa.

4. Streszczenie w języku angielskim

Prostate cancer (PCa) is one of the most common cancers in men worldwide, diagnosed in over a million patients annually. Despite the slow progression of the disease, and often late diagnosis, PCa can have a varied course. Lymphovascular invasion (LVI), defined as the unequivocal presence of cancer cells within endothelial-lined vascular spaces, is an important prognostic factor indicating a more aggressive disease course and an increased risk of biochemical recurrence and metastasis. This can significantly impact the clinical effectiveness of available therapeutic options.

In this doctoral dissertation, which includes a series of three publications, the clinical value of LVI in patients undergoing radical prostatectomy (RP) was analyzed to identify preoperative risk factors for LVI in postoperative histopathology, evaluate associated postoperative risk factors, and assess the phenomenon of LVI lateralization in the context of lymph node metastasis.

The studies used retrospective data from patients who underwent RP, including demographic information, laboratory and imaging results, as well as prostate biopsy data. Long-term patient follow-up provided information on the postoperative course of the disease. Histopathological samples were fixed in buffered formalin and embedded in paraffin. Tissue sections were made with a microtome and then stained with hematoxylin and eosin (H&E). Histopathology was assessed by experienced uropathologists who used a standardized reporting system. The evaluation also included the analysis of the presence and lateralization of LVI. In cases of diagnostic uncertainty, podoplanin staining was performed. Statistical analyses allowed for the identification of significant predictors and postoperative outcomes related to LVI. Additionally, a systematic review with a meta-analysis identified preoperative factors in the literature predisposing to LVI in final histopathology.

Research confirms the key role of LVI in assessing the risk and aggressiveness of PCa. A systematic review with a meta-analysis confirmed that prostate-specific antigen (PSA) levels, clinical T stage, and Gleason score from prostate biopsy are the strongest preoperative predictors of LVI in PCa patients. In contrast, prostate volume, body mass index, and age showed no significant correlation with LVI. Many preoperative factors identified through a systematic review of the literature correlated with LVI in final histopathology, confirming their importance in risk prognosis. The second publication demonstrated that unilateral LVI correlates with unilateral lymph node involvement in PCa patients with lymph node metastases (pN+), particularly in cases of right-sided LVI. In contrast, left-sided LVI is associated with

higher clinical pT stages and a higher proportion of bilateral lymph node involvement cases. The final publication emphasizes the crucial role of LVI in predicting prostate cancer prognosis. This study was the first, to the best of the authors' knowledge, to reveal the association between LVI and the number of affected lymph nodes in pN+ patients. A higher Gleason score, clinical T3-4 stage defined by magnetic resonance imaging, higher preoperative PSA level, and a percentage of positive biopsy cores exceeding 50% are the strongest predictors of LVI. The results highlight the importance of considering LVI in assessing the risk in PCa patients and may contribute to the reevaluation of therapeutic strategies, aiming to optimize treatment and extend survival in PCa patients.

5. Wprowadzenie do rozprawy doktorskiej

Rak gruczołu krokowego jest najczęstszym nowotworem złośliwym diagnozowanym u mężczyzn i drugą główną przyczyną zgonów z powodu nowotworów w tej grupie na świecie[1]. W Polsce, podobnie jak w innych krajach rozwiniętych, regularnie obserwuje się wzrost zachorowalności[2]. Jest to związane zarówno ze starzeniem się populacji, jak i poprawą metod diagnostycznych, które umożliwiają wykrywanie choroby na coraz wcześniejszym etapie. Do kluczowych postępów w diagnostyce raka prostaty zaliczyć można między innymi wprowadzenie wieloparametrycznego rezonansu magnetycznego (mpMRI, *multiparametric magnetic resonance imaging*), biopsji celowanej stercza, pozytonowej tomografii emisyjnej (PET, *positron emission tomography*) oraz wykorzystywanie ligandu antygenu błony komórek stercza (PSMA, *prostate-specific membrane antigen*), które znacząco zwiększyły precyzję rozpoznawania oraz możliwość wczesnego wykrywania tej choroby[3].

W leczeniu zlokalizowanego raka prostaty kluczową rolę odgrywa radykalna prostatektomia. Jest to procedura polegająca na całkowitym usunięciu gruczołu krokowego oraz, w zależności od zaawansowania choroby, węzłów chłonnych miednicy. Prostatektomia radykalna nie tylko eliminuje źródło nowotworu, ale także umożliwia szczegółowe badanie histopatologiczne, dostarczające cennych informacji prognostycznych, które są niezbędne do spersonalizowanego podejścia terapeutycznego po operacji.

Jednym z parametrów ocenianych podczas badania histopatologicznego jest limfoangioinwazja (*lymphovascular invasion*, LVI), która jest definiowana jako jednoznaczna (ang. *unequivocal*) obecność komórek nowotworowych w wyścielonych śródbłonkiem przestrzeniach naczyniowych, które nie posiadają podścieliska mięśniowego[4], lub jako obecność zatorów nowotworowych (ang. *tumor emboli*) w małych naczyniach wewnątrzgruczołowych[5–7]. LVI, określana również mianem inwazji mikronaczyniowej[8–10], jest identyfikowana za pomocą standardowego barwienia H&E. W przypadkach wątpliwych, stosuje się dodatkowe barwienie immunohistochemiczne podoplaniną (PDPN, D2-40), glikoproteiną umożliwiającą identyfikację naczyń limfatycznych[11]. Technika ta pozwala na odróżnienie inwazji nowotworowej w naczyniach żylnych od inwazji w naczyniach limfatycznych, co jest istotne w kontekście bieżących badań naukowych[12,13].

LVI jest uznawana za czynnik prognostyczny predysponujący do bardziej agresywnego przebiegu nowotworu i zwiększonego ryzyka jego progresji, co może mieć kluczowe znaczenie dla dalszego postępowania terapeutycznego, w tym decyzji o zastosowaniu terapii adjuwantowej[14–17]. Choć wartość prognostyczna LVI jest już dobrze udokumentowana

w badaniach na preparatach pooperacyjnych, możliwe i istotne jest także jej wykrywanie w materiale z biopsji gruczołu krokowego[18,19].

Europejskie Towarzystwo Urologiczne (EAU, *The European Association of Urology*) w swoich wytycznych podkreśla, że obecność LVI w materiale z biopsji powinna skłonić do rezygnacji z aktywnego nadzoru (AS, *active surveillance*) i wdrożenia leczenia radykalnego[20]. Jednakże, mimo że LVI jest uznawane za istotny pooperacyjny czynnik ryzyka, nie ma wyraźnych wskazań, jak obecność LVI powinna wpływać na dalsze postępowanie po radykalnej prostatektomii.

Badania potwierdzają, że LVI jest indywidualnym czynnikiem ryzyka w raku prostaty, niezależnie od innych tradycyjnych czynników, takich jak wysoki poziom swoistego antygenu sterczowego (PSA, *prostate-specific antigen*), zaawansowanie kliniczne (pT, *pathologic tumor stage*) czy stopień zaawansowania patomorfologicznego według skali Gleasona (GS, *Gleason score*)[21–32]. W ostatnich latach przeprowadzono liczne badania koncentrujące się na roli LVI jako markera prognostycznego w raku stercza. Wyniki tych badań bywają sprzeczne lub niejednoznaczne, jednakże LVI często koreluje z wznową biochemiczną (BCR, *biochemical recurrence*), gorszymi parametrami przeżyciowymi, a także przerzutami do węzłów chłonnych oraz rozsiewem ogólnym raka prostaty[33–40].

LVI może stanowić istotne ogniwo pomiędzy lokalnie zaawansowaną chorobą a przerzutami do węzłów chłonnych. Zależność LVI oraz inwazji nowotworu na węzły chłonne odgrywa szczególną rolę w badaniach naukowych ostatnich lat ze względu na możliwość eskalacji prostatektomii radykalnej o wykonanie rozszerzonej limfadenektomii w obrębie miednicy mniejszej (ePLND, *extended pelvic lymph node dissection*). Badania sugerują jednak, że limfadenektomia, choć stanowi złoty standard w ocenie zajęcia węzłów chłonnych w raku prostaty, nie wpływa na parametry przeżyciowe pacjentów i może zwiększać ryzyko powikłań śród- i pooperacyjnych[41]. Z tego powodu, coraz więcej głosów odnosi się do możliwości wykonania limfadenektomii jednostronnej, ipsilateralnie ograniczonej do węzłów chłonnych po stronie ogniska nowotworu w sterczu[42]. LVI jest parametrem, który może być oceniany lateralnie, indywidualnie w lewym i prawym płacie gruczołu krokowego. Znaczenie zjawiska lateralizacji LVI w kontekście wpływu na jednostronną inwazję węzłową, pozostaje niezbadane.

6. Cel badań

Celem głównym mojej rozprawy doktorskiej jest szczegółowa ocena klinicznej wartości LVI jako niezależnego czynnika ryzyka u pacjentów po RP. Przyjęte założenia szczegółowe mają na celu dogłębne zrozumienie wpływu LVI na postępowanie kliniczne oraz wyniki leczenia PCa.

1. **Identyfikacja przedoperacyjnych czynników ryzyka limfoangioinwazji**. Przeprowadzony przegląd systematyczny oraz metaanaliza dostępnych danych pozwoliły na identyfikację oraz ilościową i jakościową analizę kluczowych przedoperacyjnych czynników ryzyka LVI wykrytej w pooperacyjnym badaniu histopatologicznym. Dodatkowo, przeprowadzone badanie retrospektywne miało na celu identyfikację tych parametrów w kontekście klinicznym.
2. **Analiza związku między lateralizacją limfoangioinwazji i przerzutów do węzłów chłonnych**. Celem tego punktu jest określenie, czy istnieje statystycznie istotna korelacja między lokalizacją LVI a stroną występowania przerzutów do węzłów chłonnych. Wyniki tej analizy mogą mieć znaczenie dla planowania zakresu limfadenektomii wykonywanej podczas RP.
3. **Ocena pooperacyjnych implikacji limfoangioinwazji**. Celem jest ocena skutków wystąpienia LVI w pooperacyjnym badaniu histopatologicznym, obejmująca analizę wyników badań obrazowych i laboratoryjnych. Poznanie tych zależności może w przyszłości umożliwić dokładniejszą stratyfikację ryzyka u pacjentów po RP oraz bardziej efektywne planowanie leczenia drugiej linii, co z kolei przyczyni się do optymalizacji wyników onkologicznych.
4. **Wyjaśnienie relacji między najistotniejszymi czynnikami ryzyka a przerzutami do węzłów chłonnych.** Analiza związku LVI oraz klasycznych czynników ryzyka (m.in. stopień w skali Gleasona, stadium zaawansowania klinicznego) z przerzutami do węzłów chłonnych. Wyniki tej analizy mogą mieć znaczenie dla prognozowania wyników leczenia i wpłynąć na przyszłe strategie diagnostyczno-terapeutyczne.

7. Materiały i metody

W niniejszym rozdziale zaprezentowano zarys metodologii przeprowadzonych badań. Szczegółowy opis zawarty jest w załączonych publikacjach.

W **Publikacji 1** dokonano przeglądu systematycznego dostępnej literatury na temat przedoperacyjnych czynników ryzyka wystąpienia LVI u pacjentów z rakiem prostaty poddanych radykalnej prostatektomii. Przegląd systematyczny został w dalszej kolejności uzupełniony metaanalizą. Przeprowadzono systematyczny przegląd literatury w trzech bazach danych: PubMed, Embase i Web of Science. Ponadto, ręcznie przeszukano bibliografie istotnych artykułów przeglądowych, aby upewnić się, że nie pominięto żadnych istotnych artykułów.

Procedura oceny zidentyfikowanych podczas wyszukiwania literatury była zgodna z kryteriami PRISMA (*Preferred Reporting Items for Systematic Reviews and Meta-Analyses*)[43], a protokół badania został zarejestrowany w międzynarodowym rejestrze systematycznych przeglądów PROSPERO pod numerem CRD42023389021. Artykuły oceniano pod kątem włączenia, korzystając z modelu PICO (*population, intervention, comparison, outcome*)[44]:

- Populacja: pacjenci z rakiem gruczołu krokowego, którzy przeszli radykalną prostatektomię.
- Interwencja: prostatektomia radykalna i pooperacyjne badanie histopatologiczne; wykrycie LVI w badanych preparatach pooperacyjnych.
- Komparator: pacjenci bez cech LVI w końcowym badaniu histopatologicznym.
- Wynik: korelacja przedoperacyjnych czynników kliniczno-patologicznych z LVI w preparacie pooperacyjnym.

Jakość włączonych badań oceniano zgodnie z wytycznymi skali Newcastle–Ottawa (NOS, *Newcastle-Ottawa Scale*)[45], obejmującymi trzy kluczowe elementy: selekcja populacji badanej, porównywalność grup oraz sposób ustalania i wiarygodność wyników.

Użyto średnich i odchylenia standardowego (SD, *standard deviation*) lub median i zakresów międzykwartylowych (IQR, *interquartile range*) dla zmiennych ciągłych. Wartości median i IQR przekształcono na średnie i SD zgodnie z metodologią opisaną przez Hozo i współpracowników[46]. Szacunki zbiorcze uzyskano korzystając ze średnich i SD dla zmiennych ciągłych oraz wskaźników zdarzeń dla zmiennych kategorycznych. Miara efektu dla zmiennych ciągłych to różnica średnich (MD, *mean difference*); dla zmiennych kategorycznych zastosowano iloraz szans (OR, *odds ratio*). Heterogenność oceniono za

pomocą testu Q oraz I^2. Chociaż nie każda metaanaliza wykazała istotną heterogenność wśród włączonych badań, w każdym przypadku stosowano modele efektów losowych ze względu na ogólnie wysoką heterogenność obserwowaną we wszystkich badaniach włączonych do przeglądu systematycznego i poszczególnych metaanaliz.

W **Publikacji 2** przeanalizowano grupę 1016 pacjentów z histologicznie potwierdzonym rakiem prostaty, którzy przeszli radykalną prostatektomię w Uniwersyteckim Centrum Urologii we Wrocławiu w latach 2012-2022. Kryteria wykluczenia obejmowały, między innymi, brak cech LVI w końcowym badaniu histopatologicznym oraz nieobecność przerzutów do węzłów chłonnych (pN0). Po zastosowaniu kryteriów wyłączenia, badanie ostatecznie objęło 96 mężczyzn.

Preparaty histopatologiczne były zbierane i przetwarzane zgodnie z wytycznymi protokołu Stanford. Próbki utrwalano w roztworze formaliny buforowanej, a następnie zatapiano w parafinie. Za pomocą mikrotomu przekroje tkanek były barwione metodą H&E. Doświadczeni uropatolodzy oceniali materiał histopatologiczny, stosując ustandaryzowany system raportowania. Ocena stopnia klinicznego zaawansowania nowotworu była zgodna z wytycznymi Amerykańskiego Wspólnego Komitetu ds. Raka (AJCC, *the American Joint Committee on Cancer*)[47], a ocena preparatów w skali Gleasona odbywała się zgodnie z konsensusem Międzynarodowego Towarzystwa Patologii Urologicznej (ISUP, *the International Society of Urological Pathology*)[11,48]. Szczegółowa ocena preparatów obejmowała ocenę obecności LVI wraz z dokumentacją lateralizacji limfoangioinwazji. W sytuacji niejasności diagnostycznej stosowano barwienie podoplaniną (D2-40, PDPN).

Analizy statystyczne objęły ocenę normalności rozkładu zmiennych za pomocą testu Shapiro-Wilka, który każdorazowo wykazał odchylenia od rozkładu normalnego dla wszystkich zmiennych. W związku z tym konsekwentnie stosowaliśmy procedury nieparametryczne. Do porównania średnich między dwiema grupami scharakteryzowanymi przez zmienne kategoryczne wykorzystano test U Manna-Whitneya. Test Kruskala-Wallisa pozwolił ocenić różnice średnich między grupami scharakteryzowanymi przez zmienne kategoryczne z co najmniej trzema odpowiedziami. Współczynnik tau-b Kendalla zastosowano do określenia zależności statystycznej między dwiema zmiennymi. Stosowano testy dwustronne, uznając różnice za statystycznie znaczące, gdy wartość *p* była mniejsza niż 0,05. Ilorazy szans obliczono w celu oceny szans na lateralizację przerzutów do węzłów chłonnych w poszczególnych podgrupach, a do obliczeń zastosowano przedział ufności (CI, *confidence interval*) na poziomie 95%.

W **Publikacji 3** przeanalizowano 861 pacjentów z histologicznie potwierdzonym, rakiem prostaty, którzy przeszli radykalną prostatektomię w Uniwersyteckim Centrum Urologii w latach 2012-2021.

Preparaty histopatologiczne zbierano i przetwarzano zgodnie z protokołem Stanford. Utrwalano je w roztworze formaliny buforowanej i zatapiano w parafinie. Za pomocą mikrotomu wykonano przekroje tkanek, które następnie barwiono metodą H&E. Doświadczeni uropatolodzy oceniali preparaty zgodnie z ustandaryzowanym systemem raportowania. Ocena stopnia klinicznego zaawansowania nowotworu była zgodna z wytycznymi AJCC[47], a ocena preparatów w skali Gleasona odbywała się zgodnie z konsensusem ISUP[11,48]. Szczegółowa analiza materiału histopatologicznego obejmowała ocenę obecności LVI, naciekania okołonerwowego (PNI, *perineural invasion*), nacieku pozatorebkowego (ECE, *extracapsular extension*) oraz dodatnich marginesów chirurgicznych (PSM, *positive surgical margin*). W sytuacjach niejasności diagnostycznych w ocenie LVI stosowano barwienie PDPN.

Analiza statystyczna obejmowała ocenę normalności rozkładu zmiennych za pomocą testów Shapiro-Wilka, które wykazały odchylenia od rozkładu normalnego dla analizowanych zmiennych. W konsekwencji stosowano procedury nieparametryczne. Test U Manna-Whitneya służył do porównywania średnich między dwiema grupami ze zmiennymi dychotomicznymi, natomiast test Kruskala-Wallisa pozwolił na ocenę różnic średnich między grupami ze zmiennymi kategorycznymi o co najmniej trzech odpowiedziach. Dodatkowo, współczynnik tau-b Kendalla zastosowano do oceny zależności statystycznej między dwiema zmiennymi. Wszystkie testy były dwustronne. Statystycznie istotne różnice między grupami występowały, gdy wartość p była mniejsza niż 0,05. Ponadto, zastosowano regresję logistyczną, aby zidentyfikować istotne czynniki przedoperacyjne jako najsilniejsze predyktory wystąpienia LVI w preparacie histopatologicznym. W analizach regresyjnych wykorzystano metodę estymacji krokowej, polegającą na iteracyjnym doborze zmiennych do modelu, w celu uzyskania najbardziej istotnego schematu. Dodatkowo, przeprowadzono regresję logistyczną w celu zidentyfikowania czynników ryzyka wystąpienia przerzutów do węzłów chłonnych, mając na celu ocenę znaczenia LVI jako potencjalnego determinantu tego zjawiska. W celu zidentyfikowania istotnych predyktorów związanych z liczbą zajętych węzłów chłonnych u pacjentów pN+, przeprowadzono analizę regresji liniowej, która pozwoliła sprawdzić dopasowanie modelu do danych medycznych.

8. Podsumowanie wyników

Publikacja 1.: Karwacki, J.; Stodolak, M.; Nowak, Ł.; Kiełb, P.; Krajewski, W.; Lemiński, A.; Szydełko, T.; Małkiewicz, B. 2024. **Preoperative Factors for Lymphovascular Invasion in Prostate Cancer: A Systematic Review and Meta-Analysis**. International Journal of Molecular Sciences, 25(2), 856.

W ramach systematycznego przeglądu literatury zidentyfikowano trzydzieści dziewięć badań obejmujących 389997 pacjentów, z czego 33995 (8,7%) miało cechy LVI w pooperacyjnym badaniu histopatologicznym. Metaanalizy objęły sześć przedoperacyjnych czynników kliniczno-patologicznych: wiek, wskaźnik masy ciała (*body mass index*, BMI), kliniczne stadium zaawansowania (cT), wynik w skali Gleasona w biopsji, przedoperacyjny poziom PSA oraz objętość stercza.

Wiek. Analiza obejmująca dwadzieścia jeden badań wskazała, że starszy wiek nie jest czynnikiem ryzyka dla LVI w końcowym badaniu histopatologicznym ($p = 0,10$; MD = 0,64; 95% CI 0,12−1,39).

BMI. Metaanaliza pięciu badań dotyczących związku między BMI a LVI wskazała na brak istotnej statystycznie korelacji ($p = 0,88$; MD = −0,03; 95% CI 0,40−0,34).

Przedoperacyjny stopień zaawansowania klinicznego nowotworu. Osiem badań oceniało związek między cT a LVI, z czego pięć włączono do metaanalizy. Wykazano, że stadium cT3 jest związane z LVI ($p < 0,0001$; OR = 3,54; 95% CI 1,97−6,38), podczas gdy stadium cT1 ma istotnie niższe prawdopodobieństwo LVI ($p = 0,02$; OR = 0,57; 95% CI 0,36−0,91). Stadium cT2 nie wykazuje związku z LVI ($p = 0,21$; OR = 1,49; 95% CI 0,80−2,79).

Stopień złośliwości histologicznej w skali Gleasona. Osiem badań oceniało związek między wynikiem w skali Gleasona ocenianym w biopsji a LVI. W metaanalizie wykazano, że GS ≥ 8 koreluje z LVI ($p < 0,00001$; OR = 4,17; 95% CI 2,38−7,31), natomiast GS 6 wiąże się ze statystycznie niższym prawdopodobieństwem LVI ($p < 0,00001$; OR = 0,28; 95% CI 0,16−0,49). Wynik GS = 7 nie koreluje z LVI ($p = 0,33$; OR = 1,27; 95% CI 0,79−2,07).

Przedoperacyjny poziom PSA. Analiza obejmująca dwadzieścia siedem badań wskazuje, że wysoki przedoperacyjny poziom PSA jest czynnikiem ryzyka dla LVI ($p = 0,0008$; MD = 5,53; 95% CI 2,30−8,75).

Objętość stercza. Metaanaliza czterech badań oceniających związek między objętością gruczołu krokowego a LVI wykazała brak istotnej korelacji (p = 0,71; MD = −0,85; 95% CI 5,33−3,63).

W ramach przeglądu systematycznego zidentyfikowano dziesięć przedoperacyjnych czynników klinicznych związanych z LVI, które uzyskano z próbek krwi lub moczu. Trzy z tych czynników były związane z PSA: przedoperacyjny poziom PSA został zbadany w dwudziestu siedmiu badaniach, z czego dziewiętnaście wykazało istotną korelację, gęstość PSA (*prostate-specific antigen density*, PSAD) była raportowana w dwóch badaniach, a procent wolnego PSA w jednym badaniu. Pozostałe czynniki istotnie skorelowane z LVI to m.in. obecność przynajmniej jednego allelu G w genie anhydrazy węglanowej 9, receptora nabłonkowego czynnika wzrostu (*epidermal growth factor receptor*, EGFR) w surowicy, greliny In1 w moczu, ekspresja mRNA antygenu komórek macierzystych stercza (*prostate stem cell antigen*, PSCA) w surowicy, rozpiętość rozkładu objętości czerwonych krwinek (*red blood cell distribution width-standard deviation*, RDW-SD), cholinesteraza w surowicy, niski całkowity cholesterol w surowicy, a także urokinaza i jej receptor w surowicy.

Analiza ujawniła także przedoperacyjne czynniki patologiczne skorelowane z LVI, w tym wynik według skali Gleasona w biopsji, średni odsetek pozytywnych bioptatów (*percent of positive biopsy cores*, PPBC), czy liczbę pozytywnych bioptatów. Inne czynniki patologiczne, takie jak PNI w próbkach biopsji i całkowita liczba bioptatów, nie wykazały korelacji w poszczególnych badaniach. Ponadto zidentyfikowano trzy przedoperacyjne czynniki związane z obrazowaniem, które były związane z LVI: wynik w skali PIRADS (ang. *Prostate Imaging Reporting and Data System*), objętość prostaty oraz objętość guza. Wynik PIRADS i objętość stercza były raportowane w kilku publikacjach, ale tylko jedna z nich wykazała ich korelację z LVI. Wśród innych przedoperacyjnych czynników, wiek był raportowany w dwudziestu badaniach, z czego cztery wykazały jego korelację z LVI. BMI, nieprawidłowość stwierdzona w badaniu *per rectum* (*digital rectal examination*, DRE), rasa oraz cT również były związane z LVI w poszczególnych badaniach.

Publikacja 2.: Karwacki, J.; Gurwin, A.; Jaworski, A.; Jarocki, M.; Stodolak, M.; Dłubak, A.; Szuba, P.; Lemiński, A.; Kaczmarek, K.; Hałoń, A.; Szydełko, T.; Małkiewicz, B. 2024. **Association of Lymphovascular Invasion with Lymph Node Metastases in Prostate Cancer—Lateralization Concept**. Cancers, 16(5), 925.

W badaniu przeanalizowano populację 96 pacjentów z rakiem prostaty z cechami LVI oraz przerzutami do węzłów chłonnych. Przedoperacyjne ustalenie stopnia zaawansowania klinicznego i histologicznego obejmowały ocenę stadium cT oraz grupy złośliwości histologicznej Gleasona (*Gleason grading group*, GGG) na podstawie biopsji. Ponadto diagnostyka obejmowała DRE, jak i ocenę stercza i miednicy mniejszej za pomocą mpMRI. W badaniu histopatologicznym preparatów z prostatektomii radykalnej, u 1 pacjenta (1,0%) zdiagnozowano chorobę w stadium pT2a, u 5 (5,2%) pT2c, u 14 (14,6%) pT3a, a u 76 (79,2%) pT3b. Średnia liczba wyciętych węzłów chłonnych wynosiła 21,5 (zakres: 5–74), natomiast średnia liczba węzłów chłonnych objętych inwazją nowotworową wynosiła 4,2 (zakres: 1–30).

Jednostronną LVI zidentyfikowano u 85 pacjentów (88,5%), z czego 61 (71,8%) wykazywało LVI wyłącznie w lewym płacie, a 24 (28,2%) wyłącznie w prawym płacie. Obustronną LVI zaobserwowano u 11 pacjentów (11,5%). W odniesieniu do stadium pT, jednostronną LVI zidentyfikowano u 1 pacjenta (1,2%) z chorobą pT2a, 5 (5,9%) z pT2c, 14 (16,5%) z pT3a i 65 (76,5%) z rakiem pT3b. Wszyscy mężczyźni z obustronną LVI wykazywali chorobę w stadium pT3b w końcowym badaniu histopatologicznym.

W kohorcie 85 pacjentów z jednostronną LVI, 61 mężczyzn (71,8%) wykazało cechy LVI wyłącznie w lewym płacie stercza, podczas gdy 24 pacjentów (28,2%) miało LVI izolowaną do prawego płata. Pod względem stadium pT, pacjenci z jednostronną lewą LVI mieli następujący rozkład: 2 pacjentów (3,3%) z chorobą pT2c, 8 (13,1%) z pT3a i 51 (83,6%) z pT3b. U pacjentów z jednostronnie prawą LVI, 1 pacjent (4,2%) miał chorobę pT2a, 3 (12,5%) pT2c, 6 (25,0%) pT3a i 14 (58,3%) pT3b.

Pacjenci z jednostronnie lewą LVI wykazali OR na ipsilateralne przerzuty do węzłów chłonnych (*lymph node invasion*, LNI) wynoszący 3,609 (95% CI 0,925–14,077), OR na wyłącznie kontralateralne LNI wynoszący 0,185 (95% CI 0,092–0,374) oraz OR na obustronne LNI wynoszący 2,795 (95% CI 1,231–6,348). Tymczasem pacjenci z jednostronnie prawą LVI wykazali OR na wyłącznie ipsilateralne LNI wynoszący 2,862 (95% CI 1,531–5,348), OR na wyłącznie kontralateralne LNI wynoszący 0,725 (95% CI 0,579–0,908) oraz OR na obustronne LNI wynoszący 0,692 (95% CI 0,525–0,913).

Publikacja 3.: Karwacki, J.; Łątkowska, M.; Jarocki, M.; Jaworski, A.; Szuba, P.; Poterek, A.; Lemiński, A.; Kaczmarek, K.; Hałoń, A.; Szydełko, T.; Małkiewicz, B. 2024. **The clinical meaning of lymphovascular invasion: preoperative predictors and postoperative implications in prostate cancer - a retrospective study.** Frontiers in Oncology, 14.

Retrospektywnie przeanalizowano dane 861 pacjentów z rakiem prostaty. Średnia wieku pacjentów w momencie diagnozy wynosiła 64,1 lat (zakres: 31–80), a średni poziom PSA wynosił 14,0 ng/mL. PPBC wynosił 39,7% (zakres: 0–100%). W badaniu histopatologicznym po radykalnej prostatektomii, 4 pacjentów (0,5%) miało nowotwór stercza w stadium pT1, 489 (57,1%) w pT2, 362 (42,3%) w pT3, a 1 pacjent (0,1%) w pT4. Spośród 647 pacjentów poddanych limfadenektomii, u 143 (22,1%) rozpoznano LNI. Łącznie 152 pacjentów (17,7%) osiągnęło status pL1 (LVI+) w końcowym badaniu histopatologicznym.

Analiza jednowymiarowa wykazała związek LVI z wieloma czynnikami kliniczno-patologicznymi, w tym z wyższym poziomem PSA w czasie diagnozy, przedoperacyjnym PSA, stadium cT, wynikiem GS w preparatach z biopsji, PPBC, cT oraz cN ocenianym za pomocą mpMRI, grupą ryzyka EAU, pooperacyjnym PSA, ECE, PSM, PNI, wyższym stadium pT oraz pN, pooperacyjnym wynikiem GS oraz większą liczbą zajętych węzłów chłonnych u pacjentów pN+.

Wyniki regresji logistycznej, przeprowadzonej metodą eliminacji wstecznej, wskazują, że najważniejszymi predyktorami LVI były: stadium kliniczne cT3-4 według MRI, wynik 3-5 w skali Gleasona w preparatach pochodzących z biopsji, przedoperacyjny poziom PSA ≥20 oraz PPBC przekraczający 50%. W analizie wielowymiarowej zarówno GS w biopsji, jak i przedoperacyjny poziom PSA nie były istotne statystycznie. Jednakże pacjenci z wynikiem GS 3-5, a także z przedoperacyjnym PSA >20 ng/ml, mieli trzykrotnie większe prawdopodobieństwo wystąpienia LVI w ostatecznym badaniu histopatologicznym. Analiza podkreśliła znaczenie MRI cT3-4 oraz PPBC >50% jako najsilniejszych predyktorów, z wartościami OR wynoszącymi odpowiednio 4,739 i 7,364.

Regresja logistyczna wykazała ponadto, że najsilniejszymi predyktorami przerzutów do węzłów chłonnych, były stadium pT3-4, ECE oraz LVI. Dodatkowo, przeprowadzono analizę regresji liniowej, aby zbadać predyktory wyższej liczby zajętych węzłów chłonnych u pacjentów pN+, ale wyniki te uznano za niesatysfakcjonujące z powodu ograniczonej liczby pacjentów.

9. Wnioski

1. Najsilniejszymi czynnikami przedoperacyjnymi związanymi z wystąpieniem LVI w ostatecznym badaniu histopatologicznym po RP są stadium kliniczne cT, wynik GS w badaniu preparatów pochodzących z biopsji oraz przedoperacyjny poziom PSA.
2. Jednostronna LVI, zwłaszcza po stronie prawej, jest silnie skorelowana z jednostronnym zajęciem węzłów chłonnych u pacjentów LVI+ pN+, co może w przyszłości wpłynąć na planowanie zakresu limfadenektomii podczas RP.
3. Wśród pacjentów pN+, pacjenci z wyłącznie lewostronną LVI, wykazali istotnie zwiększoną częstość przypadków obustronnego zajęcia węzłów chłonnych oraz występowania wyższych stadiów zaawansowania histopatologicznego pT.
4. Wyższe stadium kliniczne T3-4 rozpoznane za pomocą mpMRI, wyższy wynik GS w badaniu histopatologicznym bioptatów, przedoperacyjny poziom PSA większy niż 20 ng/ml oraz odsetek zajętych bioptatów przekraczający 50% są najsilniejszymi predyktorami LVI w pooperacyjnym badaniu histopatologicznym.
5. LVI jest skorelowana z licznymi niekorzystnymi parametrami histopatologicznymi (m.in. ECE, PSM, PNI), a także z większą liczbą zajętych węzłów chłonnych u pacjentów pN+.
6. LVI jest jednym najsilniejszych niezależnych czynników ryzyka wystąpienia przerzutów do węzłów chłonnych.

10. Etyka badań

Przedstawione badania nie stanowiły eksperymentu medycznego w rozumieniu art. 21 ust. 1 ustawy z dnia 5 grudnia 1996 r. i zawodach lekarza i lekarza dentysty (Dz. U. z 2018 r. poz 617) i nie wymagały uzyskania opinii Komisji Bioetycznej, o której mowa w art. 29 ust. 1 ww. ustawy.

11. Piśmiennictwo

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12. Artykuły z cyklu publikacji w formie załączników

12.1. Artykuł pierwszy

Tytuł:

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Review

Preoperative Factors for Lymphovascular Invasion in Prostate Cancer: A Systematic Review and Meta-Analysis

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Abstract: Lymphovascular invasion (LVI) is one of the most important prognostic factors in prostate cancer (PCa) and is correlated with worse survival rates, biochemical recurrence (BCR), and lymph node metastasis (LNM). The ability to predict LVI preoperatively in PCa may be useful for proposing variations in the diagnosis and management strategies. We performed a systematic review and meta-analysis to identify preoperative clinicopathological factors that correlate with LVI in final histopathological specimens in PCa patients. Systematic literature searches of PubMed, Embase, and Web of Science were performed up to 31 January 2023. A total of thirty-nine studies including 389,918 patients were included, most of which were retrospective and single-center. PSA level, clinical T stage, and biopsy Gleason score were significantly correlated with LVI in PCa specimens. Meta-analyses revealed that these factors were the strongest predictors of LVI in PCa patients. Prostate volume, BMI, and age were not significant predictors of LVI. A multitude of preoperative factors correlate with LVI in final histopathology. Meta-analyses confirmed correlation of LVI in final histopathology with higher preoperative PSA, clinical T stage, and biopsy Gleason score. This study implies advancements in risk stratification and enhanced clinical decision-making, and it underscores the importance of future research dedicated to validation and exploration of contemporary risk factors in PCa.

Keywords: prostate cancer; lymphovascular invasion; radical prostatectomy; histopathological examination; prognostic factors; preoperative risk assessment; meta-analysis

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1. Introduction

Prostate cancer (PCa) is a prevalent malignancy with substantial clinical implications, variable outcomes, and an incidence of 1.4 million new cases in 2020 worldwide [1]. Lymphovascular invasion (LVI), a histopathological finding commonly defined as the unequivocal presence of tumor cells within endothelium lined spaces, has been associated with aggressive disease features and adverse prognostic outcomes, including lymph node invasion, and decreased survival rates [2–4]. Accurate preoperative prediction of LVI may be crucial for treatment decision-making in PCa patients. Additionally, both LVI and associated factors might provide added value to existing nomograms for nodal involvement [5–8] and risk classification systems [9].

The objective of this review was to identify clinicopathological factors that can predict LVI in PCa patients prior to undergoing radical prostatectomy (RP). By synthesizing the available evidence, we attempt to provide a comprehensive understanding of the predictive value of preoperative factors for LVI in PCa, and thus, for tumor aggressiveness

and disease progression. The findings of this study may contribute to improved risk stratification by facilitating the identification of those at higher risk of LVI and its associated adverse outcomes.

2. Results

2.1. Study Characteristics

We identified thirty-nine eligible studies, including 389,997 patients, 33,995 of whom were LVI-positive (8.7%) (Table 1). One study [10] included 79 PCa patients, although the exact number of LVI-positive patients was not disclosed. Of thirty-nine included papers, seventeen were retrospective and single-center [11–27], twelve were retrospective and multi-center [28–39], eight were prospective and single-center [10,40–46], and two were retrospective and database-registry-based [47,48]. Most commonly, LVI was defined as the unequivocal presence of tumor cells within endothelial-lined spaces. Figure 1 displays a PRISMA flowchart depicting the inclusion of articles.

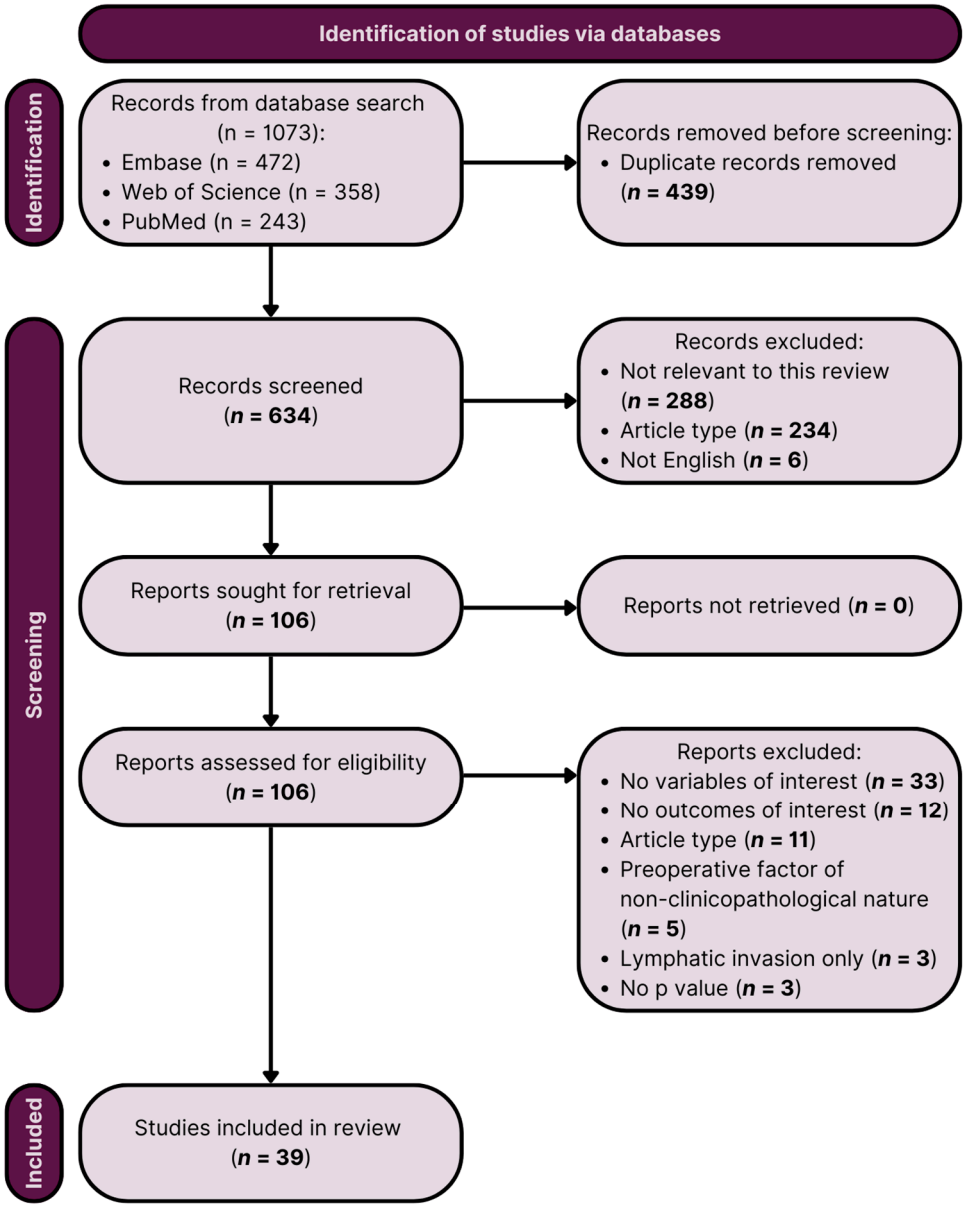

Figure 1. PRISMA (Preferred Reporting Items of Systematic Reviews and Meta-Analyses) flow diagram of the study selection process.

Table 1. Study characteristics of the 39 included studies.

Study	Country	Journal	Study Design	Study Period	LVI+ and LVI− [*n*]	LVI+ [*n*]	LVI+ [%]	LVI− [*n*]	Definition of LVI	Preoperative Predictors of LVI (*p*-Value)	NOS
Antunes et al., 2006 [11]	Brazil	*International Brazilian Journal of Urology*	retrospective, single-center	1993–2000	428	47	11.0	381	presence of tumor cells within an endothelium lined space	• age (0.372) • cT stage (0.003) • GS (0.169) • PPBC (mean: <0.001; ranges: 0.006) • PSA (mean: 0.004; ranges: 0.006)	8
Brooks et al., 2006 [28]	USA	*Cancer*	retrospective, multi-center	1991–2001	160	18	11.3	142	unequivocal presence of tumor cells within a vascular or lymphatic, endothelial-lined space	• age (0.60) • PSA (0.44)	7
Cheng et al., 2005 [12]	USA	*The Journal of Urology*	retrospective, single-center	1990–1998	504	106	21.0	398	unequivocal presence of tumor cells in an endothelium lined space	• age (0.20) • PSA (<0.0001)	8
D'Andrea et al., 2018 [29]	multi-center	*Urologic Oncology*	retrospective, multi-center	2000–2011	6041	693	11.5	5348	unequivocal presence of tumor cells within an endothelium lined space without underlying muscular walls	• serum cholinesterase (<0.01)	7
De La Taille et al., 2000 [20]	USA	*European Urology*	retrospective, single-center	1993–1998	241	30	12.4	211	unequivocal presence of tumor cells within simple endothelial-lined tissue spaces without underlying muscular walls	• DRE abnormalities (0.16) • GS (0.14) • PNI (0.09) • PSA (0.09)	8
Elharram et al., 2012 [40]	Canada	*The Canadian Journal of Urology*	prospective, single-center	2008–2010	138	5	3.6	133	none	• PNI (0.499)	5
Fajkovic et al., 2016 [32]	multi-center	*Urologic Oncology*	retrospective, multi-center	2000–2011	6678	767	11.5	5911	presence of tumor cells within an endothelium lined space	• age (0.054) • PSA (0.59)	8

Table 1. *Cont.*

Study	Country	Journal	Study Design	Study Period	LVI+ and LVI− [*n*]	LVI+ [*n*]	LVI+ [%]	LVI− [*n*]	Definition of LVI	Preoperative Predictors of LVI (*p*-Value)	NOS
Fawzy et al., 2015 [41]	Egypt	*Medical Oncology*	prospective, single-center	not specified	112	52	46.4	60	none	• PSCA mRNA (0.02)	6
Ferrari et al., 2004 [21]	USA	*Adult Urology*	retrospective, single-center	1984–1999	620	110	17.7	510	LVI was in small channels consisting of only an endothelial layer, identified by its smooth luminal surface, and lined with one or two narrow endothelial cells	• age (NA) • PSA (<0.0001)	8
Galiabovitch et al., 2016 [22]	Australia	*BJUI International*	retrospective, single-center	2004–2012	1267	82	6.5	1185	unequivocal presence of tumor cells in an endothelial-lined space	• age (0.26) • PSA (<0.001)	8
Gesztes et al., 2022 [23]	USA	*Scientific Reports*	retrospective, single-center	1993–2013	188	50	26.6	138	tumor cells' presence within spaces lined by lymphovascular endothelium with characteristic podoplanin staining	• age (0.14) • PSA (0.0027) • race (0.0796)	8
Jamil et al., 2021 [48]	multi-center	*Clinical Genitourinary Cancer*	retrospective, database registry	2010–2015	232,704	17,758	7.6	214,946	presence of tumor cells in lymphatic channels or blood vessels within the primary tumor	• age (<0.0001) • PSA (0.01) • race (AA: <0.0001; other: 0.002)	8
Jeon et al., 2009 [24]	Korea	*International Journal of Urology*	retrospective, single-center	1995–2004	237	41	17.3	196	unequivocal presence of tumor cells within an endothelium lined space without muscular walls	• age (0.865) • PSA (0.002) • prostate volume (0.160) • PSA density (<0.001) • cT stage (0.544)	8

Table 1. *Cont.*

Study	Country	Journal	Study Design	Study Period	LVI+ and LVI− [*n*]	LVI+ [*n*]	LVI+ [%]	LVI− [*n*]	Definition of LVI	Preoperative Predictors of LVI (*p*-Value)	NOS
Jiménez Vacas et al., 2021 [10]	Spain	*The Journal of Clinical Endocrinology & Metabolism*	prospective, single-center	2013–2015	79	not specified	-	not specified	none	• In1-ghrelin serum level (<0.001)	4
Jung et al., 2011 [25]	Korea	*Annals of Surgical Oncology*	retrospective, single-center	2005–2009	407	27	6.6	380	unequivocal presence of tumor cells in an endothelium lined space	• age (0.024) • BMI (0.268) • D'Amico classification (<0.001) • PSA (0.075) • prostate volume (0.647)	8
Kang et al., 2016 [26]	Korea	*Annals of Surgical Oncology*	retrospective, single-center	2003–2014	2034	252	12.4	1782	presence of tumor emboli in intraprostatic vessels, particularly within the lumen of the endothelium	• age (0.303) • GS (<0.001) • BMI (0.857) • cT stage (<0.001) • DM (0.192) • DRE abnormalities (<0.001) • hypertension (0.117) • prostate volume (0.148) • PSA (<0.001)	8
Kim et al., 2021 [27]	Korea	*International Journal of Clinical Oncology*	retrospective, single-center	1997–2019	389	59	15.2	330	none	• BMI (0.043)	6
Kızılay et al., 2020 [33]	Turkey	*Prostate International*	retrospective, multi-center	not specified	177	10	5.6	167	none	• PIRADS score (0.032)	5

Table 1. *Cont.*

Study	Country	Journal	Study Design	Study Period	LVI+ and LVI− [*n*]	LVI+ [*n*]	LVI+ [%]	LVI− [*n*]	Definition of LVI	Preoperative Predictors of LVI (*p*-Value)	NOS
Lin et al., 2019 [42]	Taiwan	*Urologic Oncology*	prospective, single-center	2012–2017	579	97	16.8	482	none	• carrying at least one G allele at CA9 rs3829078 (0.008) • PSA (<0.001)	7
Loeb et al., 2006 [34]	USA	*Urology*	retrospective, multi-center	1989–2004	1709	118	6.9	1591	presence of tumor emboli in small intraprostatic vessels	• PSA (<0.0001) • PSA velocity (0.3)	8
Lotan et al., 2004 [35]	USA	*The Journal of Urology*	retrospective, multi-center	1994–2002	605	32	5.3	573	none	• PPBC (0.736)	6
Luo et al., 2012 [13]	Taiwan	*Kaohsiung Journal of Medical Sciences*	retrospective, single-center	1998–2010	87	18	20.7	69	none	• age (0.746) • PSA (0.009) • risk classification (0.003)	6
Malaeb et al., 2007 [36]	USA	*Urologic Oncology*	retrospective, multi-center	1994–2002	628	34	5.4	594	none	• age (0.559)	6
May et al., 2006 [37]	Germany	*BJUI International*	retrospective, multi-center	1996–2003	412	42	10.2	370	unequivocal existence of tumor cells in an endothelium lined space with no underlying muscular walls	• age (0.261) • cT stage (0.811) • PSA density (<0.001) • PSA (<0.001) • PPBC (0.001)	8
Milanese et al., 2009 [43]	Italy	*The Journal of Urology*	prospective, single-center	2005–2006	30	4	13.3	26	none	• EGFR (0.005) • PSA (0.120) • uPAR (0.094)	6
Mitsuzuka et al., 2015 [38]	Japan	*Prostate Cancer and Prostatic Disease*	retrospective, multi-center	2000–2009	1160	121	10.4	1039	unequivocal presence of tumor cells within endothelial-lined channels on routine light microscopic examination	• age (0.017) • GS (<0.001) • cT stage (<0.001) • PSA (0.006) • tumor volume (<0.001)	8

Table 1. *Cont.*

Study	Country	Journal	Study Design	Study Period	LVI+ and LVI− [*n*]	LVI+ [*n*]	LVI+ [%]	LVI− [*n*]	Definition of LVI	Preoperative Predictors of LVI (*p*-Value)	NOS
Ohno et al., 2016 [14]	Japan	*Molecular and Clinical Oncology*	retrospective, single-center	2002–2010	562	148	26.3	414	none	• low serum total cholesterol level (0.014)	6
Park et al., 2016 [39]	South Korea	*Scientific Reports*	retrospective, multi-center	2001–2012	1210	260	21.5	950	presence of cancer cells within an arterial, venous, or lymphatic lumen on routine hematoxylin and eosin sections	• age (0.603) • GS (<0.001) • BMI (0.213) • no. of positive biopsy cores (<0.001) • PSA (<0.001) • prostate volume (0.025) • total no. of biopsy cores (0.088)	8
Rakic et al., 2021 [47]	USA	*Urologic Oncology*	retrospective, database registry	2010–2015	126,682	12,632	10.0	114,050	presence of tumor cells in lymphatic channels or blood vessels within the primary tumor, but not the lymph nodes	• age (<0.0001) • PSA (<0.0001)	8
Sato et al., 2020 [15]	Japan	*The Tohoku Journal of Experimental Medicine*	retrospective, single-center	2005–2011	116	12	10.3	104	none	• DSGb5 expression in prostate biopsy specimens (0.027)	5
Shariat et al., 2004 [30]	USA	*The Journal of Urology*	retrospective, multi-center	1994–2004	630	32	5.1	598	unequivocal presence of tumor cells within an endothelium lined space without underlying muscular walls	• age (0.1) • cT stage (<0.001) • GS (<0.001) • PPBC (<0.001) • PSA (0.004)	8
Shariat et al., 2006 [44]	USA	*European Urology*	prospective, single-center	1994–2002	351	13	3.7	338	none	• % fPSA (0.003) • PSA (0.901)	6

Table 1. *Cont.*

Study	Country	Journal	Study Design	Study Period	LVI+ and LVI− [*n*]	LVI+ [*n*]	LVI+ [%]	LVI− [*n*]	Definition of LVI	Preoperative Predictors of LVI (*p*-Value)	NOS
Shariat et al., 2007 [31]	USA	*Journal of Clinical Oncology*	retrospective, multi-center	1994–2004	255	29	11.4	226	none	• cT stage (0.078) • GS (0.47) • PSA (0.238) • uPA (0.002) • uPAR (<0.001)	7
Shin et al., 2020 [16]	Korea	*Prostate International*	retrospective, single-center	2009–2016	216	14	6.5	202	none	• visible tumor in MRI (0.876)	5
Van den Ouden et al., 1998 [45]	The Nether-lands	*Urologia In-ternationalis*	prospective, single-center	1977–1994	273	20	7.3	253	unequivocal presence of tumor cells within endothelial-lined spaces	• PSA (0.1)	7
Wang et al., 2022 [17]	China	*Frontiers in Endocrinol-ogy*	retrospective, single-center	2018–2021	348	53	15.2	295	presence of tumor cells within an endothelial-lined space that is usually devoid of a muscular wall	• age (0.769) • BMI (0.053) • DM (0.852) • hypertension (0.133) • NHT (0.446) • PSA (<0.001) • RDW-SD (0.035)	8
Wang et al., 2022 [18]	China	*Frontiers in Oncology*	retrospective, single-center	2018–2021	348	54	15.5	294	none	• platelets (0.868)	6
Yamamoto et al., 2008 [19]	Japan	*International Journal of Urology*	retrospective, single-center	1994–2005	94	26	27.7	68	unequivocal presence of tumor cells in an endothelium lined space	• cT stage (0.859) • GS (0.053) • PSA (0.022)	8
Yee et al., 2010 [46]	USA	*BJUI International*	prospective, single-center	2004–2007	1298	129	9.9	1169	unequivocal presence of tumor cells within an endothelium lined space	• age (NA) • PSA (<0.001)	8

AA = African American; BMI = body mass index; DM = diabetes mellitus; DRE = digital rectal examination; DSGb5 = disialosyl globopentaosylceramide; EGFR = epidermal growth factor receptor; GS = Gleason score; NA = not available; NOS = Newcastle Ottawa Scale; PNI = perineural invasion; PPBC = percent of positive biopsy cores; PSA = prostate-specific antigen; PSCA = prostate stem cell antigen; uPA = urokinase-type plasminogen activator; uPAR = urokinase-type plasminogen activator receptor.

The initial database search yielded 1073 records, and after removing 439 duplicates, 634 articles underwent abstract analysis. Of these, 234 were excluded based on article type, and an additional 6 were excluded due to non-English language. The screening process for study identification excluded 288 studies deemed 'not relevant to this review', primarily involving malignancies other than PCa or animal samples. A total of 106 articles were retrieved and assessed for eligibility through comprehensive manuscript analysis. Ultimately, 39 articles met the inclusion criteria and were included in the systematic review.

The NOS scores for the included studies varied from 4 to 9. Consequently, the methodological quality of the eligible manuscripts was categorized as moderate or high (see Table S1) and thus deemed appropriate for this systematic review and meta-analysis. It is noteworthy that all selected papers exhibited a high RoB, primarily attributed to their retrospective design. The RoB assessment, generated using the robvis tool [49], is presented in Figure 2.

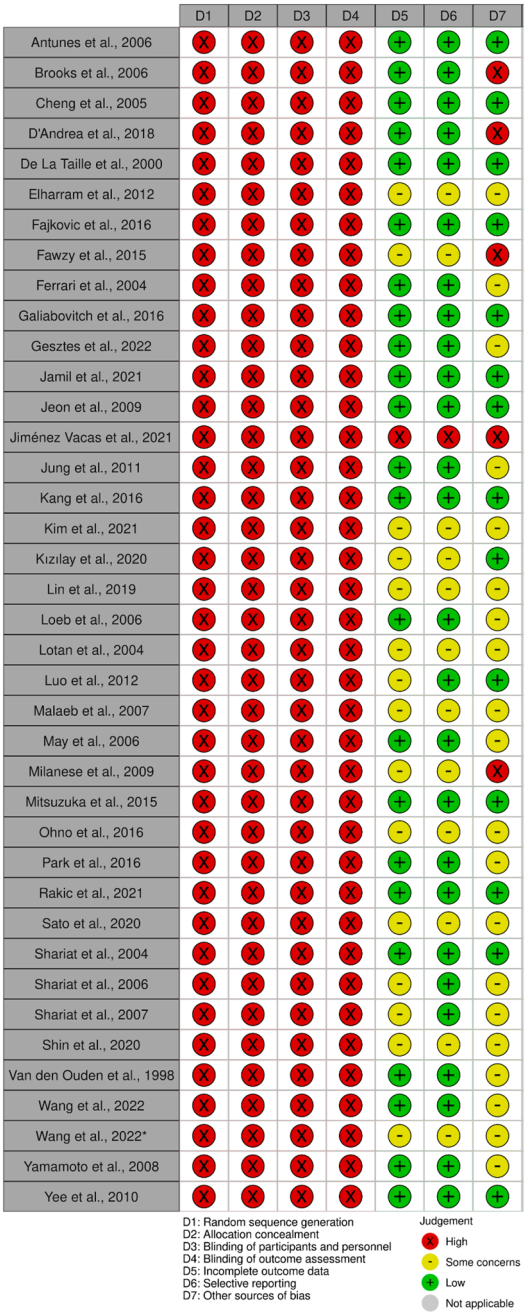

Figure 2. Risk of bias assessment chart [10–48]. * [18].

2.2. Meta-Analyses

Meta-analyses concerned six preoperative clinicopathological factors: age, BMI, clinical T stage, biopsy Gleason score (GS), preoperative PSA, and prostate volume (Figures 3 and 4). Factors associated with occurrence of LVI in RP specimens included clinical T3 stage ($p < 0.0001$; OR = 3.54), biopsy Gleason score ≥ 8 ($p < 0.00001$; OR = 4.17), and preoperative PSA ($p = 0.0008$; MD = 5.53). Age ($p = 0.10$; MD = 0.64), BMI ($p = 0.88$; MD = −0.03), and prostate volume ($p = 0.71$; MD = −0.85) were uncorrelated with LVI.

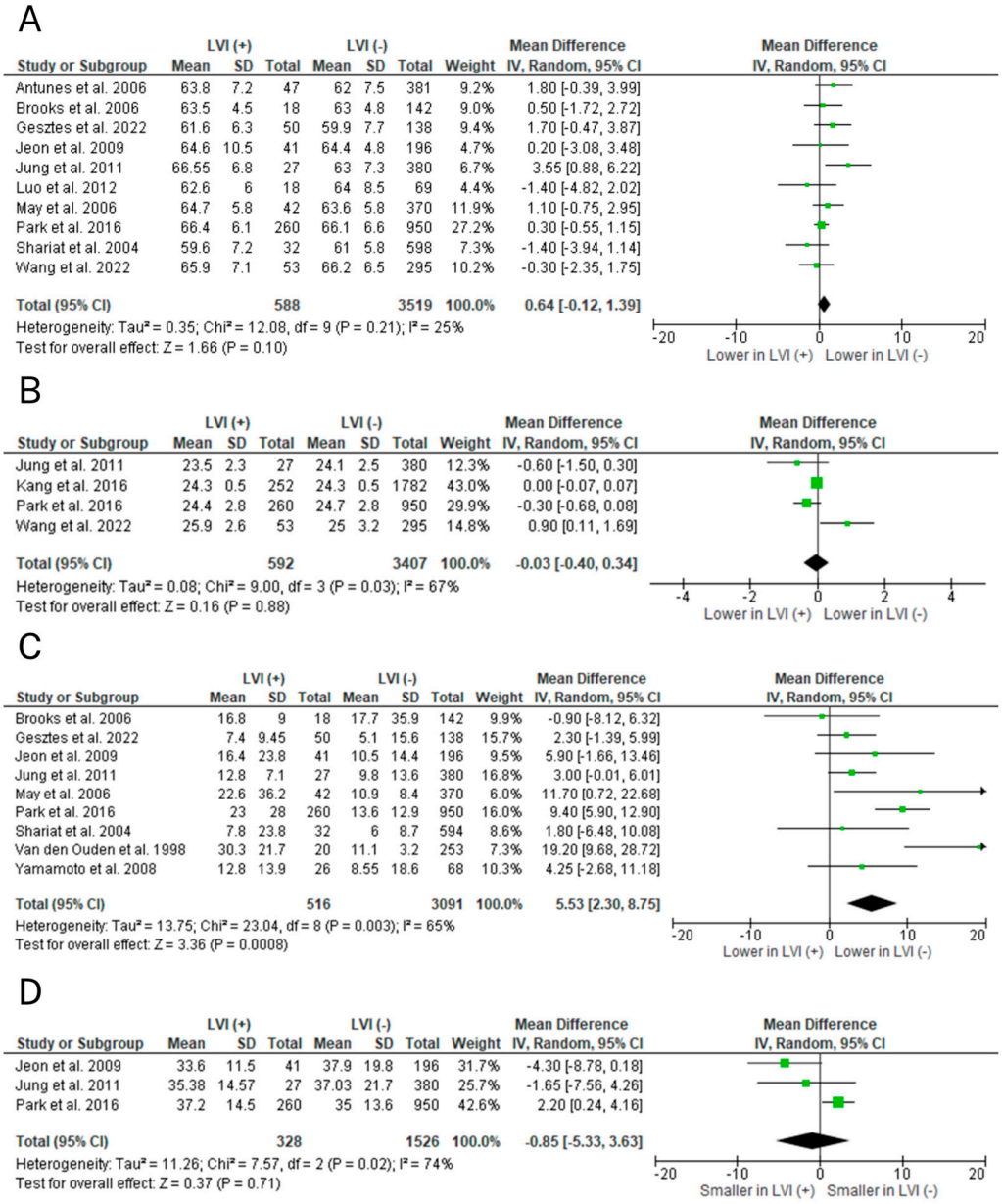

Figure 3. Forest plots of mean differences (MD) in random effects models predicting lymphovascular invasion (LVI) preoperatively: (**A**) age, (**B**) body mass index (BMI), (**C**) prostate-specific antigen (PSA), and (**D**) prostate volume [11,13,17,19,23–26,28,30,37,39,45]. CI = confidence interval; df = degree of freedom; IV = inverse variance; M-H = Mantel–Haenszel; SD = standard deviation.

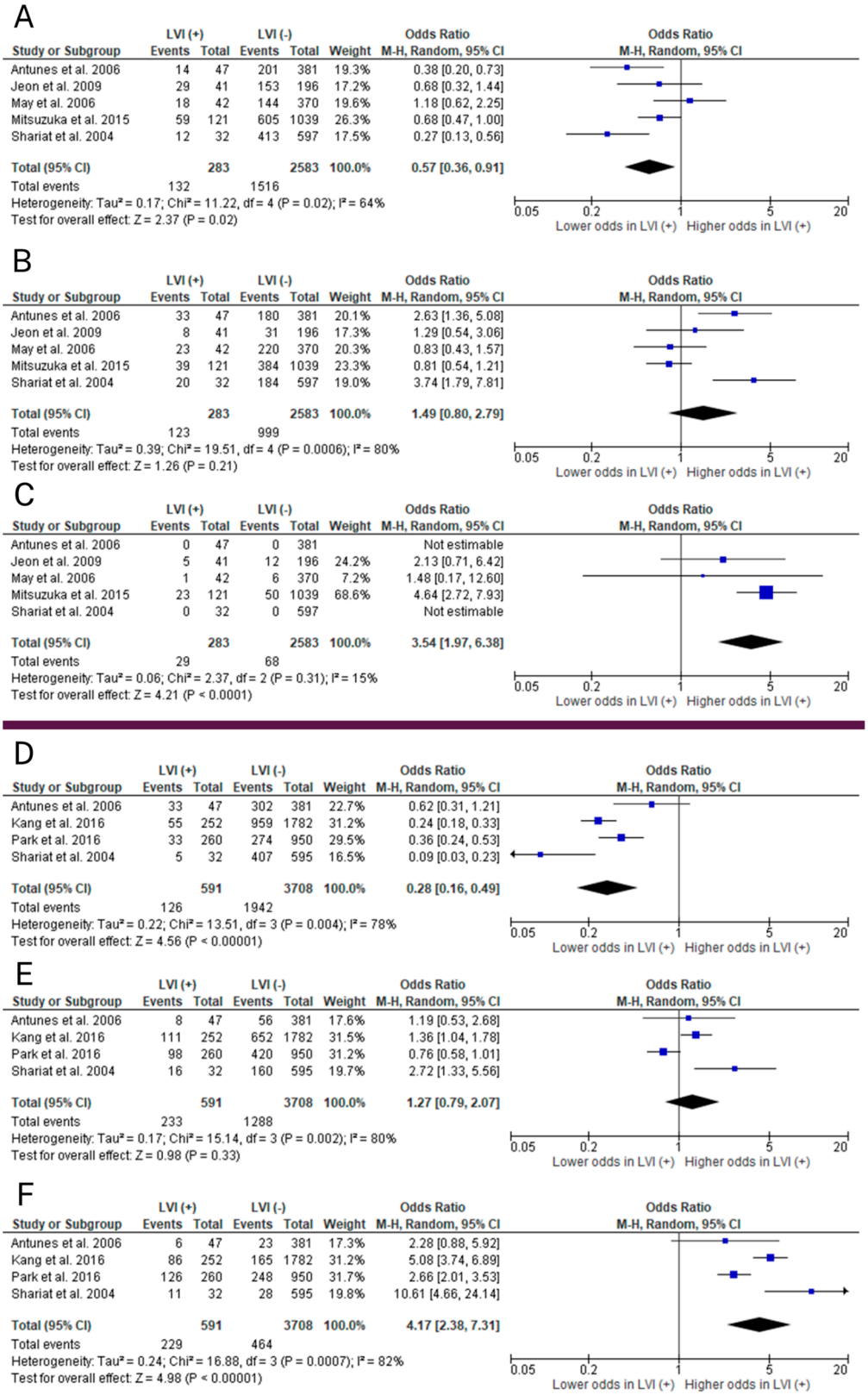

Figure 4. Forest plots of odds ratios (OR) in random effects models predicting lymphovascular invasion (LVI) preoperatively: clinical T stage (cT)—(**A**) cT1, (**B**) cT2, and (**C**) cT3; biopsy Gleason score (GS)—(**D**) GS = 6, (**E**) GS = 7, and (**F**) GS $\geq$ 8 [11,24,26,30,37–39]. CI = confidence interval; df = degree of freedom; IV = inverse variance; M-H = Mantel–Haenszel; SD = standard deviation.

2.2.1. Age

A total of twenty-one studies investigated the correlation between age and LVI [11–13,17,19,21–26,28,30,32,36–39,46–48]. Due to substantial diversity of data presentation, eleven of them were excluded, leaving ten studies that made the final meta-analysis [11,13,17,23–25,28,30,37,39]. A total of 4107 patients were analyzed, 588 of whom were LVI-positive. Overall, results from the random-effects meta-analysis model indicate that older age is not a risk factor for LVI in the final histopathology ($p = 0.10$; MD = 0.64; 95% CI −0.12, 1.39).

2.2.2. BMI

A total of five studies investigated the correlation between BMI and LVI [17,25–27,39]. Due to substantial diversity of data presentation, one of them was excluded, leaving four studies that made the final meta-analysis [17,25,26,39]. A total of 3999 patients were analyzed, 592 of whom were LVI-positive. Overall, results from the random-effects meta-analysis model indicate that BMI is uncorrelated with LVI in the final histopathology ($p = 0.88$; MD = −0.03; 95% CI 0.40, 0.34).

2.2.3. Clinical T Stage

A total of eight studies investigated the correlation between clinical T stage and LVI [11,19,24,26,30,31,37,38]. Due to substantial diversity of data presentation, three of them were excluded, leaving five studies that made the final meta-analysis [11,24,30,37,38]. A total of 2866 patients were analyzed, 283 of whom were LVI-positive. Overall, results from the random-effects meta-analysis model indicate that stage T3 is associated with LVI in the final histopathology ($p < 0.0001$; OR = 3.54; 95% CI 1.97, 6.38). Stage T1 has a significantly lower probability of LVI ($p = 0.02$; OR = 0.57; 95% CI 0.36, 0.91). Clinical stage T2 did not correlate with LVI ($p = 0.21$; OR = 1.49; 95% CI 0.80, 2.79).

2.2.4. Gleason Score

A total of eight studies investigated the correlation between biopsy GS and LVI [11,19,20,26,30,31,38,39]. Due to substantial diversity of data presentation, four of them were excluded, leaving four studies that made the final meta-analysis [11,26,30,39]. A total of 4299 patients were analyzed, 591 of whom were LVI-positive. Overall, results from the random-effects meta-analysis model indicate that GS $\geq$8 is correlated with LVI in the final histopathology ($p < 0.00001$; OR = 4.17; 95% CI 2.38, 7.31). Patients with a GS of 6 have a statistically lower probability of LVI in the final specimens ($p < 0.00001$; OR = 0.28; 95% CI 0.16, 0.49). A GS of 7 did not correlate with LVI ($p = 0.33$; OR = 1.27; 95% CI 0.79, 2.07).

2.2.5. Preoperative PSA

A total of twenty-seven studies investigated the correlation between preoperative PSA levels and LVI [11–13,17,19–26,28,30–32,34,37–39,42–48]. Due to substantial diversity of data presentation, eighteen of them were excluded, leaving nine studies that made the final meta-analysis [19,23–25,28,30,37,39,45]. A total of 3607 patients were analyzed, 516 of whom were LVI-positive. Overall, results from the random-effects meta-analysis model indicate that high preoperative PSA is a risk factor for LVI in the final histopathology ($p = 0.0008$; MD = 5.53; 95% CI 2.30, 8.75).

2.2.6. Prostate Volume

A total of four studies investigated the correlation between prostate volume and LVI [24–26,39]. Due to substantial diversity of data presentation, one of them was excluded, leaving three studies that made the final meta-analysis [24,25,39]. A total of 1854 patients were analyzed, 328 of whom were LVI-positive. Overall, results from the random-effects meta-analysis model indicate that prostate volume is uncorrelated with LVI in final specimens ($p = 0.71$; MD = −0.85; 95% CI −5.33, 3.63).

2.3. Results of the Systematic Review

The review of collected data revealed several clinical, pathological, imaging, and other prognostic factors correlated with LVI in RP specimens (Table 2 and Figure 5).

Table 2. Quantity of articles analyzing clinicopathological prognostic factors found to be significantly correlated with LVI in at least two separate studies.

Predictor	Number of Studies	Patients with LVI/All Patients (%)
PSA	19	31,958/371,858 (8.6)
age	4	30,538/360,953 (8.5)
GS	4	695/5272 (13.2)
cT stage	4	241/2454 (9.8)
PPBC	3	121/1470 (8.2)
PSAD	2	83/649 (12.8)

LVI = lymphovascular invasion; PSA = prostate-specific antigen; GS = Gleason score; cT stage = clinical T stage; PPBC = percent of positive biopsy cores; PSAD = prostate-specific antigen density.

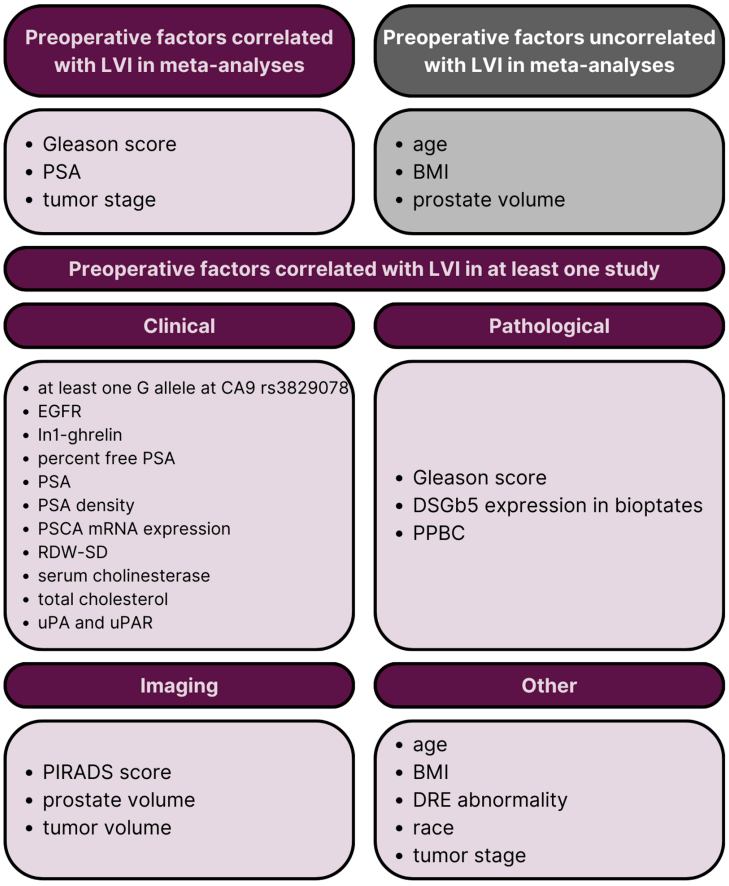

Figure 5. A visual overview of various clinicopathological preoperative factors that correlated with LVI in at least one study. LVI = lymphovascular invasion; PSA = prostate-specific antigen; BMI = body mass index; CA9 = carbon anhydrase 9; EGFR = epidermal growth factor receptor; PSCA = prostate stem cell antigen; mRNA = messenger ribonucleic acid; RDW-SD = red blood cell distribution width; uPA = urokinase-type plasminogen activator; uPAR = urokinase-type plasminogen activator receptor; DSGb5 = disialosyl globopentaosyl ceramide; PPBC = percent of positive biopsy cores; PIRADS = Prostate Imaging Reporting & Data System; DRE = digital rectal examination.

2.3.1. Preoperative Clinical Factors

We identified ten preoperative clinical factors, acquired from blood or urine samples, correlated with LVI: three of them were associated with PSA—preoperative PSA (including PSA at diagnosis) was reported by twenty-seven studies [11–13,17,19–26,28,30–32,34,37–39,42–48], and nineteen of them revealed a significant correlation [11–13,17,19,21–24,26,30,34,37–39,42,46–48]; PSA density (PSAD) was reported by two studies [24,37]; and percent free PSA was reported by one study [44]. The other factors significantly correlated with LVI included carrying at least one G allele at carbon anhydrase 9 (CA9) rs3829078 (acquired from serum) [42], serum epidermal growth factor receptor (EGFR) [43], urine In1-ghrelin [10], serum prostate stem cell antigen (PSCA) messenger ribonucleic acid (mRNA) expression [41], red blood cell distribution width (RDW-SD) [17], serum cholinesterase [29], low serum total cholesterol [14], serum urokinase-type plasminogen activator (uPA) [31], and serum uPA receptor (uPAR) [31]. Other, uncorrelated preoperative clinical factors included PSA velocity [34] and platelets [18].

2.3.2. Preoperative Pathological Factors

This systematic review revealed four preoperative pathological factors correlated with LVI: biopsy GS, reported by eight studies [11,19,20,26,30,31,38,39] and associated with LVI by four of them [26,30,38,39]; percent of positive biopsy cores (PPBC), reported by four studies [11,30,35,37] and significantly correlated with LVI by three of them [11,30,37]; number of positive biopsy cores, reported by one study [39]; and disialosyl globopentaosyl ceramide (DSGb5) expression in biopsy specimens, reported by one study [15]. Other pathological factors in our review were uncorrelated in particular studies, such as perineural invasion in biopsy specimens [20,40] and total number of biopsy cores [39].

2.3.3. Preoperative Imaging-Related Factors

Our review identified three preoperative imaging-related factors associated with LVI: PIRADS score, reported and correlated with LVI by one study [33]; prostate volume, reported by four studies [24–26,39] and correlated with LVI by one of them [39]; and tumor volume, associated with LVI by one study [38].

2.3.4. Other Preoperative Factors

We identified various other preoperative factors correlated with LVI, which included the following: age, reported by twenty studies [11–13,17,21–26,28,30,32,36–39,46–48] and correlated by four of them [25,38,47,48] (two studies did not provide the *p*-value [21,46], although one of them [21] reported no correlation); body mass index (BMI), reported by five studies [17,25–27,39] and correlated with LVI by one of them [27]; digital rectal examination abnormality, reported by two studies [20,26] and associated with LVI by one of them [26]; race, reported by two studies [23,48] and associated with LVI by one of them [48] (in case of the study by Jamil et al. [48], African American (AA) and other races were associated with higher LVI prevalence in comparison to Caucasian race); and clinical tumor stage (cT), reported by eight studies [11,19,24,26,30,31,37,38] and associated with LVI by four of them [11,26,30,38]. Additionally, one study [13] reported a correlation between the risk group classification and LVI. Another study [25] revealed that D'Amico classification correlated with LVI. Both classification systems are multifactorial; thus, we did not include them in Figure 5.

3. Discussion

LVI is considered an adverse pathological feature and has been consistently associated with an increased risk of disease progression and poor outcomes. Studies have shown that patients with LVI are more likely to have biochemical recurrence, tumor metastasis, and lower survival rates [2–4]. Additionally, LVI is also associated with unfavorable subpathologies, including cribriform and intraductal patterns [50]. In this study, we aimed to

identify preoperative clinical and pathological factors that correlate with LVI, to enhance our ability to predict its occurrence and guide treatment decisions.

Predicting the occurrence of LVI in prostate cancer may have significant implications for patient prognosis and treatment planning. By preoperatively identifying patients at higher risk of LVI, clinicians could potentially offer closer surveillance, neoadjuvant therapy, or more aggressive surgical strategies, for instance, omitting the nerve-sparing technique, opting for wider tissue margins, or using a more extended lymph node dissection (LND) template.

Accurate detection of metastatic lymph nodes enables clinicians to make informed decisions regarding appropriate treatment approaches, such as extended LND or targeted radiation therapy [51]. Traditional imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI) have limitations in detecting small or micrometastatic lymph nodes [52]. Thus, incorporating the evaluation of LVI status into preoperative assessments can help identify patients who may benefit from more extended LND templates or adjuvant therapies. Despite the established association between LVI and lymph node metastasis (LNM), it is noteworthy that existing prognostic nomograms and other risk evaluation tools often do not incorporate LVI and many of its predictors as risk factors. To improve risk stratification and enhance the clinical utility of prognostic tools, it might be beneficial to incorporate LVI and associated risk factors into algorithms to provide a more comprehensive assessment of the individual patient's risk profile, facilitating more informed treatment decisions. Furthermore, identified prognostic factors for LVI could have an impact on the biopsy-associated decision process. Many pathologists do not include LVI in biopsy specimen reports, which may be caused by the relative rarity of this finding [53] or the resemblance to many histopathological artifacts [50]. Nevertheless, the EAU guidelines state that patients with LVI-positive biopsy should be excluded from active surveillance [9]. Thus, including additional markers could have an impact on clinicians' and pathologists' decisions regarding inclusion of LVI in the biopsy report.

Predicting LVI occurrence enables researchers to identify high-risk patient populations for further investigation. Clinical trials can be designed specifically to evaluate novel treatment approaches or interventions targeting patients with LVI. Improved understanding of LVI's biological mechanisms and associated biomarkers may lead to the development of targeted therapies or interventions as well as more accurate prognostic tools.

It is crucial to acknowledge that further research and data are needed to refine the accuracy of LVI prediction. While certain clinicopathological factors, such as preoperative PSA, cT stage, and biopsy GS, have shown significant correlations with LVI, there may be additional as-yet-unknown factors that are associated with its occurrence. Therefore, ongoing investigations and prospective studies are warranted to enhance our understanding of LVI predictors and develop comprehensive models that encompass a broader range of variables.

An intriguing aspect of this study is the observed lack of correlation between age and LVI. While our findings suggest no significant association, it is noteworthy that existing literature in the field presents inconsistent perspectives on the role of age as a risk factor in PCa [54,55]. Some studies indicate an association between older age and worse prognosis with unfavorable outcomes, whereas others underscore the insignificance of this correlation [56]. Importantly, the studies included in our meta-analysis on the age–LVI association were primarily retrospective, contributing to the complexity of our observations. Furthermore, it is crucial to highlight that although the heterogeneity in our meta-analysis was low (I^2 = 25%), the highest-volume studies by Rakic et al. and Jamil et al. (see Table 1), unfortunately, were not incorporated into the meta-analysis due to differences in data presentation. These studies, displaying a statistically significant correlation between LVI and age, were excluded due to the unavailability of specific parameters (mean, range, SD) necessary for the meta-analysis. This underscores the challenge of synthesizing evidence from diverse studies and emphasizes the need for standardized reporting in future research.

Our study is burdened with some limitations that should be acknowledged. Firstly, many included studies in our systematic review were of retrospective nature, which introduces inherent limitations such as potential selection bias and the inability to establish causal relationships. Additionally, the reliance on retrospective data may be associated with incomplete or missing information, leading to potential inaccuracies or inconsistencies in the results. Secondly, the studies included in our analysis were predominantly single-center studies, which may limit the generalizability of the findings. The results might have been influenced by specific patient populations, treatment protocols, or institutional practices. Thirdly, the factors associated with LVI in our meta-analyses are major prognostic factors for PCa aggressiveness itself. To establish the mechanisms behind LVI, it would be valuable to search for prognostic factors correlated with LVI, but not with a higher stage, grade, or other adverse pathological outcomes, in future studies.

In conclusion, our study has identified several preoperative clinical and pathological factors that correlate with LVI in PCa patients. These factors hold potential as predictive markers for the presence of LVI and may improve risk stratification and treatment planning. The association of LVI with worse outcomes, as demonstrated in previous studies, underscores the importance of predicting LVI to guide treatment decisions. Further research is warranted to validate our findings, investigate underlying mechanisms, and develop comprehensive risk stratification models that incorporate LVI as a predictive factor.

4. Materials and Methods

4.1. Search Strategy

Two review authors (J.K. and M.S.) independently performed a computerized systematic literature search of the PubMed, Embase, and Web of Science databases in June 2023. Only articles written in English with the full text available, without time limitations, were considered. The following terms and keywords were employed:

- PubMed: 'prostate cancer' AND ('microvascular invasion' or 'lymphovascular invasion') using Medical Subject Headings (MeSH) terms;
- Embase: ('prostate cancer'/exp OR 'prostate cancer' OR (('prostate'/exp OR prostate) AND ('cancer'/exp OR cancer))) AND (lymphovascular OR microvascular) AND invasion;
- Web of Science: (ALL = (prostate cancer)) AND ALL = (lymphovascular invasion OR microvascular invasion).

The references of the relevant review articles were also manually screened to ensure that no additional eligible papers were inadvertently omitted.

4.2. Inclusion Criteria

All authors participated in the design of the search strategy and inclusion criteria. Our procedure for evaluating records identified during the literature search followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) criteria [57]. The study protocol was registered a priori on the International Prospective Register of Systematic Reviews (PROSPERO) with the registration number CRD42023389021. The final list of included articles was selected with the consensus of all collaborating authors, verifying that they met the inclusion criteria.

4.3. Study Eligibility and Quality/Risk of Bias Assessment

Studies were assessed for eligibility using the PICO (population, intervention, comparison, outcome) approach:

- Population: patients with PCa who underwent RP.
- Intervention: RP and final histopathological examination; patients with LVI in final specimens.
- Comparison: patients without LVI in final histopathology.
- Outcome: preoperative clinicopathological factors and their correlation with LVI in RP specimens.

Additionally, studies included in the systematic review were required to fulfill the following inclusion criteria: (1) original article, (2) human research, (3) English language, (4) access to the full manuscript, (5) prostate cancer, (6) LVI evaluated in RP specimens, and (7) association between various preoperative clinicopathological factors and LVI assessed (p-value revealed). The exclusion criteria were: (1) non-comparative studies—reviews, letters, conference papers, editorial comments, replies from authors, or case reports, (2) studies not reporting outcomes of interest.

The included studies underwent quality evaluation based on the Newcastle–Ottawa Scale (NOS) guidelines [58], encompassing three key domains:

(1) Selection of the study population;
(2) Comparability of the groups;
(3) Ascertainment of the outcome.

A summary of the quality assessment is provided in Table S1.

The assessment of the risk of bias (RoB) followed the principles outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* [59].

4.4. Statistical Analysis

Means and standard deviations (SDs) or medians and interquartile ranges (IQRs) were utilized for continuous variables. All median and IQR values were converted to means and SDs using the methodology described by Hozo et al. [60]. Pooled estimates were obtained using means and SDs for continuous variables and event rates for categorical variables. The effect measure used for continuous variables was the mean difference (MD), and odds ratio (OR) was used for categorical variables. The study applied 95% confidence intervals (95% CI). Heterogeneity was assessed through the Chi-square-based Q test and I^2. While not every meta-analysis demonstrated significant heterogeneity among the included studies, random-effect models were consistently employed in each case. This decision was based on the high overall heterogeneity observed across all studies included in the systematic review.

It is noteworthy to highlight that specific studies were excluded from certain meta-analyses due to variations in data presentation. For instance, when median and range information were available, we could derive the mean and incorporate the corresponding articles into the meta-analysis. However, in instances where articles solely provided the median value for a particular parameter, inclusion in the meta-analysis became unfeasible. Similar criteria were applied to categorical parameters (e.g., cT stage). If the data presentation did not permit the event rates to be inferred (e.g., number of patients with cT1, cT2, and cT3, with and without LVI), the study was excluded from the meta-analysis, even if it presented an association with a certain parameter. In the subsections of each meta-analysis, all included and excluded studies were meticulously cited, enabling a comprehensive individual examination of each excluded study.

5. Conclusions

In conclusion, our study demonstrates that several preoperative clinicopathological factors are significantly correlated with LVI in final histopathological specimens of PCa patients. Notably, preoperative PSA levels, clinical T stage, and biopsy Gleason score emerged as the strongest predictors of LVI in PCa patients. These findings highlight the importance of considering these factors in the preoperative assessment of PCa patients to accurately predict the likelihood of LVI occurrence. While factors such as prostate volume, BMI, and age did not exhibit significant correlations with LVI, further research is warranted to explore additional potential predictors and refine the predictive models. Additionally, integrating novel predictors into future approaches, such as the development of preoperative nomograms, could enhance risk stratification, disease staging, and treatment decision-making. Overall, our findings contribute to a better understanding of LVI in PCa and provide valuable insights for clinical practice and future research endeavors.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/ijms25020856/s1.

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

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12.2. Artykuł drugi

Tytuł:

Association of Lymphovascular Invasion with Lymph Node Metastases in Prostate Cancer—Lateralization Concept

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Association of Lymphovascular Invasion with Lymph Node Metastases in Prostate Cancer—Lateralization Concept

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Simple Summary: Prostate cancer (PCa) patients often face uncertainties in treatment decisions, particularly regarding lymphadenectomy. This study, involving 96 PCa patients, explores the significance of lymphovascular invasion (LVI) laterality in influencing lymph node invasion (LNI) patterns. Out of these patients, 63.5% exhibited LVI exclusively on the left, 25.0% on the right, and 11.5% on both sides. Significant correlations were observed between LVI laterality and lymph node involvement ($p < 0.001$), especially on the right side. Left-sided LVI correlated with higher cancer stage ($p = 0.047$) and greater odds of bilateral lymph node involvement. This pioneering study emphasizes the need for future prospective, multi-center investigations, ideally incorporating preoperative LVI assessment, to refine PCa treatment decisions.

Abstract: Background. Lymphovascular invasion (LVI) is a vital but often overlooked prognostic factor in prostate cancer. As debates on lymphadenectomy's overtreatment emerge, understanding LVI laterality gains importance. This study pioneers the investigation into PCa, aiming to uncover patterns that could influence tailored surgical strategies in the future. Methods. Data from 96 patients with both LVI and lymph node invasion (LNI) were retrospectively analyzed. All participants underwent radical prostatectomy (RP) with modified-extended pelvic lymph node dissection (mePLND). All specimens underwent histopathological examination. The assessment of LVI was conducted separately for the right and left lobes of the prostate. Associations within subgroups were assessed using U-Mann–Whitney and Kruskal–Wallis tests, as well as Kendall's tau-b coefficient, yielding *p*-values and odds ratios (ORs). Results. Out of the 96 patients, 61 (63.5%) exhibited exclusive left-sided lymphovascular invasion (LVI), 24 (25.0%) had exclusive right-sided LVI, and 11 (11.5%) showed bilateral LVI. Regarding nodal involvement, 23 patients (24.0%) had LNI solely on the left, 25 (26.0%) exclusively on the right, and 48 (50.0%) on both sides. A significant correlation was observed between lateralized LVI and lateralized LNI ($p < 0.001$), particularly in patients with right-sided LVI only. LN-positive patients with left-sided LVI tended to have higher pT stages ($p = 0.047$) and increased odds ratios (OR) of bilateral LNI (OR = 2.795; 95% confidence interval [CI]: 1.231–6.348) compared to those with exclusive right-sided LVI (OR = 0.692; 95% CI: 0.525–0.913). Conclusions.

Unilateral LVI correlates with ipsilateral LNI in PCa patients with positive LNs, notably in cases of exclusively right-sided LVI. Left-sided LVI associates with higher pT stages and a higher percentage of bilateral LNI cases.

Keywords: prostate cancer; radical prostatectomy; lymphovascular invasion; histopathological examination; lymph node invasion; nodal involvement lateralization; pelvic lymph node dissection

1. Introduction

Lymphovascular invasion (LVI), also referred to as microvascular invasion or vessel tumor embolus, is a critical histopathological feature observed in various malignancies [1–8]. In prostate cancer (PCa), the second-most prevalent solid tumor globally, LVI has emerged as a pivotal factor linked to adverse prognostic outcomes [9–13]. In the context of radical prostatectomy (RP), a primary treatment modality for localized PCa, the significance of LVI is underscored by its association with unfavorable clinical outcomes, including lymph node invasion (LNI) [10,12]. Despite LVI being a well-established risk factor for nodal metastasis, there is currently no debate regarding the lateralization of LVI and its potential association with lateralized LNI. To our knowledge, this study represents the first comprehensive analysis of LVI lateralization in PCa, aiming to elucidate its potential correlation with lateralized nodal involvement and explore relevant clinicopathological differences.

Our primary objective is to explore whether the lateralization of LVI, occurring exclusively in the left lobe, right lobe, or both lobes of the prostate, holds significance in terms of LNI. Specifically, we aim to determine if there is an association between the side of LVI and ipsilateral LNI. Additionally, we seek to investigate potential differences in clinicopathological data among patients exhibiting varying patterns of LVI lateralization. By addressing these questions, our study endeavors to contribute novel insights into the intricate relationship between LVI lateralization and nodal metastasis in PCa, paving the way for more informed clinical decision-making in the management of this prevalent malignancy, with implications for the potential application of unilateral lymphadenectomy, particularly in the context of ongoing debates around the feasibility and advantages of this approach [14,15].

2. Materials and Methods

2.1. Patient Population and Surgical Technique

A cohort of 1016 patients with histologically confirmed PCa undergoing RP at the University Center of Excellence in Urology, Wrocław, Poland, between 2012 and 2022 was analyzed. Exclusion criteria encompassed neoadjuvant therapy, absence of LVI in final histopathology (pL0), negative lymph nodes (pN0), and incomplete clinicopathological data. Following the exclusion criteria, the study ultimately comprised 96 men with positive lymph nodes (LNs) and LVI. Patient selection is depicted in Figure 1. Clinical T staging followed the 2016 TNM classification, with prostate biopsies obtained through transrectal ultrasound (TRUS)-guided systematic, targeted, or combined approaches. Baseline characteristics and clinical parameters were retrospectively collected. Preoperative data included age, preoperative serum PSA levels, biopsy Gleason score (Gleason Grading Groups, GGG), and clinical tumor (cT) stage assessed via digital rectal examination (DRE), bone scintigraphy, and magnetic resonance imaging (MRI). Surgical approaches for RP comprised either open with an ascending technique or laparoscopic with transperitoneal access. Modified-extended pelvic lymph node dissection (mePLND) was conducted, involving the obturator fossa, external, internal, and common iliac vessels, presacral regions, and Marcille's fossa. A comprehensive description of the lymphadenectomy template was previously published in our other study [16]. Perioperative and histopathological data included pathological T (pT) stage, postoperative Gleason Grading Group (GGG),

number of removed LNs, and positive LN count. Excised LNs underwent histopathological examination as separate specimens.

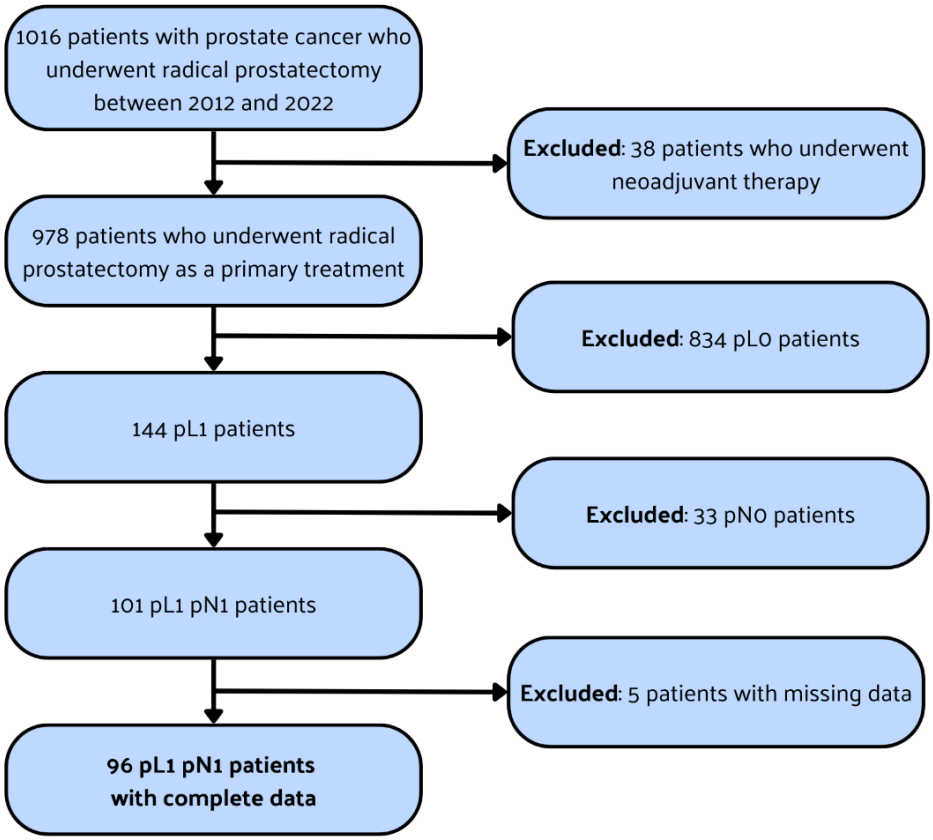

Figure 1. Flowchart illustrating the process of patient selection. pL0: negative lymphovascular invasion (LVI) in histopathological examination; pL1: positive LVI in histopathological examination; pN0: negative lymph node invasion (LNI) in histopathological examination; pN1: positive LNI in histopathological examination.

2.2. Histopathological Examination

Following the Stanford protocol guidelines, surgical specimens underwent collection and processing. The specimens were fixed in a neutral buffered formalin solution, followed by embedding in paraffin. Utilizing a microtome, tissue samples were sectioned and stained with hematoxylin and eosin (H&E). Experienced uropathologists evaluated slides, adhering to a standardized reporting system. Pathological staging adhered to the American Committee's guidelines for the Staging System for Prostate Cancer, and Gleason scores were determined in accordance with the International Society of Urological Pathology (ISUP) PCa grading consensus [17,18]. A detailed examination of pathological findings included the assessment of LVI presence, with documentation of laterality—whether LVI was exclusive to the left, right, or both sides of the prostate gland. LVI was defined as the unequivocal presence of tumor cells within endothelial-lined spaces lacking underlying muscular walls or the presence of tumor emboli in small intraprostatic vessels [19,20]. LVI analysis encompassed evaluations in both prostate and seminal vesicles. Within our study cohort, all patients exhibited LVI exclusively in prostate specimens, with no instances of LVI in seminal vesicles. Although the presence of LVI in seminal vesicles was not an exclusion criterion, it is an infrequent occurrence in our center's experience. In situations of diagnostic ambiguity, podoplanin (D2-40 or PDPN) staining was employed to assist uropathologists in their decision-making process.

2.3. Statistical Analysis

Statistical analyses were conducted using PS Imago Pro 9.0 with a Polish license. Continuous variables were presented as means ± standard deviation (SD) or median (range), while categorical variables were expressed as numbers (percentage). The normal distribution of variables was assessed using Shapiro–Wilk tests, revealing a significant deviation from the normal distribution for all analyzed variables [21]. Consequently, nonparametric measures were employed.

To compare mean levels between two groups with categorical variables, the U-Mann–Whitney test was utilized. The Kruskal–Wallis test assessed differences in mean levels among groups with categorical variables, each with at least three levels. Additionally, Kendall's tau-b coefficient was applied to determine the statistical dependence between two variables. A two-sided testing approach was consistently employed, considering statistically significant differences when the p-value was less than 0.05.

Odds ratios (ORs) were calculated to assess the odds for LNI lateralization in subgroups, specifically in patients with LVI exclusively in the left lobe, exclusively in the right lobe, and in both lobes. A confidence interval (CI) of 95% was applied for these calculations.

The utilization of a Marimekko chart was employed as a graphical representation to elucidate associations between LVI and LNI while highlighting their respective ratios. This approach was chosen for its effectiveness in visually conveying the intricate relationships and proportions between these variables, offering a comprehensive and accessible portrayal of the data.

3. Results

3.1. Patient Population

The mean age of patients at the time of diagnosis was 64.3 years, ranging from 41 to 78 years, and the median prostate-specific antigen (PSA) level was 22.0 ng/mL. Preoperative staging and grading involved the assessment of clinical tumor (cT) stage and Gleason Grading Group (GGG) at biopsy. Clinical examination included both digital rectal examination (DRE) and magnetic resonance imaging (MRI) evaluation. Following histopathological examination of RP specimens, 1 patient (1.0%) had pT2a disease, 5 patients (5.2%) had pT2c disease, 14 patients (14.6%) had pT3a disease, and 76 patients (79.2%) presented with pT3b disease. The mean number of dissected LNs was 21.5 (range: 5–74), while the mean number of positive LNs was 4.2 (range: 1–30). The median percentage of positive LNs (calculated by dividing the number of positive LNs by the total number of resected LNs) was 13.4% (range: 2–100%). LNI was evenly distributed between unilateral and bilateral occurrences, each observed in 48 patients (50%). The tumor location involved both lobes of the prostate in all cases, with varying percentages of tissue occupancy. Table 1 presents the comprehensive clinicopathological data for the entire study population.

3.2. Unilateral and Bilateral Lymphovascular Invasion

Unilateral LVI was identified in 85 patients (88.5%), with 61 patients (71.8%) exhibiting LVI exclusively in the left lobe and 24 patients (28.2%) exclusively in the right lobe. Bilateral LVI was observed in 11 patients (11.5%). Regarding pT stage, unilateral LVI was identified in 1 patient (1.2%) with pT2a disease, 5 patients (5.9%) with pT2c disease, 14 patients (16.5%) with pT3a disease, and 65 patients (76.5%) with pT3b cancer. All men with bilateral LVI exhibited pT3b disease in the final histopathology. The mean number of dissected LNs was 21.2 (range: 5–74) in unilateral LVI patients and 23.5 (range: 12–35) in bilateral LVI patients. Additionally, the mean number of positive LNs was 4.1 (range: 1–30) in unilateral LVI patients and 4.4 (range: 1–9) in bilateral LVI patients. The mean percentage of positive LNs was 19.7% (range: 2.4–100%) in unilateral LVI patients and 17.7% (range: 4.5–31.6%) in bilateral LVI patients.

In the group of 96 pL1 pN1 patients included in the study and 38 unincluded pL1 pN0 patients (n = 144), 87 (60.4%) had LVI only on the left side, 40 (27.8%) had LVI only on the right, and 16 (11.1%) had LVI on both sides of the prostate.

Table 1. Characteristics of patient population.

Clinicopathological Data	All Patients (*n* = 96)
Age	64.3 ± 6.8; 64.5 (41–78)
Preoperative PSA	27.9 ± 25.8; 22.0 (2.3–174)
cT stage	
cT1	3 (3.1%)
cT2	52 (54.2%)
cT3	37 (38.5%)
cT4	4 (4.2%)
Biopsy GGG	
1	17 (17.7%)
2	22 (22.9%)
3	22 (22.9%)
4	17 (17.7%)
5	18 (18.8%)
pT stage	
pT2a	1 (1.0%)
pT2c	5 (5.2%)
pT3a	14 (14.6%)
pT3b	76 (79.2%)
Pathological GGG	
1	0 (0.0%)
2	13 (13.5%)
3	30 (31.3%)
4	12 (12.5%)
5	41 (42.7%)
Number of removed LNs	21.5 ± 10.5; 20.0 (5–74)
Number of positive LNs	4.2 ± 4.7; 3 (1–30)
% of positive LNs	19.5 ± 17.2%; 13.4% (2–100%)
LVI laterality	
Unilateral	85 (88.5%)
Bilateral	11 (11.5%)
LNI laterality	
Unilateral	48 (50.0%)
Bilateral	48 (50.0%)

All continuous data are presented as mean ± SD and median (range). All interval data are presented as number and percent. PSA: prostate-specific antigen; cT: clinical tumor stage; GGG: Gleason Grading Group; pT: pathological tumor stage; LNs: lymph nodes; LVI: lymphovascular invasion; LNI: lymph node invasion.

Table 2 shows the clinicopathological data in the subgroups of 85 unilateral LVI patients and 11 bilateral LVI patients. Figure 2 depicts the patient distribution, classifying them into unilateral left, unilateral right, and bilateral groups based on LVI laterality. Similarly, Figure 3 illustrates the distribution of patients, categorizing them into unilateral left, unilateral right, and bilateral groups based on nodal invasion laterality.

Table 2. Comparison of clinicopathological data in patients with unilateral and bilateral lymphovascular invasion.

Clinicopathological Data	Patients with Unilateral LVI (*n* = 85)	Patients with Bilateral LVI (*n* = 11)
Age	64.6 ± 6.5; 64.6 (42–78)	61.3 ± 8.6; 64.2 (41–71)
Preoperative PSA	28.1 ± 24.8; 22.9 (2.3–174.0)	26.3 ± 33.7; 14.3 (7.9–124.9)
Clinical T stage		
cT1	3 (3.5%)	0 (0.0%)
cT2	45 (52.9%)	7 (63.6%)
cT3	34 (40.0%)	3 (27.3%)
cT4	3 (3.5%)	1 (9.1%)
Biopsy GGG		
1	17 (20.0%)	0 (0.0%)
2	17 (20.0%)	5 (45.5%)
3	18 (21.2%)	4 (36.4%)
4	16 (18.8%)	1 (9.1%)
5	17 (20.0%)	1 (9.1%)
Laterality		
Left	61 (71.8%)	-
Right	24 (28.2%)	-
Pathological T stage		
pT2a	1 (1.2%)	0 (0.0%)
pT2c	5 (5.9%)	0 (0.0%)
pT3a	14 (16.5%)	0 (0.0%)
pT3b	65 (76.5%)	11 (100.0%)
Pathological GGG		
1	0 (0.0%)	0 (0.0%)
2	12 (27.1%)	1 (9.1%)
3	23 (27.1%)	7 (63.6%)
4	11 (12.9%)	1 (9.1%)
5	39 (45.9%)	2 (18.2%)
Number of removed LNs	21.2 ± 10.9; 20.0 (5–74)	23.5 ± 7.2; 24.0 (12–35)
Number of positive LNs	4.1 ± 5.0; 3.0 (1–30)	4.4 ± 2.7; 5.0 (1–9)
% of positive LNs	19.7 ± 18.0%; 13.3% (2.4–100%)	17.7 ± 9.2%; 20.0% (4.5–31.6%)

All continuous data are presented as mean ± SD and median (range). All interval data are presented as number and percent. LVI: lymphovascular invasion; PSA: prostate-specific antigen; cT: clinical tumor stage; GGG: Gleason Grading Group; pT: pathological tumor stage; LNs: lymph nodes.

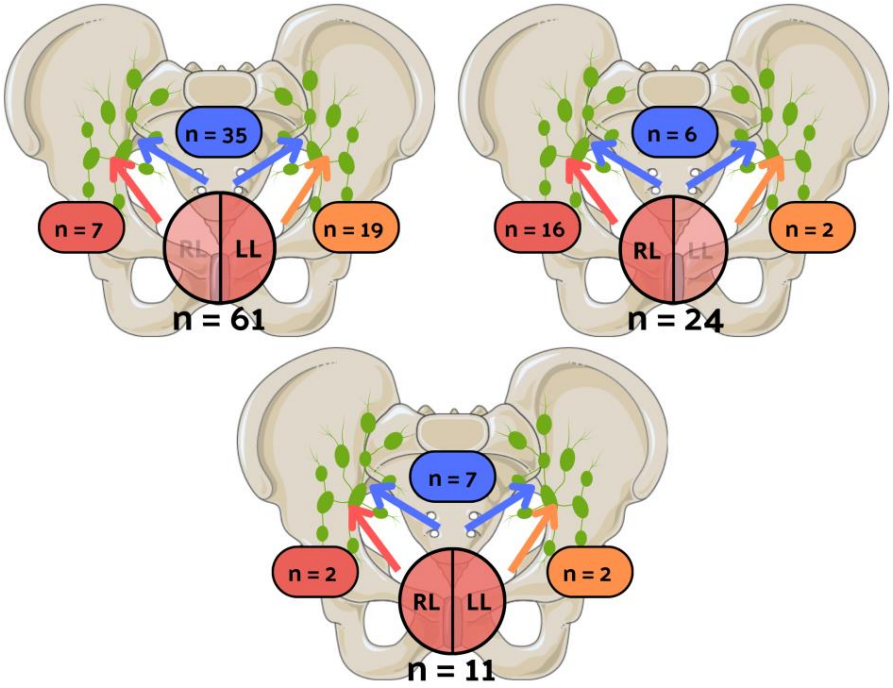

Figure 2. The visual illustration of patients' distribution, categorizing them into unilateral left, unilateral right, and bilateral groups based on lymphovascular invasion (LVI) laterality. Yellow color represents the number of patients with positive lymph nodes only on the left side, red color represents patients with nodal involvement exclusively on the right side, and blue color represents patients with bilateral nodal invasion. n: number of patients; RL: LVI in the right lobe; LL: LVI in the left lobe.

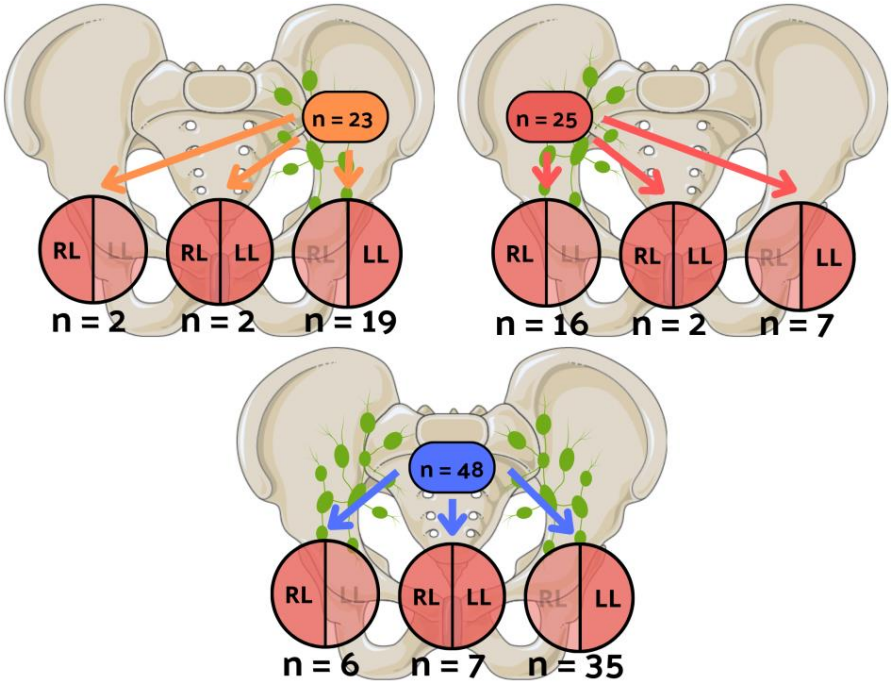

Figure 3. The visual illustration of patients' distribution, categorizing them into unilateral left, unilateral right, and bilateral groups based on nodal invasion laterality. Yellow color represents the number of patients with positive lymph nodes only on the left side, red color represents patients with nodal involvement exclusively on the right side, and blue color represents patients with bilateral nodal invasion. n: number of patients; RL: lymphovascular invasion (LVI) in the right lobe; LL: LVI in the left lobe.

3.3. Unilateral Left and Unilateral Right Lymphovascular Invasion

In the cohort of 85 patients with unilateral LVI, the majority, 61 individuals (71.8%), exhibited LVI exclusively in the left lobe, while 24 patients (28.2%) had LVI isolated to the right lobe. Regarding pT stage, unilateral left LVI patients exhibited the following distribution: 2 patients (3.3%) had pT2c disease, 8 patients (13.1%) had pT3a, and 51 (83.6%) had pT3b disease. In unilateral right LVI patients, 1 patient (4.2%) had pT2a disease, 3 patients (12.5%) had pT2c disease, 6 patients (25.0%) had pT3a, and 14 (58.3%) had pT3b. The mean numbers of positive LNs were 4.3 (range: 1–23) and 3.8 (range: 1–30) in the unilateral left and right LVI groups, respectively. A comprehensive presentation of clinicopathological data, including associations with LVI laterality along with corresponding *p*-values, is provided in Table 3.

Table 3. Comparison of clinicopathological data in patients with unilateral left and unilateral left right lymphovascular invasion.

Clinicopathological Data	Patients with Unilateral Left LVI (*n* = 61)	Patients with Unilateral Right LVI (*n* = 24)	*p*-Value
Age	64.6 ± 6.4; 64.9 (42.2–76.8)	64.8 ± 6.8; 63.8 (54.2–78.0)	0.792
Preoperative PSA	30.2 ± 27.4; 24.2 (2.3–174.0)	22.9 ± 15.9; 19.7 (4.4–76.0)	0.287
Clinical T stage			0.463
cT1	3 (4.9%)	0 (0.0%)	
cT2	31 (50.8%)	14 (58.3%)	
cT3	24 (39.3%)	10 (41.7%)	
cT4	3 (4.9%)	0 (0.0%)	
Biopsy GGG			0.143
1	9 (14.8%)	8 (33.3%)	
2	14 (23.0%)	3 (12.5%)	
3	13 (21.3%)	5 (20.8%)	
4	10 (16.4%)	6 (25.0%)	
5	15 (24.6%)	2 (8.3%)	
Pathological T stage			**0.047**
pT2a	0 (0.0%)	1 (4.2%)	
pT2c	2 (3.3%)	3 (12.5%)	
pT3a	8 (13.1%)	6 (25.0%)	
pT3b	51 (83.6%)	14 (58.3%)	
Pathological GGG			0.464
1	0 (0.0%)	0 (0.0%)	
2	8 (13.1%)	4 (16.7%)	
3	14 (23.0%)	9 (37.5%)	
4	9 (14.8%)	2 (8.3%)	
5	30 (49.2%)	9 (37.5%)	
Number of removed LNs	21.5 ± 10.2; 20.0 (5–67)	20.5 ± 12.6; 18.5 (9–74)	0.379
Number of positive LNs	4.3 ± 4.5; 3.0 (1–23)	3.8 ± 6.2; 2.0 (1–30)	0.069
% of positive LNs	20.8% ± 18.5%; 16.7% (2.4–100%)	16.9% ± 16.7%; 10% (3.6–61.1%)	0.135
LNI laterality			**<0.001**
Unilateral left	19 (31.1%)	2 (8.3%)	
Unilateral right	7 (11.5%)	16 (66.7%)	
Bilateral	35 (56.4%)	6 (25.0%)	

All continuous data are presented as mean ± SD and median (range). All interval data are presented as number and percent. LVI: lymphovascular invasion; PSA: prostate-specific antigen; cT: clinical tumor stage; GGG: Gleason Grading Group; pT: pathological tumor stage; LNs: lymph nodes.

3.4. Odds Ratios and Patient Distribution

Unilateral left LVI patients exhibited an OR of 3.609 (95% CI: 0.925–14.077) for exclusive ipsilateral LNI, an OR of 0.185 (95% CI: 0.092–0.374) for exclusive contralateral LNI, and an OR of 2.795 (95% CI: 1.231–6.348) for bilateral LNI. Meanwhile, unilateral right LVI patients demonstrated an OR of 2.862 (95% CI: 1.531–5.348) for exclusive ipsilateral LNI, an OR of 0.725 (95% CI: 0.579–0.908) for exclusive contralateral LNI, and an OR of 0.692 (95% CI: 0.525–0.913) for bilateral LNI. The detailed ORs and their 95% CIs are outlined in Table 4, while Figure 4 visually represents the proportional relationships in our study cohort through a Marimekko chart.

Table 4. Odds ratios and 95% confidence intervals illustrating the associations between lymphovascular invasion laterality and lymph node invasion laterality in prostate cancer patients.

LNI Laterality	Patients with Unilateral Left LVI (*n* = 61)	OR (95% CI)	Patients with Unilateral Right LVI (*n* = 24)	OR (95% CI)
Unilateral left	19 (31.1%)	3.609 (0.925–14.077)	2 (8.3%)	0.725 (0.579–0.908)
Unilateral right	7 (11.5%)	0.185 (0.092–0.374)	16 (66.7%)	2.862 (1.531–5.348)
Bilateral	35 (57.4%)	2.795 (1.231–6.348)	6 (25.0%)	0.692 (0.525–0.913)

LNI: lymph node invasion; LVI: lymphovascular invasion; n: number of patients; OR: odds ratio; CI: confidence interval.

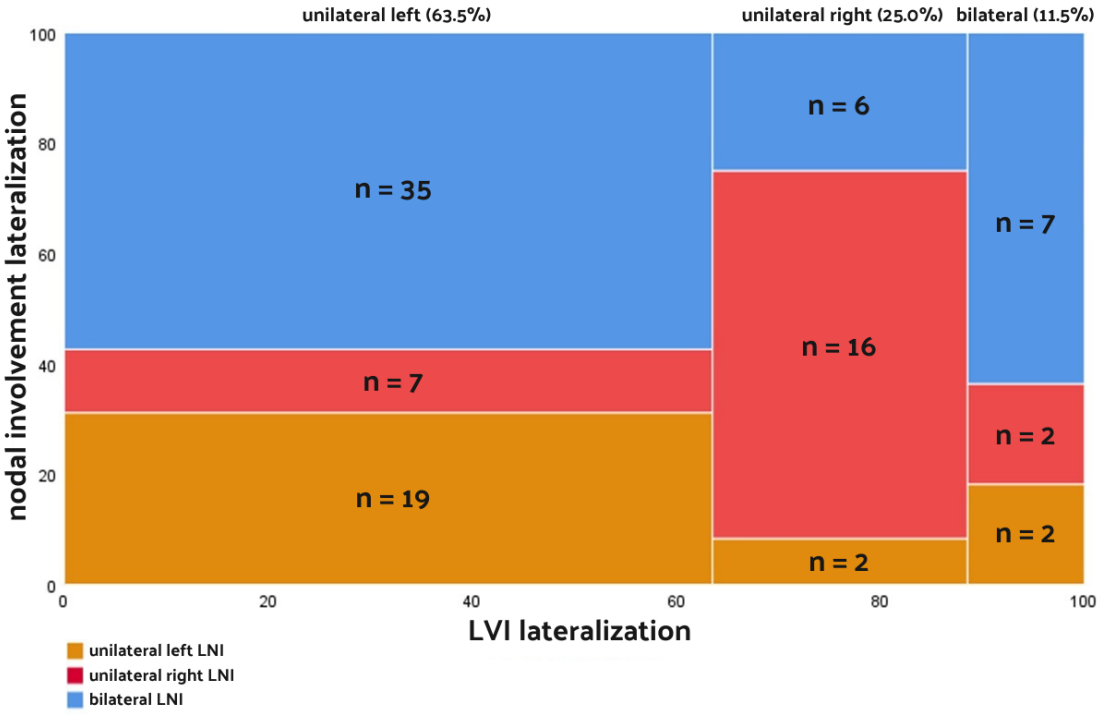

Figure 4. The Marimekko chart depicting the proportional relationship between lymphovascular invasion and lymph node invasion. LVI: lateralization; LNI: lymph node invasion; n: number of patients.

4. Discussion

This study is the first to evaluate the laterality of LVI in PCa and its correlation with the lateralization of nodal involvement. While the impact of LVI on lateralized LNI has been explored in various malignancies such as thyroid, oropharyngeal, and rectal cancers, the specific investigation of LVI laterality in the setting of PCa has not been previously undertaken [22–29]. Existing studies have primarily focused on the broader question of

whether LVI influences lateralized LNI, omitting an in-depth exploration of LVI laterality itself [22,23].

LVI is a significant histopathological finding linked to unfavorable outcomes such as biochemical recurrence (BCR), nodal metastases, and other adverse histopathological consequences [30]. Notably, various studies support LVI as an independent factor associated with a worse prognosis. The meta-analysis by Jiang et al. reported a correlation between LVI and BCR (HR = 1.25; 95% CI: 1.17, 1.34; $p < 0.001$, multivariate analysis) as well as nodal involvement (OR = 18.56; 95% CI: 7.82–44.06) [30]. This aligns with findings from previous meta-analyses and large cohort studies [12,13,31,32]. Additionally, existing research has identified associations between LVI and distant metastases [33,34].

The ongoing debate in the PCa field regarding ipsi- and contralateral LNI, coupled with emerging studies on sentinel LN mapping, particularly heightens the relevance of our investigation [15,16,35–37]. Bilateral pelvic lymphadenectomy performed during RP remains the gold standard for nodal staging [38]. Despite its debatable therapeutic utility and an increased risk of procedure-associated morbidity, its position in the current guidelines is well-established [38–43]. Nonetheless, a growing perspective suggests that a subset of patients may benefit from unilateral PLND. A recent investigation conducted by Martini et al. identified the absence of high-risk disease features as a potential characteristic that might offer substantial benefits to patients undergoing ipsilateral PLND while omitting contralateral LNs [15]. Future investigations could enhance the process of patient selection for unilateral lymphadenectomy by incorporating additional factors. LVI, a histopathological parameter assessable not only in the final histopathology but also preoperatively through prostate biopsy, holds potential for providing valuable insights into the lateralization of PCa progression and metastasis, particularly when considering the distinct assessment of the left and right lobes separately. With the inclusion of preoperative factors that could facilitate early patient selection in the management process, LVI, along with other parameters, could play a significant role in determining candidates for unilateral lymphadenectomy [44]. Moreover, this study holds significance in the era of continually advancing imaging techniques that could offer greater insights into the lateralization concept in PCa [45,46]. Integrating multiple factors (such as LVI, dominant tumor location, or perineural invasion) assessed individually on the right and left sides of the prostate, along with modern imaging techniques, could pave the way for unilateral lymphadenectomy in selected patients. This approach may help avoid the adverse outcomes associated with bilateral PLND, including longer operative time and a higher burden of perioperative complications [39].

Our study revealed that lateral LVI is associated with lateralization of LNI in LN-positive PCa patients ($p < 0.001$). This correlation is particularly pronounced in unilateral right pL1 patients, as over half of patients (35/61; 56.4%) with LVI exclusively on the left side of the prostate exhibited bilateral LNI. Notably, LN-positive patients exhibiting LVI exclusively on the right side appear to manifest a lower risk disease phenotype compared to those with exclusive left-sided LVI. This observation aligns with the identified correlation with pT stage ($p = 0.047$), emphasizing a predilection for exclusively right-sided LNI. However, cautious interpretation of these findings is warranted due to the limited size of the patient cohort and the proximity of the p-value confirming the correlation with pT stage to the significance threshold ($p = 0.047$). Furthermore, the dissonance between the left- and right-LVI groups may also be attributed to the complex anatomical lymphatic drainage. Although studies have explored lymphatic drainage patterns and their association with specific lymph node groups, the complexity of intraprostatic lymphatic vessels remains unclear [47–49]. Moreover, the obstruction of intraprostatic lymphatic system, and the surgical manipulation itself, could lead to uneven distribution of unilateral right and left LVI patients [50].

In the unilateral left LVI group, the occurrence of ipsilateral LNI was 2.71 times higher (19/7) than contralateral LNI. Conversely, in the unilateral right LVI group, patients with ipsilateral LNI were 8 times more prevalent (16/2) than those with contralateral

LNI. Notably, among patients with bilateral nodal metastases (n = 48), the majority (35/48, 72.9%) exhibited unilateral left LVI in the prostate gland, while only seven individuals (7/48, 14.6%) had bilateral LVI. Several factors may contribute to these observations, including the relatively small cohort size, and the lack of information on nerve-sparing approaches during surgery, as well as lymphatic system complexity. Nevertheless, we believe that our study can contribute additional insights to the concept of lateralization in PCa nodal metastasis, potentially enriching the discussion on unilateral lymphadenectomy and identifying the patients who could benefit the most from this approach. Perhaps incorporating the laterality of LVI into the existing parameters of the lateralization concept could provide another argument either in favor of or against unilateral PLND in selected patients.

In discussing the limitations of our study, it is imperative to acknowledge the constraints posed by the relatively small patient cohort. The modest sample size may have impacted the statistical power, influencing the significance of p-values. This limitation underscores the necessity for further investigations with larger cohorts to validate and strengthen the observed correlations. Additionally, the retrospective and single-center nature of the data collection poses inherent limitations. A multi-center approach and a prospective study design would enhance the generalizability and robustness of the findings. Furthermore, the inclusion of LVI status from biopsy specimens, in addition to the final histopathology, could provide a more comprehensive understanding of the temporal aspects of LVI development and progression. A notable consideration is the absence of data on dominant tumor location, which could offer valuable insights into the laterality issue. Although the tumors in our patient cohort were predominantly located in both lobes, the lack of information on specific tumor locations within the lobes limits our ability to explore the potential impact of tumor localization on LVI laterality. Finally, the racial disparity in PCa diagnosis and management, particularly evident in the contrasting outcomes between African-American and Caucasian men, underscores a crucial aspect of PCa research. Thus, it is important to note that our study's patient cohort consisted solely of Caucasian men from the Polish population, limiting the generalizability of our findings.

5. Conclusions

In this retrospective analysis, we observed a correlation between unilateral LVI and ipsilateral LNI in patients with positive LNs in PCa, particularly pronounced in cases where LVI exclusively occurred in the right prostate lobe. Notably, individuals with LVI restricted to the left side tended to exhibit higher pT stages in our study cohort. To the best of our knowledge, this study represents the first investigation on the laterality of LVI in PCa. However, cautious interpretation is warranted given the study's limited sample size. Future inquiries should ideally adopt a prospective, multi-center design, encompassing more extensive data on primary tumor location. Moreover, integrating preoperative LVI assessment at biopsy, alongside the standard postoperative evaluation in final histopathology, has the potential to enhance our overall comprehension of PCa progression. Additionally, it could provide valuable insights into preoperative decision-making alterations.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Wroclaw Medical University (protocol code KB-755/2022, approved on 27 October 2022).

Informed Consent Statement: Participants were routinely provided with informed consent for the scientific utilization of anonymized treatment data during their hospital stay.

Data Availability Statement: The data supporting the findings of this study are available upon request. Please contact the corresponding author for access to the dataset.

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

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12.3. Artykuł trzeci

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The clinical meaning of lymphovascular invasion: preoperative predictors and postoperative implications in prostate cancer - a retrospective study

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The clinical meaning of lymphovascular invasion: preoperative predictors and postoperative implications in prostate cancer - a retrospective study

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Introduction: Lymphovascular invasion (LVI) is a pivotal histopathological parameter in prostate cancer (PCa), holding significant prognostic implications. Our study pursued a dual objective: firstly, to identify preoperative factors associated with LVI, aiming to unveil markers facilitating the recognition of patients prone to LVI during postoperative examination; and secondly, to assess postoperative outcomes correlated with LVI.

Methods: We retrospectively analyzed 861 nonmetastatic PCa patients who underwent radical prostatectomy (RP), investigating preoperative factors and postoperative outcomes. Surgical specimens were processed following established guidelines. Statistical analyses utilized non-parametric tests to assess the association between LVI and both pre- and postoperative factors. Furthermore, logistic regression analyses were utilized to develop models aimed at identifying the most significant predictors of LVI and pN1 status, respectively.

Results: Numerous preoperative factors exhibited significant correlations with LVI, offering valuable clinical insights. Logistic regression identified magnetic resonance imaging (MRI)-based clinical tumor stage (cT) 3-4, biopsy Gleason Grading Group (GGG) 3-5, preoperative prostate specific antigen (PSA) ≥20 and percentage of positive biopsy cores (PPBC) ≥50% as the strongest preoperative predictors of LVI. Additionally, the study uncovered an association between LVI and postoperative outcomes, including postoperative PSA (*p* value <0.001), extracapsular extension (ECE) (<0.001), positive surgical margins (PSM) (<0.001), perineural invasion (PNI) (<0.001), pathological tumor stage (pT)

(<0.001), pathological lymph node status (pN) (<0.001), postoperative GGG (<0.001), and operative time (0.023). Notably, the study revealed a novel and substantial association between LVI and an increased number of positive lymph nodes in pN+ patients in the univariate analysis (<0.001). Furthermore, we have found an association between LVI and pN1 status in the logistic regression analysis (odds ratio [OR] = 23.905; p <0.001).

Conclusion: Our findings underscore the pivotal role of LVI in influencing the prognosis of prostate cancer (PCa). The study acknowledges the challenges associated with preoperative LVI assessment and emphasizes the need for future research to unravel the factors associated with this histopathological finding. Significantly, our research stands out as the first, to the best of our knowledge, to reveal the association between LVI and the number of positive lymph nodes in pN+ patients.

KEYWORDS

prostate cancer, radical prostatectomy, lymphovascular invasion, histopathological examination, oncologic staging, prognostic factors

1 Introduction

Lymphovascular invasion (LVI), also known as microvascular invasion (1–3) or vessel tumor embolus (4–6), is most often defined as the unequivocal presence of tumor cells within endothelial-lined spaces (7). In the context of prostate cancer (PCa), the second most common malignancy in men worldwide (8), LVI has emerged as a pivotal histopathological parameter with significant prognostic implications.

The pathological evaluation of radical prostatectomy (RP) specimens assumes paramount importance in predicting patient outcomes accurately. Traditionally, key histopathological determinants such as Gleason score, pathological tumor (pT) stage, lymph node status (pN), or surgical margin status have informed prognostication. However, multiple systematic reviews and meta-analyses consistently demonstrate that the presence of LVI in final histopathology (pL1) is associated with adverse clinical outcomes, including higher rates of biochemical recurrence, diminished survival rates, and an increased likelihood of unfavorable histopathological features such as perineural invasion (PNI), positive surgical margins (PSM), and nodal involvement (7, 9–11). In cases where evidence of LVI is identified within a prostate cancer needle biopsy specimen, it is recommended that patients forego active surveillance (AS) and opt for radical treatment (12, 13). The presence of LVI in the final histopathological assessment is considered unfavorable, as it is associated with other adverse pathological outcomes and unfavorable survival rates, as indicated by the guidelines of the European Association of Urology (EAU) (13).

The controversy surrounding LVI primarily emanates from the reliance on retrospective studies for data analysis. Furthermore, it is exacerbated by instances where LVI exhibits significance in predicting biochemical recurrence (BCR) only within univariate settings but loses significance in multivariate analyses, as observed in certain studies (4, 14, 15). Additionally, the issue is compounded by the considerable variability in reported LVI frequencies, ranging widely from 3.6% to 53% (16, 17).

Our study aims to address the existing gaps in the literature by focusing on the pivotal role of LVI in PCa prognosis. Specifically, our primary objective is to identify preoperative factors associated with the presence of LVI, shedding light on potential predictive markers in the context of PCa. Additionally, our research group endeavors to elucidate the intricate relationship between LVI and adverse histopathological outcomes, thereby enhancing our understanding of the broader implications of LVI in this context. Through our investigation, we aim to contribute valuable insights to the field, ultimately advancing the clinical management and prognostication of PCa patients.

2 Materials and methods

2.1 Patient population and clinicopathological data

We analyzed 861 patients with histologically confirmed nonmetastatic PCa who underwent RP at University Center of Excellence in Urology in Wrocław, Poland, between September 2012 and November 2021. The exclusion criteria comprised missing LVI status (pLx). We decided not to exclude patients with the history of neoadjuvant therapy. In pursuit of maximizing our dataset, we opted to include patients with missing data. The

patient counts (n) with available data for each covariate can be found in Tables 1, 2, situated adjacent to the respective variables.

The clinical T stage was assessed according to the TNM classification from 2016 (18); the prostate biopsy was obtained by TRUS-guided systematic, targeted, or combined biopsy. The following baseline characteristics and clinical parameters were retrospectively collected and evaluated for each patient. Preoperative data included: age at the time of surgery, body weight and body mass index (BMI), smoking status and pack-years, biopsy serum PSA (PSA at diagnosis) and preoperative serum PSA level, testosterone level, albumin level, preoperative hemoglobin level, platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), biopsy Gleason score (Gleason Grading Groups, GGG), percentage of positive systematic biopsy cores (PPBC), clinical T (cT) stage assessed after digital rectal examination (DRE), scintigraphy results, cT and cN stages proposed after MRI, prostate volume, and EAU risk group classification.

The surgical approach for RP involved either open with an ascending technique or laparoscopic with extra- or transperitoneal access. In both cases, a modified-extended pelvic lymphadenectomy (mePLND) was performed (19), encompassing the removal of tissues around the obturator fossa, internal and external iliac arteries, extending to the distal part of the common iliac artery, as well as presacral regions and Marcille's fossa. Peri- and postoperative data we collected included: blood loss, blood transfusion, postoperative hemoglobin, postoperative PSA, extracapsular extension (ECE), surgical margins, PNI, LVI status (pL0 or pL1), pathological T (pT) and pN stages, postoperative Gleason scores, number of positive lymph nodes in pN+ patients, and operative time.

2.2 Pathologic examination

Surgical specimens were collected and processed according to the Stanford protocol guidelines. The specimens were fixed in a neutral buffered formalin solution and embedded in paraffin. Tissue samples were sectioned using a microtome and stained with hematoxylin and eosin (H&E). Experienced uropathologists evaluated the sample slides and documented the results based on a standardized reporting system. Pathological stages were defined according to the American Committee's guidelines for the Staging System for Prostate Cancer (20), and Gleason scores were determined following the International Society of Urological Pathology (ISUP) PCa grading consensus (21). Detailed pathological findings for the presence of LVI, PNI, ECE, and surgical margins were also examined and documented. LVI was defined as the unequivocal presence of tumor cells within endothelial-lined spaces with no underlying muscular walls (22) or the presence of tumor emboli in small intraprostatic vessels (23). The analysis of LVI included evaluations of both prostate and seminal vesicle specimens. In our study cohort, all patients showed LVI exclusively in prostate specimens, with no instances observed in seminal vesicles. While the presence of LVI in seminal vesicles was not a specific exclusion criterion, it is a rare event based on our center's experience. In cases where diagnostic uncertainty arose, podoplanin (D2-40 or PDPN) staining was utilized to aid uropathologists in their decision-making process.

2.3 Statistical analysis

All statistical analyses were carried out using PS Imago Pro 9.0, 2022, polish license. Data were expressed as means ± SD and/or median (range) for continuous variables and number (percentage) for categorical variables. To assess the normal distribution of variables, we employed the Shapiro-Wilk tests (24). The distribution of all variables subjected to analysis significantly deviated from a normal distribution. Consequently, the research team relied on nonparametric measures with lower formal requirements. Specifically, the U-Mann-Whitney test was used to compare mean levels between two groups with dichotomous variables. The Kruskal-Wallis test assessed differences in mean levels among groups with categorical variables, each having at least three levels. Additionally, Kendall's tau-b coefficient was applied to determine if two variables can be considered statistically dependent. In all cases, a two-sided testing approach was applied. Statistically significant differences between groups occur when the test statistic (p-value) is less than 0.05. Additionally, logistic regression made it possible to identify significant preoperative factors that are the strongest predictors of LVI. In the analyses, a stepwise estimation method was employed, involving the iterative selection of variables for the model. In the initial step, the model is computed for all potential variables. Subsequent iterations eliminate the least fitting variables that disrupt the model's significance and coefficient of determination. Ultimately, the method enables the attainment of the most optimal model tailored to the selected variables. Initially, six models were tested, each comprising seven variables (cT, cN, biopsy GGG, biopsy PSA (or PSA at diagnosis), preoperative PSA, PPBC, and MRI based cT), which were appropriately coded. Furthermore, we conducted an additional logistic regression analysis to identify significant factors that serve as predictors of pN1 status, aiming to evaluate the significance of LVI as a potential determinant for nodal involvement. This model incorporated eight variables, including postoperative GGG, pT stage, PPBC, preoperative PSA level, ECE, PSM, PNI, and LVI. Additionally, we carried out a linear regression analysis to identify predictors associated with the number of positive lymph nodes in pN1 patients.

3 Results

Mean patient age at diagnosis was 64.1 years (range 31 to 80), and mean PSA was 14.0 ng/mL. The mean percent of positive biopsy cores (PPBC) was 39.7% (range 0 to 100%). 4 (0.5%) of the 861 patients had pT1 disease after histopathological examination, 489 (57.1%) had pT2 disease, 362 (42.3%) had pT3 disease, and 1 patient (0.1%) had pT4 disease. Of 647 patients, 143 (22.1%) showed lymph node involvement. In the whole analyzed cohort of 861 patients, 152 (17.7%) obtained pL1 status in the final histopathology.

TABLE 1 Association of lymphovascular invasion with preoperative clinicopathological parameters in 861 patients who underwent radical prostatectomy.

Characteristic	*n*	pL0 (*n* = 709; 82.3%)	*n*	pL1 (*n* = 152; 17.7%)	*p* value
Demographic characteristics					
Age at RP, years	708	64.1 ± 6.3, 65 (31-80)	152	63.9 ± 6.6, 64 (41-78)	0.714
Body mass, kg	602	85.4 ± 13.4, 85 (52-130)	136	87.3 ± 13.5, 85 (52-140)	0.230
BMI	595	27.9 ± 3.9, 27.7 (18-43.9)	134	28.3 ± 4, 27.9 (18.4-45.2)	0.414
Pack-years (in smokers)	125	21.4 ± 13.5, 20 (2-80)	27	25 ± 16, 20 (0.6-60)	0.275
Clinical parameters					
Biopsy PSA, ng/ml	458	11.6 ± 10.6, 8.4 (1-104)	87	22.3 ± 22.8, 17 (2.8-149)	**<0.001**
Preoperative PSA, ng/ml	664	11.6 ± 10.4, 8.6 (0-97.5)	145	24.6 ± 23.3, 18.7 (0.4-174)	**<0.001**
Testosterone, ng/ml	338	3.7 ± 1.6, 3.5 (0.1-9.6)	63	3.9 ± 1.9, 3.8 (0.1-9)	0.400
Albumins, ng/ml	313	4.4 ± 0.3, 4.5 (3.5-5.7)	52	4.4 ± 0.3, 4.4 (3.3-4.9)	0.064
Preoperative Hgb, g/dl	692	14.1 ± 1.3, 14.9 (9.4-19)	147	14.7 ± 1.2, 14.9 (10.2-17.3)	0.493
PLR	304	139.8 ± 55.5, 129.9 (7.5-335.6)	52	139.6 ± 52, 133.8 (61.8-274.7)	0.933
NLR	307	3.2 ± 3.4, 2.6 (0.4-38.2)	52	3.5 ± 4.6, 2.5 (0.9-34.6)	0.984
Clinical T stage					**<0.001**
cT1	77	96.3%	3	3.7%	
cT2	523	85.9%	86	14.1%	
cT3	66	54.5%	55	45.5%	
cT4	1	25%	3	75%	
Pathological parameters					
Biopsy GGG					**<0.001**
GGG1	372	92.8%	29	7.2%	
GGG2	153	84.1%	29	15.9%	
GGG3	67	71.3%	27	28.7%	
GGG4	74	72.5%	28	27.5%	
GGG5	28	46.7%	32	53.3%	
PPBC, %	364	35 ± 23, 31 (0-100)	86	51 ± 29, 58 (0-100)	**<0.001**
Imaging parameters					
Preoperative scintigraphy					0.823
no changes	301	82.9%	62	17.1%	
3 or less changes	11	68.8%	5	31.3%	
over 3 changes	2	100%	0	0%	
MRI T stage					**<0.001**
cT1	16	100%	0	0%	
cT2	137	85.1%	24	14.9%	
cT3	20	52.6%	18	47.4%	
cT4	1	100%	0	0%	
MRI N stage					**0.003**
cN0	177	82.3%	38	17.7%	

(Continued)

TABLE 1 Continued

Characteristic	*n*	pL0 (*n* = 709; 82.3%)	*n*	pL1 (*n* = 152; 17.7%)	*p* value
Imaging parameters					
cN1	5	45.5%	6	54.5%	
Prostate volume, ml	544	40.5 ± 19.6, 36 (2-220)	107	42 ± 18.8, 40 (15-130)	0.239
Other					
EAU risk group					**<0.001**
1	146	96.1%	6	3.9%	
2	179	94.2%	11	5.8%	
3	234	75.5%	76	24.5%	
4	54	55.1%	44	44.9%	

All continuous data is presented as mean ± SD and/or median (range). All interval data is presented as number and percent. n, number of patients; pL0, patients without lymphovascular invasion in final histopathology; pL1, patients with lymphovascular invasion in final histopathology; RP, radical prostatectomy; BMI, body mass index; PSA, prostate specific antigen; Hgb, hemoglobin; PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; cT, clinical tumor stage; GGG, Gleason Grading Group; PPBC, percentage of positive biopsy cores; MRI, magnetic resonance imaging; cN, clinical lymph node status; EAU, The European Association of Urology.

TABLE 2 Association of lymphovascular invasion with various peri- and postoperative clinicopathological parameters in 861 patients who underwent radical prostatectomy.

Characteristic	*n*	pL0 (*n* = 709; 82.3%)	*n*	pL1 (*n* = 152; 17.7%)	*p* value
Clinical parameters					
Blood loss, ml	656	657.7 ± 413.1, 600 (0-3,300)	143	733 ± 520.6, 600 (100-3,600)	0.244
Blood transfusion	695	0.2 ± 0.8, 0 (0-10)	151	0.3 ± 1.1, 0 (0-8)	0.278
Postoperative Hgb, g/dl	673	12.3 ± 1.3, 12.3 (6.7-16.6)	142	12.2 ± 1.4, 12.2 (7.3-16.8)	0.254
Postoperative PSA, ng/ml	342	0.2 ± 1.3, 0 (0-18)	95	1.4 ± 4.5, 0.1 (0-35)	**<0.001**
Histopathological parameters					
ECE					**<0.001**
negative	475	95.4%	23	4.6%	
focal	115	74.7%	39	25.3%	
diffuse	115	56.4%	89	43.6%	
Surgical margin					**<0.001**
negative	376	90.8%	38	9.2%	
≤ 3 mm	139	79.4%	36	20.6%	
> 3 mm	171	69.5%	76	30.5%	
PNI					**<0.001**
negative	75	97.4%	2	2.6%	
positive	608	81.1%	142	18.9%	
Pathological T stage					**<0.001**
pT1	4	100%	0	0%	
pT2	474	96.9%	15	3.1%	
pT3	226	62.4%	136	37.6%	
pT4	0	0%	1	100%	

(Continued)

TABLE 2 Continued

Characteristic	*n*	pL0 (*n* = 709; 82.3%)	*n*	pL1 (*n* = 152; 17.7%)	*p* value
Histopathological parameters					
Pathological N stage					**<0.001**
pN-	463	91.9%	41	8.1%	
pN+	36	25.2%	107	74.8%	
Postoperative GGG					**<0.001**
GGG1	121	99.2%	1	0.8%	
GGG2	276	92.6%	22	7.4%	
GGG3	164	78.8%	44	21.2%	
GGG4	62	79.5%	16	20.5%	
GGG5	76	53.5%	66	46.5%	
Positive LNs in pN+ patients	36	1.9 ± 2.1, 1 (1-12)	107	4.07 ± 4.8, 3 (1-31)	**<0.001**
Other					
Operative time, minutes	665	174.3 ± 47.8, 165 (60-375)	148	184.6 ± 49.4, 180 (75-375)	**0.023**

All continuous data is presented as mean ± SD and/or median (range). All interval data is presented as number and percent. n, number of patients; pL0, patients without lymphovascular invasion in final histopathology; pL1, patients with lymphovascular invasion in final histopathology; Hgb, hemoglobin; PSA, prostate specific antigen; ECE, extracapsular extension; PNI, perineural invasion; pT, pathological tumor stage; pN, pathological lymph node status; GGG, Gleason Grading Group; LNs, lymph nodes.

Tables 1, 2 show the association of LVI with pre- and postoperative clinicopathological variables. On univariate analyses, LVI was associated with higher PSA at diagnosis (biopsy PSA; $p < 0.001$), preoperative PSA (<0.001), clinical T stage (<0.001), biopsy GGG (<0.001), PPBC (<0.001), clinical T stage assessed with MRI (<0.001), MRI N stage (0.003), the EAU risk group (<0.001), postoperative PSA (<0.001), ECE (<0.001), PSM (<0.001), PNI (<0.001), higher pT stage (<0.001), pN stage (<0.001), postoperative GGG (<0.001), higher number of positive LNs in pN+ patients (<0.001), and with higher operative time (0.023).

The results of the logistic regression, conducted with the backward elimination method, are presented in Table 3. Among the identified predictors, MRI findings denoting clinical stage cT3-4, biopsy GGG of 3-5, preoperative PSA levels ≥20, and PPBC exceeding 50% emerged as the most influential factors. In the multivariate analysis, it is notable that both biopsy GGG and preoperative PSA levels were not statistically significant, as indicated by their respective p-values of 0.051 and 0.077. Nevertheless, patients with GGG 3-5 exhibited an odds ratio (OR) of 3.005 for having LVI, while patients with preoperative PSA levels exceeding 20 ng/ml demonstrated OR of 2.899. The logistic regression model underscored the significance of MRI clinical stage cT3-4 and a PPBC exceeding 50% as the strongest predictors. These factors exhibited OR of 4.739 and 7.364, respectively. The initial model incorporated three additional variables: clinical stage cT1-2 vs. cT3-4, cN0 vs. cN+, and biopsy PSA <20 vs. ≥20. Summary results for the regression model from Table 3 were as follows: $n = 861$, percentage of correct classifications = 88.1%, Nagelkerke's R2 = 0.458, Cox and Snell's R2 = 0.287, Hosmer-Lemeshow Test = 0.208. To ensure robust and reliable results, a total of six different models were tested with varying coding schemes for the same variables, exploring different threshold levels. All six models are presented in the Supplementary Table 1 in the Supplementary Material.

The results of logistic regression, investigating predictors of pN1 status, are summarized in Table 4. Among the analyzed factors, three showed statistical significance: pT3-4 (OR = 5.315; $p < 0.001$), extracapsular extension (ECE) (OR = 4.795; $p = 0.016$), and LVI (OR = 23.905; $p < 0.001$). The analysis included 295 patients. Additionally, the results of linear regression, examining predictive

TABLE 3 Logistic regression results with LVI occurrence in a final histopathological examination as a dependent variable.

Predictors	B	Wald	Statistical significance	Exp(B)
Biopsy GGG 3-5	1.100	3.807	0.051	3.005
MRI cT3-4	1.556	7.128	0.008	4.739
PPBC >50%	1.997	10.058	0.002	7.364
Preoperative PSA ≥20	1.064	3.122	0.077	2.899
Model constant	-9.481	32.997	0.000	0.000

B, unstandardized regression weight; exp(B), odds ratio; GGG, Gleason Grading Group; MRI, magnetic resonance imaging; cT, clinical tumor stage; PPBC, percent of positive biopsy cores; PSA, prostate specific antigen.

TABLE 4 Logistic regression results with pN1 as a dependent variable.

Predictors	B	Wald	Statistical significance	Exp(B)
Postoperative GGG 3-5	-0.329	0.489	0.485	0.720
pT3-4	1.671	13.355	0.000	5.315
PPBC >50%	0.888	1.497	0.221	2.430
Preoperative PSA ≥20	0.071	0.018	0.893	1.074
ECE	1.568	5.769	0.016	4.795
PSM	0.434	0.767	0.381	1.544
PNI	-0.398	0.118	0.731	0.672
LVI	3.174	45.440	0.000	23.905
Model constant	-8.311	11.673	0.001	0.000

B, unstandardized regression weight; exp(B), odds ratio; GGG, Gleason Grading Group; pT, pathological tumor stage; PPBC, percent of positive biopsy cores; PSA, prostate specific antigen; ECE, extracapsular extension; PSM, positive surgical margin; PNI, perineural invasion; LVI, lymphovascular invasion.

factors for the number of positive lymph nodes in pN1 patients, are provided in Supplementary Table 2 in the Supplementary Material. Due to the limited number of included patients (n = 74), the significance of these results is deemed unsatisfactory. However, for transparency and completeness, we have chosen to present these findings in the Supplementary Material.

Over a median follow-up period of 42 months, ranging from 3 to 102 months, 70 out of 423 patients (16.5%) experienced PSA failure, and 43 out of 414 patients (10.4%) exhibited disease progression. During this observation period, 10 out of 408 patients (2.5%) died, with 2 of these deaths attributed to PCa. The 5-year overall survival rate was 98.8%, and the 5-year cause-specific survival rate stood at 100%. Among 58 patients, the time from RP to BCR was known, with a mean duration of 19.2 months. In 42 patients classified as L0, the mean BCR-free survival period was 18.6 months, while in the remaining 16 patients classified as L1, it extended to 20.8 months with no statistically significant correlation observed.

4 Discussion

The objective of our research was two-fold. Primarily, we aimed to identify preoperative factors that are associated with the presence of LVI. This goal was driven by the aspiration to uncover preoperative markers that could aid in the identification of patients prone to LVI during postoperative examination. The rationale behind this endeavor is clear: if patients with evidence of LVI in their biopsy specimens can be identified preoperatively, it is imperative that they opt for RP or radiotherapy instead of embarking on active surveillance. In line with this, our findings point to several preoperative factors that demonstrate a significant correlation with LVI, providing valuable insights for clinical practice. As we consider future research directions, it is crucial to emphasize the ideal scenario: investigating the correlation of preoperative factors with LVI in biopsy specimens rather than relying solely on the final histopathological examination, as conducted in our study. This approach holds the potential to enhance risk stratification and further refine therapeutic decision-making in PCa management. The logistic regression identified preoperative PSA, PPBC, and GGG as robust predictors of LVI, consistent with findings from previous studies (5, 15, 25–32). Notably, we also identified MRI-based cT as a significant predictor of LVI, a factor not previously described in the literature to the best of our knowledge. While Kizilay et al. demonstrated a correlation between LVI and PIRADS score, Shin et al. (33) tumor visible of MRI was uncorrelated with LVI (p = 0.876) (33, 34). Our study suggests that cT, as determined by radiologists based on MRI, could be a valuable predictor for pL1 PCa. This factor may play a pivotal role in treatment planning, serving as an influential decision-making element.

Our secondary goal was to assess postoperative outcomes correlated with LVI, and among these outcomes, one of the most important discoveries was the relationship between LVI and the number of positive LNs in patients with nodal involvement. The mean number of positive LNs demonstrated a noteworthy discrepancy between patients without and with LVI in the pN+ group, registering means of 1.9 and 4.07, respectively, with a median of 1 and 3 ($p < 0.001$). This observation underscores the substantial clinical relevance of LVI within the context of PCa prognosis, particularly given the established association of nodal metastasis and poorer survival outcomes, as documented in prior studies (35–37).

Considering the pivotal finding of our study, which, to our best knowledge, is the first to establish a correlation between LVI and an elevated number of positive LNs in pN+ patients, it becomes increasingly apparent that the judicious selection of patients at higher risk of harboring LVI in their histopathological specimens is vital. Such patients could benefit from a more personalized therapeutic approach, potentially involving the consideration of LND as an integral component of their treatment strategy or/and a wider LND template. Notably, our study revealed instances of LVI in patients classified as low-risk according to their biopsy GGG, with 7.2% exhibiting LVI in the postoperative histopathological examination. These findings highlight the need for future investigations to focus on the analysis of preoperative factors that

may predict LVI in biopsy specimens, as this represents the sole opportunity for risk stratification before surgery.

In essence, our study emphasizes the critical implications of LVI in PCa, underscoring the need for tailored approaches in patient management, particularly in selecting the appropriate candidates for radical treatment, even in cases traditionally considered low-risk. On the contrary, a study conducted by Semba et al. has brought to light a paradox where low-risk patients demonstrate favorable oncological outcomes despite the presence of LVI in final histopathological specimens (38). This observation underscores the pressing need for future research endeavors focused on unraveling the preoperative factors associated with LVI within a broader patient population. It is worth considering that future studies should place a particular emphasis on discerning the importance of LVI in intermediate-risk patients. This demographic represents a challenging 'grey area' where making treatment decisions can be notably complex. Determining whether to opt for radical treatment or active surveillance, whether to conduct lymph node dissection, and other critical decisions are all aspects that demand further exploration within this patient subgroup.

One of the inherent challenges in interpreting LVI lies in the difficulty of its proper assessment during histopathological examination. This intricacy may contribute to the substantial heterogeneity observed in the reporting of LVI across different studies, with incidences ranging widely from 3.6% to 53% (16, 17). The underlying reasons for such variability remain elusive and warrant further investigation. In our study, pL1 patients comprised 17.7% of the investigated population, aligning with the range described in the literature.

Our study is not without limitations. Notably, a majority of the patients in our cohort underwent open RP, which may not entirely align with current global trends favoring robotic or laparoscopic approaches. Additionally, the presence of missing data for some patients, albeit a consequence of the study's large sample size, may have introduced a degree of selection bias. Furthermore, the retrospective and single-center nature of our study can impact its generalizability to broader clinical settings. It's important to acknowledge that our study had limited power to conduct comprehensive survival analyses, as a substantial number of patients lacked complete data on survival and biochemical recurrence. Nevertheless, it's essential to underscore that the primary aim of our investigation was not to extensively evaluate the effect of LVI on survival outcomes but rather to discern its preoperative and postoperative correlates. Furthermore, we did not conduct multivariate analysis specifically on postoperative outcomes associated with LVI. Consequently, the force of correlation between LVI and the number of positive LNs in pN+ patients was explored in univariate analysis only. Lastly, our study is rooted in clinical and histopathological data from PCa patients. However, it lacks specific data on the pathomorphological characteristics of the tumors. Therefore, a more comprehensive investigation of histological subtypes (such as intraductal adenocarcinoma or the cribriform pattern) could provide new insights into LVI across various subtypes, thus potentially improving the quality of the scientific evidence. Despite these limitations, it is essential to emphasize that postoperative outcome assessment, while in a univariate setting, contributes valuable insights to the broader understanding of LVI's clinical implications in PCa.

In conclusion, our study adds a significant dimension to the understanding of LVI's clinical implications in PCa. By revealing its association with the number of positive LNs, we emphasize the importance of identifying LVI as a prognostic factor, particularly in patients with lymph node involvement. Ideally, further studies should focus on the assessment of LVI during the biopsy. The preoperative factors linked to LVI provide actionable insights for risk stratification and clinical decision-making. Although the interpretation of LVI remains challenging and the reported incidences are highly variable, our study contributes to bridging the knowledge gap in this field and offers critical guidance for the diagnosis of PCa patients. Subsequent investigations should aim to unravel the underlying factors contributing to the observed heterogeneity in reporting LVI and to validate the practical utility of preoperative markers in clinical practice. Moreover, future research endeavors should focus on low- and intermediate-risk PCa patients. Emphasizing the assessment of LVI in biopsy specimens, rather than relying solely on RP specimens, would be crucial for enhancing preoperative risk stratification. Ideally, prospective, multi-center studies are warranted to provide a more comprehensive understanding of LVI's clinical implications across diverse patient populations.

5 Conclusions

Our study highlights the pivotal role of LVI in PCa prognosis. Analyzing 861 PCa patients, we identified key preoperative predictors for LVI, including MRI-based cT, biopsy GGG, preoperative PSA, and PPBC. Notably, our research reveals a novel association between LVI and an increased number of positive LNs in pN+ patients in the univariate analysis. Despite study limitations, such as its retrospective nature and potential selection bias, our findings emphasize the significance of LVI in PCa, urging personalized approaches in patient prognosis-related decision-making. Future studies should delve into LVI's implications for intermediate-risk patients and address the heterogeneity in LVI reporting across studies, as well as LVI as a possible biopsy finding.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving humans were approved by Ethics Committee of Wroclaw Medical University. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the

participants' legal guardians/next of kin because the study has been conducted in accordance with the national legislation and institutional requirements.

Author contributions

JK: Conceptualization, Methodology, Project administration, Writing – original draft. MŁ: Formal analysis, Methodology, Writing – original draft. MJ: Conceptualization, Writing – review & editing. AJ: Methodology, Writing – original draft. PS: Writing – review & editing, Formal analysis. AP: Writing – review & editing, Methodology. AL: Writing – review & editing. KK: Writing – review & editing. TS: Writing – review & editing, Conceptualization. AH: Investigation, Methodology, Writing – review & editing. BM: Funding acquisition, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2024.1349536/full#supplementary-material

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13. Oświadczenia współautorów w formie załączników

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Uniwersytet Medyczny im. Piastów Śląskich we Wrocławiu

Wrocław, 13.05.2024

OŚWIADCZENIE WSPÓŁAUTORA

Oświadczam, że w pracy:

1. Karwacki, J.; Gurwin, A.; Jaworski, A.; Jarocki, M.; Stodolak, M.; Dłubak, A.; Szuba, P.; Lemiński, A.; Kaczmarek, K.; Hałoń, A.; Szydełko, T.; Małkiewicz, B. 2024. Association of Lymphovascular Invasion with Lymph Node Metastases in Prostate Cancer—Lateralization Concept. Cancers, 16(5), 925

moim wkładem było współtworzenie bazy danych pacjentów oraz porządkowanie danych w celu przygotowania do analizy statystycznej. Dodatkowo, zajmowałem się tworzeniem opisu zależności między jednostronną limfoangioinwazją a zmiennymi kliniczno-patologicznymi, które zostały przedstawione w tabeli 3. Ponadto, przeprowadziłem edycję grafiki 4.

Wyrażam zgodę na włączenie wyżej wymienionych prac, którym jestem współautorem, do cyklu publikacji, na podstawie których będzie oparta rozprawa doktorska lek. Jakuba Karwackiego.

Andrzej Dłubak
……
Podpis

UNIWERSYTET MEDYCZNY
IM. PIASTÓW ŚLĄSKICH WE WROCŁAWIU

Lek. Adam Gurwin
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Uniwersytet Medyczny im. Piastów Śląskich we Wrocławiu

Wrocław, 13.05.2024

OŚWIADCZENIE WSPÓŁAUTORA

Oświadczam, że w pracy:

1. Karwacki, J.; Gurwin, A.; Jaworski, A.; Jarocki, M.; Stodolak, M.; **Dłubak, A.; Szuba, P.; Lemiński, A.; Kaczmarek, K.; Hałoń, A.; Szydełko, T.; Małkiewicz, B. 2024.** Association of Lymphovascular Invasion with Lymph Node Metastases in Prostate Cancer—Lateralization Concept. Cancers, 16(5), 925

moim udziałem było współtworzenie bazy danych pacjentów oraz praca merytoryczno-redakcyjna nad wstępnym manuskryptem. Pomagałem w interpretacji wyników analizy statystycznej oraz udzielałem wsparcia w pisaniu dyskusji.

Wyrażam zgodę na włączenie wyżej wymienionych prac, którym jestem współautorem, do cyklu publikacji, na podstawie których będzie oparta rozprawa doktorska lek. Jakuba Karwackiego.

Podpis

UNIWERSYTET MEDYCZNY
IM. PIASTÓW ŚLĄSKICH WE WROCŁAWIU

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Wrocław, 13.05.2024

OŚWIADCZENIE WSPÓŁAUTORA

Oświadczam, że w niżej wymienionych pracach:

1. **Karwacki, J.; Gurwin, A.; Jaworski, A.; Jarocki, M.; Stodolak, M.; Dłubak, A.; Szuba, P.; Lemiński, A.; Kaczmarek, K.; Hałoń, A.; Szydełko, T.; Małkiewicz, B. 2024.** Association of Lymphovascular Invasion with Lymph Node Metastases in Prostate Cancer—Lateralization Concept. Cancers, 16(5), 925
2. **Karwacki, J.; Łątkowska, M.; Jarocki, M.; Jaworski, A.; Szuba, P.; Poterek, A.; Lemiński, A.; Kaczmarek, K.; Hałoń, A.; Szydełko, T.; Małkiewicz, B. 2024.** The clinical meaning of lymphovascular invasion: preoperative predictors and postoperative implications in prostate cancer - a retrospective study. Frontiers in Oncology, 14

moją rolą było przeprowadzenie analizy patomorfologicznej preparatów pochodzących z zabiegów prostatektomii radykalnej, a także ocena merytoryczna opisu metodologii badania histopatologicznego w manuskrytach.

Wyrażam zgodę na włączenie wyżej wymienionych prac, którym jestem współautorką, do cyklu publikacji, na podstawie których będzie oparta rozprawa doktorska lek. Jakuba Karwackiego.

.....
Podpis

UNIWERSYTET MEDYCZNY
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Wrocław, 13.05.2024

OŚWIADCZENIE WSPÓŁAUTORA

Oświadczam, że w niżej wymienionych pracach:

1. Karwacki, J.; Gurwin, A.; Jaworski, A.; Jarocki, M.; Stodolak, M.; Dłubak, A.; Szuba, P.; Leminski, A.; Kaczmarek, K.; Hałoń, A.; Szydełko, T.; Małkiewicz, B. 2024. Association of Lymphovascular Invasion with Lymph Node Metastases in Prostate Cancer Lateralization Concept. Cancers, 16(5), 925
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moją rolą było współtworzenie pierwotnej formy manuskryptów, w których byłem odpowiedzialny za współtworzenie treści dyskusji oraz uporządkowanie danych tabelarycznych.

Wyrażam zgodę na włączenie wyżej wymienionych prac, którym jestem współautorem, do cyklu publikacji, na podstawie których będzie oparta rozprawa doktorska lek. Jakuba Karwackiego.

Michał T. Jarocki
.....
Podpis

UNIWERSYTET MEDYCZNY
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Wrocław, 13.05.2024

OŚWIADCZENIE WSPÓŁAUTORA

Oświadczam, że w niżej wymienionych pracach:

1. Karwacki, J.; Gurwin, A.; Jaworski, A.; Jarocki, M.; Stodolak, M.; Dłubak, A.; Szuba, P.; Leminski, A.; Kaczmarek, K.; Hałoń, A.; Szydełko, T.; Małkiewicz, B. 2024. Association of Lymphovascular Invasion with Lymph Node Metastases in Prostate Cancer—Lateralization Concept. Cancers, 16(5), 925
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moją rolą było współtworzenie pierwotnej formy manuskryptu. Skupiłem się na wsparciu merytorycznym przy opisywaniu wyników, a także pomogłem utworzyć zrąb metodologii oraz dyskusji powyższych pracy naukowej.

Wyrażam zgodę na włączenie wyżej wymienionych prac, którym jestem współautorem, do cyklu publikacji, na podstawie których będzie oparta rozprawa doktorska lek. Jakuba Karwackiego.

Arkadiusz Jaworski
Podpis

UNIWERSYTET MEDYCZNY
IM. PIASTÓW ŚLĄSKICH WE WROCŁAWIU

Dr n. med. Krystian Kaczmarek
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Pomorski Uniwersytet Medyczny w Szczecinie

Szczecin, 13.05.2024

OŚWIADCZENIE WSPÓŁAUTORA

Oświadczam, że w niżej wymienionych pracach:

1. Karwacki, J.; Gurwin, A.; Jaworski, A.; Jarocki, M.; Stodolak, M.; Dłubak, A.; Szuba, P.; Lemiński, A.; Kaczmarek, K.; Hałoń, A.; Szydełko, T.; Małkiewicz, B. 2024. Association of Lymphovascular Invasion with Lymph Node Metastases in Prostate Cancer—Lateralization Concept. Cancers, 16(5), 925
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moją rolą było współprojektowanie metodologii badań oraz współtworzenie pierwotnej formy manuskryptów, a także pomoc przy współtworzeniu tabel i grafik.

Wyrażam zgodę na włączenie wyżej wymienionych prac, którym jestem współautorem, do cyklu publikacji, na podstawie których będzie oparta rozprawa doktorska lek. Jakuba Karwackiego.

Krystian Kaczmarek

……..
Podpis

UNIWERSYTET MEDYCZNY
IM. PIASTÓW ŚLĄSKICH WE WROCŁAWIU

Lek. Paweł Kiełb
Uniwersyteckie Centrum Urologii
Klinika Urologii Małoinwazyjnej i Robotycznej
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Wrocław, 13.05.2024

OŚWIADCZENIE WSPÓŁAUTORA

Oświadczam, że w pracy:

1. Karwacki, J.; Stodolak, M.; Nowak, Ł.; Kiełb, P.; Krajewski, W.; Leminski, A.; Szydełko, T.; Małkiewicz, B. 2024. Preoperative Factors for Lymphovascular Invasion in Prostate Cancer: A Systematic Review and Meta-Analysis. International Journal of Molecular Sciences, 25(2), 856,

moim udziałem było współtworzenie pierwotnego manuskryptu publikacji, a także pomoc w ustaleniu odpowiednich fraz zastosowanych podczas systematycznego przeglądu literatury.

Wyrażam zgodę na włączenie wyżej wymienionych prac, którym jestem współautorem, do cyklu publikacji, na podstawie których będzie oparta rozprawa doktorska lek. Jakuba Karwackiego.

PAWEŁ KIEŁB
LEKARZ
3501961

Podpis

UNIWERSYTET MEDYCZNY
IM. PIASTÓW ŚLĄSKICH WE WROCŁAWIU

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Klinika Urologii Małoinwazyjnej i Robotycznej
Uniwersytet Medyczny im. Piastów Śląskich we Wrocławiu

Wrocław, 13.05.2024

OŚWIADCZENIE WSPÓŁAUTORA

Oświadczam, że w pracy:

1. **Karwacki, J.; Stodolak, M.; Nowak, Ł.; Kiełb, P.; Krajewski, W.; Lemiński, A.; Szydełko, T.; Małkiewicz, B. 2024.** Preoperative Factors for Lymphovascular Invasion in Prostate Cancer: A Systematic Review and Meta-Analysis. International Journal of Molecular Sciences, 25(2), 856

moją rolą była korekta finalnej formy manuskryptu, a także wsparcie merytoryczne podczas procesu analizy statystycznej w ramach prowadzonych metaanaliz.

Wyrażam zgodę na włączenie wyżej wymienionych prac, którym jestem współautorem, do cyklu publikacji, na podstawie których będzie oparta rozprawa doktorska lek. Jakuba Karwackiego.

Prof. dr hab. n. med.
WOJCIECH KRAJEWSKI
specjalista urolog
lekarz
2848755

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Podpis

UNIWERSYTET MEDYCZNY
IM. PIASTÓW ŚLĄSKICH WE WROCŁAWIU

Dr hab. n. med. Artur Lemiński
Katedra i Klinika Urologii i Onkologii Urologicznej
Pomorski Uniwersytet Medyczny w Szczecinie

Szczecin, 13.05.2024

OŚWIADCZENIE WSPÓŁAUTORA

Oświadczam, że w niżej wymienionych pracach:

1. Karwacki, J.; Stodolak, M.; Nowak, Ł.; Kiełb, P.; Krajewski, W.; Lemiński, A.; Szydełko, T.; Małkiewicz, B. 2024. Preoperative Factors for Lymphovascular Invasion in Prostate Cancer: A Systematic Review and Meta-Analysis. International Journal of Molecular Sciences, 25(2), 856,

moim udziałem było merytoryczne wsparcie podczas rewizji pierwotnej wersji artykułu, a także konsultacja strategii wyszukiwania publikacji w ramach przeglądu systematycznego.

2. Karwacki, J.; Gurwin, A.; Jaworski, A.; Jarocki, M.; Stodolak, M.; Dłubak, A.; Szuba, P.; Lemiński, A.; Kaczmarek, K.; Hałoń, A.; Szydełko, T.; Małkiewicz, B. 2024. Association of Lymphovascular Invasion with Lymph Node Metastases in Prostate Cancer—Lateralization Concept. Cancers, 16(5), 925,

moją rolą było współprojektowanie metodologii badania oraz ocena merytoryczna przeprowadzonej analizy statystycznej.

3. Karwacki, J.; Łątkowska, M.; Jarocki, M.; Jaworski, A.; Szuba, P.; Poterek, A.; Lemiński, A.; Kaczmarek, K.; Hałoń, A.; Szydełko, T.; Małkiewicz, B. 2024. The clinical meaning of lymphovascular invasion: preoperative predictors and postoperative implications in prostate cancer - a retrospective study. Frontiers in Oncology, 14,

moją rolą było przeprowadzenie edycji oraz rewizji pierwotnej formy manuskryptu.

Wyrażam zgodę na włączenie wyżej wymienionych prac, którym jestem współautorem, do cyklu publikacji, na podstawie których będzie oparta rozprawa doktorska lek. Jakuba Karwackiego.

dr hab. n. med. Artur Lemiński
lekarz
specjalista w zakresie urologii
.....1.1850.21.....
Podpis

UNIWERSYTET MEDYCZNY
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Lek. Małgorzata Łątkowska
Katedra i Klinika Okulistyki
Uniwersytet Medyczny im. Piastów Śląskich we Wrocławiu

Wrocław, 13.05.2024

OŚWIADCZENIE WSPÓŁAUTORA

Oświadczam, że w pracy:

1. Karwacki, J.; Łątkowska, M.; Jarocki, M.; Jaworski, A.; Szuba, P.; Poterek, A.; Lemiński, A.; Kaczmarek, K.; Hałoń, A.; Szydełko, T.; Małkiewicz, B. 2024. The clinical meaning of lymphovascular invasion: preoperative predictors and postoperative implications in prostate cancer - a retrospective study. Frontiers in Oncology, 14,

moją rolą było współtworzenie grafik oraz rewizja treści w ostatecznej formie manuskryptu. Ponadto, pomogłam w opracowaniu oraz interpretacji analizy statystycznej.

Wyrażam zgodę na włączenie wyżej wymienionych prac, którym jestem współautorką, do cyklu publikacji, na podstawie których będzie oparta rozprawa doktorska lek. Jakuba Karwackiego.

Małgorzata Łątkowska
.....
Podpis

UNIWERSYTET MEDYCZNY
IM. PIASTÓW ŚLĄSKICH WE WROCŁAWIU

Dr hab. n. med. Bartosz Małkiewicz, prof. UMW
Uniwersyteckie Centrum Urologii
Klinika Urologii Małoinwazyjnej i Robotycznej
Uniwersytet Medyczny im. Piastów Śląskich we Wrocławiu

Wrocław, 13.05.2024

OŚWIADCZENIE WSPÓŁAUTORA

Oświadczam, że w niżej wymienionych pracach:

1. Karwacki, J.; Stodolak, M.; Nowak, Ł.; Kiełb, P.; Krajewski, W.; Lemiński, A.; Szydełko, T.; Małkiewicz, B. 2024. Preoperative Factors for Lymphovascular Invasion in Prostate Cancer: A Systematic Review and Meta-Analysis. International Journal of Molecular Sciences, 25(2), 856
2. Karwacki, J.; Gurwin, A.; Jaworski, A.; Jarocki, M.; Stodolak, M.; Dłubak, A.; Szuba, P.; Lemiński, A.; Kaczmarek, K.; Hałoń, A.; Szydełko, T.; Małkiewicz, B. 2024. Association of Lymphovascular Invasion with Lymph Node Metastases in Prostate Cancer—Lateralization Concept. Cancers, 16(5), 925
3. Karwacki, J.; Łątkowska, M.; Jarocki, M.; Jaworski, A.; Szuba, P.; Poterek, A.; Lemiński, A.; Kaczmarek, K.; Hałoń, A.; Szydełko, T.; Małkiewicz, B. 2024. The clinical meaning of lymphovascular invasion: preoperative predictors and postoperative implications in prostate cancer - a retrospective study. Frontiers in Oncology, 14,

mój udział polegał na współtworzeniu założeń, celów i metodologii, szeroko pojętej superwizji dotyczącej każdego elementu procesu tworzenia manuskryptu, ocenie spełnienia warunków formalnych publikacji, rewizji i korekcie merytorycznej manuskryptów oraz pozyskiwaniu funduszy na pokrycie kosztów procesów publikacyjnych.

Wyrażam zgodę na włączenie wyżej wymienionych prac, którym jestem współautorem, do cyklu publikacji, na podstawie których będzie oparta rozprawa doktorska lek. Jakuba Karwackiego.

Bartosz Małkiewicz

.....
Podpis

UNIWERSYTET MEDYCZNY
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Wrocław, 13.05.2024

OŚWIADCZENIE WSPÓŁAUTORA

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moim udziałem było wprowadzenie danych liczbowych do programu statystycznego celem utworzenia wykresów drzewkowych oraz pomoc w interpretacji wyników metaanaliz.

Wyrażam zgodę na włączenie wyżej wymienionych prac, którym jestem współautorem, do cyklu publikacji, na podstawie których będzie oparta rozprawa doktorska lek. Jakuba Karwackiego.

.....
Podpis

UNIWERSYTET MEDYCZNY
IM. PIASTÓW ŚLĄSKICH WE WROCŁAWIU

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Uniwersytet Medyczny im. Piastów Śląskich we Wrocławiu

Wrocław, 13.05.2024

OŚWIADCZENIE WSPÓŁAUTORA

Oświadczam, że w pracy:

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moją rolą było współtworzenie pierwotnej formy manuskryptu, pomoc w opracowaniu metodologii powyższego badania, a także współtworzenie treści dyskusji.

Wyrażam zgodę na włączenie wyżej wymienionych prac, którym jestem współautorem, do cyklu publikacji, na podstawie których będzie oparta rozprawa doktorska lek. Jakuba Karwackiego.

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Podpis

UNIWERSYTET MEDYCZNY
IM. PIASTÓW ŚLĄSKICH WE WROCŁAWIU

Lek. Marcel Stodolak
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Klinika Urologii Małoinwazyjnej i Robotycznej
Uniwersytet Medyczny im. Piastów Śląskich we Wrocławiu

Wrocław, 13.05.2024

OŚWIADCZENIE WSPÓŁAUTORA

Oświadczam, że w niżej wymienionych pracach:

1. Karwacki, J.; Stodolak, M.; Nowak, Ł.; Kiełb, P.; Krajewski, W.; Lemiński, A.; Szydełko, T.; Małkiewicz, B. 2024. Preoperative Factors for Lymphovascular Invasion in Prostate Cancer: A Systematic Review and Meta-Analysis. International Journal of Molecular Sciences, 25(2), 856,

moją rolą była pierwsza selekcja prac przeprowadzona w ramach przeglądu systematycznego literatury, a także współtworzenie pierwotnej formy manuskryptu.

2. Karwacki, J.; Gurwin, A.; Jaworski, A.; Jarocki, M.; Stodolak, M.; Dłubak, A.; Szuba, P.; Lemiński, A.; Kaczmarek, K.; Hałoń, A.; Szydełko, T.; Małkiewicz, B. 2024. Association of Lymphovascular Invasion with Lymph Node Metastases in Prostate Cancer—Lateralization Concept. Cancers, 16(5), 925,

moją rolą była współpraca przy pisaniu pierwotnej formy manuskryptu oraz asysta przy współtworzeniu grafik. Ponadto, byłem współodpowiedzialny za zbieranie, archiwizowanie i porządkowanie danych pacjentów.

Wyrażam zgodę na włączenie wyżej wymienionych prac, którym jestem współautorem, do cyklu publikacji, na podstawie których będzie oparta rozprawa doktorska lek. Jakuba Karwackiego.

Marcel Stodolak
.....
Podpis

UNIWERSYTET MEDYCZNY
IM. PIASTÓW ŚLĄSKICH WE WROCŁAWIU

Dr n. społ. Przemysław Szuba
Wydział Ekonomiczny
Uniwersytet WSB Merito w Opolu

Opole, 13.05.2024

OŚWIADCZENIE WSPÓŁAUTORA

Oświadczam, że w niżej wymienionych pracach:

1. Karwacki, J.; Gurwin, A.; Jaworski, A.; Jarocki, M.; Stodolak, M.; Dłubak, A.; Szuba, P.; Leminski, A.; Kaczmarek, K.; Hałoń, A.; Szydełko, T.; Małkiewicz, B. 2024. Association of Lymphovascular Invasion with Lymph Node Metastases in Prostate Cancer—Lateralization Concept. Cancers, 16(5), 925,
2. Karwacki, J.; Łątkowska, M.; Jarocki, M.; Jaworski, A.; Szuba, P.; Poterek, A.; Leminski, A.; Kaczmarek, K.; Hałoń, A.; Szydełko, T.; Małkiewicz, B. 2024. The clinical meaning of lymphovascular invasion: preoperative predictors and postoperative implications in prostate cancer - a retrospective study. Frontiers in Oncology, 14,

moją rolą było współudział w opracowaniu statystyki oraz wsparcie merytoryczne przy interpretacji wyników badań.

Wyrażam zgodę na włączenie wyżej wymienionych prac, którym jestem współautorem, do cyklu publikacji, na podstawie których będzie oparta rozprawa doktorska lek. Jakuba Karwackiego.

Przemysław Szuba
.....
Podpis

UNIWERSYTET MEDYCZNY
IM. PIASTÓW ŚLĄSKICH WE WROCŁAWIU

Prof. dr hab. n. med. Tomasz Szydełko
Uniwersyteckie Centrum Urologii
Klinika Urologii Małoinwazyjnej i Robotycznej
Uniwersytet Medyczny im. Piastów Śląskich we Wrocławiu

Wrocław, 13.05.2024

OŚWIADCZENIE WSPÓŁAUTORA

Oświadczam, że w niżej wymienionych pracach:

1. Karwacki, J.; Stodolak, M.; Nowak, Ł.; Kiełb, P.; Krajewski, W.; Lemiński, A.; Szydełko, T.; Małkiewicz, B. 2024. Preoperative Factors for Lymphovascular Invasion in Prostate Cancer: A Systematic Review and Meta-Analysis. International Journal of Molecular Sciences, 25(2), 856,

moim udziałem było doradzanie przy planowaniu metodologii przeglądu systematycznego oraz korekta krytyczna manuskryptu.

2. Karwacki, J.; Gurwin, A.; Jaworski, A.; Jarocki, M.; Stodolak, M.; Dłubak, A.; Szuba, P.; Lemiński, A.; Kaczmarek, K.; Hałoń, A.; Szydełko, T.; Małkiewicz, B. 2024. Association of Lymphovascular Invasion with Lymph Node Metastases in Prostate Cancer—Lateralization Concept. Cancers, 16(5), 925,
3. Karwacki, J.; Łątkowska, M.; Jarocki, M.; Jaworski, A.; Szuba, P.; Poterek, A.; Lemiński, A.; Kaczmarek, K.; Hałoń, A.; Szydełko, T.; Małkiewicz, B. 2024. The clinical meaning of lymphovascular invasion: preoperative predictors and postoperative implications in prostate cancer - a retrospective study. Frontiers in Oncology, 14,

mój udział polegał na kierowaniu Uniwersyteckim Centrum Urologii, w którym leczono pacjentów stanowiących próby kontrolną oraz badawczą w powyższych badaniach naukowych, doradzaniu przy planowaniu metodologii badań, a także korekcie manuskryptów.

Wyrażam zgodę na włączenie wyżej wymienionych prac, którym jestem współautorem, do cyklu publikacji, na podstawie których będzie oparta rozprawa doktorska lek. Jakuba Karwackiego.

.....
Podpis

14. *Curriculum Vitae*

Jakub Karwacki

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Wykształcenie

2017-2023 | UNIWERSYTET MEDYCZNY IM. PIASTÓW ŚLĄSKICH WE WROCŁAWIU

- Kierunek główny: Wydział Lekarski
- Stopień naukowy: Lekarz

Doświadczenie zawodowe

2023-OBECNIE | UNIWERSYTECKI SZPITAL KLINICZNY WE WROCŁAWIU

- Stanowisko: Lekarz stażysta

2023-OBECNIE | UNIWERSYTET MEDYCZNY IM. PIASTÓW ŚLĄSKICH WE WROCŁAWIU

- Jednostka: Katedra Fizjologii i Patofizjologii, Zakład Patofizjologii
- Stanowisko: Asystent dydaktyczny

Szkolenia

2023 | WROCŁAW | ULTRASONOGRAFICZNA DIAGNOSTYKA JAMY BRZUSZNEJ

- Poziom: Średniozaawansowany
- Organizator: Fundacja „Mocni na starcie”

2022 | LESZNO | POINT OF CARE: PODSTAWY USG JAMY BRZUSZNEJ

- Poziom: Podstawowy
- Organizator: Fundacja „Mocni na starcie”

Aktywność w organizacjach naukowych

2021-2023 | STUDENCKIE KOŁO NAUKOWE CENTRUM UROLOGII

- Jednostka: Centrum Urologii Uniwersytetu Medycznego im. Piastów Śląskich we Wrocławiu
- Pozycja: Przewodniczący

Dorobek naukowy

PUBLIKACJE NAUKOWE

- 12 publikacji naukowych w międzynarodowych czasopismach
- Całkowity impact factor (IF): 59,2
- Całkowita punktacja Ministerstwa Edukacji i Nauki: 1610

ABSTRAKTY KONFERENCYJNE

- 4 abstrakty wygłoszone podczas konferencji ogólnopolskich i międzynarodowych

Nagrody

2023 | IX INTERNATIONAL STUDENTS’ CONFERENCE OF YOUNG MEDICAL RESEARCHERS

- Nagroda: II miejsce za prezentację pracy pt. *„Diagnostic value of radio-guided sentinel lymph node dissection in patients with prostate cancer undergoing radical prostatectomy with modified-extended lymphadenectomy*” podczas sesji urologicznej.

Języki

ANGIELSKI

- Poziom: C2

FRANCUSKI

- Poziom: B1

15. Dorobek naukowy

Wykaz publikacji

Jakub Karwacki

1. Publikacje w czasopismach naukowych

1.1 Publikacje w czasopiśmie z IF

Lp	Opis bibliograficzny	IF	Punkty
1	Małkiewicz Bartosz, Knura Miłosz, Łątkowska Małgorzata, Kobylański Maximilian, Nagi Krystian, Janczak Dawid, Chorbińska Joanna, Krajewski Wojciech, **Karwacki Jakub**, Szydełko Tomasz: Patients with positive lymph nodes after radical prostatectomy and pelvic lymphadenectomy - do we know the proper way of management?, Cancers, 2022, vol. 14, nr 9, art.2326 [18 s.], DOI:10.3390/cancers14092326	5,2	140
2	Małkiewicz Bartosz, Bugla Błażej, Czarnecki Maciej, **Karwacki Jakub**, Długosz Paulina, Gurwin Adam, Kiełb Paweł, Lemiński Artur, Krajewski Wojciech, Jędrzejuk Diana, Bolanowski Marek, Hałoń Agnieszka, Szydełko Tomasz: Diagnostic value of radio-guided sentinel node detection in patients with prostate cancer undergoing radical prostatectomy with modified-extended lymphadenectomy, Cancers, 2022, vol. 14, nr 20, art.5012 [12 s.], DOI:10.3390/cancers14205012	5,2	140
3	Małkiewicz Bartosz, Gurwin Adam, **Karwacki Jakub**, Nagi Krystian, Knecht-Gurwin Klaudia, Hober Krzysztof, Łyko Magdalena, Kowalczyk Kamil, Krajewski Wojciech, Kołodziej Anna, Szydełko Tomasz: Management of bladder cancer patients with clinical evidence of lymph node invasion (cN+), Cancers, 2022, vol. 14, nr 21, art.5286 [27 s.], DOI:10.3390/cancers14215286	5,2	140
4	**Karwacki Jakub**, Kiełbik Aleksander, Szlasa Wojciech, Sauer Natalia, Kowalczyk Kamil, Krajewski Wojciech, Saczko Jolanta, Kulbacka Julita, Szydełko Tomasz, Małkiewicz Bartosz: Boosting the immune response - combining local and immune therapy for prostate cancer treatment, Cells, 2022, vol. 11, nr 18, art.2793 [26 s.], DOI:10.3390/cells11182793	6	140
5	Małkiewicz Bartosz, Kiełb Paweł, **Karwacki Jakub**, Czerwińska Róża, Długosz Paulina, Lemiński Artur, Nowak Łukasz, Krajewski Wojciech, Szydełko Tomasz: Utility of lymphadenectomy in prostate cancer: where do we stand?, Journal of Clinical Medicine, 2022, vol. 11, nr 9, art.2343 [16 s.], DOI:10.3390/jcm11092343	3,9	140
6	Małkiewicz Bartosz, Kiełb Paweł, Kobylański Maximilian, **Karwacki Jakub**, Poterek Adrian, Krajewski Wojciech Piotr, Zdrojowy Romuald, Szydełko Tomasz: Sentinel lymph node techniques in urologic oncology: current knowledge and application, Cancers, 2023, vol. 15, nr 9, art.2495 [19 s.], DOI:10.3390/cancers15092495	5,2*	200
7	Dłubak Andrzej, **Karwacki Jakub**, Logoń Katarzyna, Tomecka Paulina, Brawańska Kinga, Krajewski Wojciech, Szydełko Tomasz, Małkiewicz Bartosz: Lymph node dissection in upper tract urothelial carcinoma: current status and future perspectives, Current Oncology Reports, 2023, vol. 25, nr 11, s. 1327-1344, DOI:10.1007/s11912-023-01460-y	4,7*	100
8	Gać Paweł, Jaworski Arkadiusz, **Karwacki Jakub**, Jarocki Michał, Ams Artur, Poręba Rafał: Coexistence of Ehlers–Danlos syndrome with coronary–pulmonary arterial fistula and other multiple coronary artery anomalies, Diagnostics, 2023, vol. 13, nr 23, art.3555 [6 s.], DOI:10.3390/diagnostics13233555	3,6*	70
9	Karwacki J, Gurwin A, Jaworski A, Jarocki M, Stodolak M, Dłubak A, Szuba P, Lemiński A, Kaczmarek K, Hałoń A, Szydełko T, Małkiewicz B. Association of Lymphovascular Invasion with Lymph Node Metastases in Prostate Cancer-Lateralization Concept. Cancers (Basel). 2024 Feb 25;16(5):925. doi: 10.3390/cancers16050925.	5,2*	200

10	Dłubak A, **Karwacki J**, Logoń K, Tomecka P, Brawańska K, Krajewski W, Szydełko T, Małkiewicz B. Lymph Node Dissection in Upper Tract Urothelial Carcinoma: Current Status and Future Perspectives. Curr Oncol Rep. 2023 Nov;25(11):1327-1344. doi: 10.1007/s11912-023-01460-y. Epub 2023 Oct 6.	4,7*	100
11	**Karwacki J**, Łątkowska M, Jarocki M, Jaworski A, Szuba P, Poterek A, Lemiński A, Kaczmarek K, Hałoń A, Szydełko T, Małkiewicz B. The clinical meaning of lymphovascular invasion: preoperative predictors and postoperative implications in prostate cancer - a retrospective study. Front Oncol. 2024 May 3;14:1349536. doi: 10.3389/fonc.2024.1349536..	4,7*	100
12	**Karwacki Jakub**, Stodolak Marcel, Nowak Łukasz, Kiełb Paweł, Krajewski Wojciech, Lemiński Artur, Szydełko Tomasz, Małkiewicz Bartosz: Preoperative factors for lymphovascular invasion in prostate cancer: a systematic review and meta-analysis, International Journal of Molecular Sciences, 2024, vol. 25, nr 2, art.856 [21 s.], DOI:10.3390/ijms25020856	5,6*	140
	Podsumowanie	59,2	1610

**IF 2022*

2. Abstrakty

Lp	Opis bibliograficzny
1	Małkiewicz Bartosz, **Karwacki Jakub**, Kiełb Paweł, Długosz Paulina, Nowak Łukasz, Chorbińska Joanna, Krajewski Wojciech, Kowalczyk Kamil, Zdrojowy Romuald, Szydełko Tomasz: Mapping of primary lymphatic landing sites of the prostate cancer using isotope imaging and radio-guided surgery. Preliminary results, W: The 51st Scientific Congress of the Polish Urological Association - PTU 2021. Warsaw, 21st - 23rd October 2021. A book of abstracts 2021, s. 29
2	Knura Miłosz, **Karwacki Jakub**, Kiełb Paweł, Krajewski Wojciech, Nowak Łukasz, Nagi Krystian, Stelmach Paweł, Kołodziej Anna, Dębiński Paweł, Małkiewicz Bartosz, Szydełko Tomasz: Clinical evaluation of therapeutic management in patients with prostate cancer with lymph node metastases treated by radical prostatectomy, W: The 51st Scientific Congress of the Polish Urological Association - PTU 2021. Warsaw, 21st - 23rd October 2021. A book of abstracts 2021, s. 30
3	**Karwacki Jakub**, Gurwin Adam, Kiełb Paweł: Diagnostic value of radio-guided sentinel node detection in patients with prostate cancer undergoing radical prostatectomy with modified-extended lymphadenectomy, W: IX International Students' Conference of Young Medical Researchers. Wroclaw, 30.03-01.04.2023. Book of abstracts 2023, 56 poz.76, ISBN 978-83-942024-5-3
4	**Karwacki Jakub**, Stodolak Marcel, Nowak Łukasz, Jarocki Michał, Jaworski Arkadiusz, Dębiński Paweł, Krajewski Wojciech, Szydełko Tomasz, Małkiewicz Bartosz: Preoperative factors for lymphovascular invasion in prostate cancer: a systematic review and meta-analysis, W: The 53rd Scientific Congress of the Polish Urological Association - PTU23. Cracow, 11th - 13th September 2023. A book of abstracts 2023, s. 20-23

Impact factor: 59,2

Punkty ministerialne: 1610,0

OSOBA SPORZADZAJĄCA: Beata Majewska
DZIAŁ BIBLIOGRAFII I BIBLIOMETRII BG UMW

Signed by / Podpisano przez:

Dominika Sidorska

Date / Data: 2024-05-20 13:17