Can 68Ga-prostate specific membrane antigen positron emission tomography / computerized tomography provide an accurate lymph node staging for patients with medium / high risk prostate cancer? A Diagnostic Meta-Analysis

Lei Peng
North Sichuan Medical University
Jinze Li
North Sichuan Medical University
Chuanyang Meng
North Sichuan Medical University
Jinming Li
Affiliated Hospital of North Sichuan Medical College
Chengyu You
North Sichuan Medical University
Dandan Tang
Shenzhen People's Hospital
Tangqiang Wei
North Sichuan Medical University
Wei Xiong
North Sichuan Medical University
Yunxiang Li (liyunxiang369@126.com)
North Sichuan Medical University

Research

Keywords: prostate cancer, lymph node, 68Gallium- prostate-specific membrane antigen, Meta-analysis

Posted Date: June 5th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-33226/v1

Version of Record: A version of this preprint was published on October 1st, 2020. See the published version at https://doi.org/10.1186/s13014-020-01675-4.

Abstract

Objective: This article aims to evaluate the diagnostic value of68Gallium-PSMA positron emission tomography/computerized tomography (68Ga-PSMA PET/CT) for lymph node (LN) staging in patients with prostate cancer (PCa) by a meta-analysis of diagnostic tests.

Methods: We systematically retrieved articles from PubMed, Embase, Web of Science with a limited period from January 1, 2016, to December 1, 2019, and Stata 15 was used for calculation and statistical analyses.

Results: Sensitivity, specificity, positive and negative likelihood ratio (PLR, NLR), diagnostic odds ratio (DOR) and 95% confidence intervals (CI) be used to evaluate the diagnostic value. A total of 10 studies were included in our meta-analysis, which included 701 individuals. The results of each consolidated summary are as follows: sensitivity of 0.84 (95% CI: 0.55-0.95), specificity of 0.95 (95% CI: 0.87-0.98), PLR and NLR was 17.19 (95% CI: 6.27, 47.17) and 0.17 (95% CI: 0.05-0.56), respectively. DOR of 4.6 (95% CI: 2.91-6.30), AUC of 0.97 (95% CI: 0.95-0.98).

Conclusion: Our study demonstrates that 68Ga-PSMA PET/CT has a high overall diagnostic value for LN staging in patients with moderate and high-risk PCa. But our conclusions still require a larger sample size, multi-center prospective randomized controlled trial to verify.

Introduction

Prostate cancer (PCa) is the second most common cancer andthefifth leading cause of cancer death indevelopedcountries[1].Although the clinical symptoms of early PCaare not obvious, pelviclymph node (LN) and bone metastasis are alsoprone tooccur[2].About15% of patients with medium and high-risk prostate cancerwerefound to have harbor lymph node invasion when performingpelviclymph node dissection (PLND) during radicalprostatectomy(RP)[3]. PLND isundoubtedly the most reliable wayto determine whether there is LNIin PCa, but this method is bothinvasive andexpensive[4]. Andcomplications such as lymphocele,lymphedema are alsoheadaches[5].According to the EAU guidelines, patientswith moderate to highrisk PCa who have an LN-positive estimatedrisk of more than 5%should undergo extend pelvic lymph nodedissection(ePLND)[6].Therefore, accurate assessment of LNstaging before surgery isimportant for the operation and patient'sprognosis.

Presurgical computerized tomography (CT) scan ormagneticresonance imaging (MRI) is helpful for LN staging, but withlimitedaccuracy[7].Prostate-specific membrane antigen (PSMA)is a surface protein thatis expressed in almost normal prostatetissues, and its expressionlevel is higher in PCatissues[8]. Inrecent years, PSMA has been introducedinto positron emissiontomography (PET) imaging[9], ^{68}Gallium-PSMApositron emissiontomography/computerized tomography(^{68}Ga-PSMA PET/CT) hasbeen proven to be better thanordinary imaging tests in detectingmetastaticPCa[10]. Relatedstudies have also shown that^{68}Ga-PSMA PET/CT is moresensitive for recurrent PCa witha low prostate-specific antigen(PSA)[11,12].

Till now, some scholars have done some research on theaccuracyof ^{68}Ga-PSMA PET/CT to determine the lymph nodestagingof PCa preoperative, but it's still unclear how itsdiagnosticvalue is. The diagnostic accuracy of 68 Ga-PSMAPET/CT todetermine lymph node staging of PCa preoperative remainsunclearbased on the current literature. The current study aimstoestablish the status of 68 Ga-PSMA PET/CT in PCa'sLNstaging.

Methods

Literature search and eligibility criteria

A systematic search of the published literature using WebofScience, EMBASE, Cochrane Database, MEDLINE was performed. Wehaveselected relevant literature from the creation of the databasetoJune 2019. And used prostate cancer, Gallium, lymph node,positronemission tomography/computerized tomography,prostate-specificmembrane antigen as the search terms and thesearch language waslimited to English. We also searched for therelevant bibliographyto avoid omissions.

The studies that were included in our research should meetthedemands as follows: patients diagnosed with LN metastatic PCausingthe gold standard pathological biopsy, studies with thediagnosticvalue of ^{68}Ga-PSMA PET/CT reflected in thestudies, andstudies with sufficient data on true positive (TP),false positive(FP), false negative (FN), and true negative (TN).For duplicatearticles, low-quality research, letters, reviews, casereport, weanalyze and exclude respectively. This process wasassessed by twoauthors (PL and LJZ), independently.

Data extraction

We incorporate the following data from each article intothemeta-analysis: author, publication year, study design, samplesize,age, Lymph node dissection, recruiting time and four datasets:TP,FP, FN, TN. Data extraction was performed by two authors (PLandLJZ) with any discrepancies resolved by a third author(WTQ).

Quality evaluation

The Quality Assessment of Diagnostic Accuracy Studies2(QUADAS-2) tool was used to evaluate the quality ofincludedstudies [13].Key domains are assessed to determine therisk of bias andapplicability. Signalling questions are included tofacilitatejudgements, with the risk being low if all signalinganswer for adomain is 'yes', and if the answer to any question is'no'suggesting potential bias exists. Concerns about applicabilityaredetermined as 'low', 'high', or 'unclear'.

Statistical analysis

We used Stata 15 (StataCorp LP, University City, Texas, USA)forstatistical analysis. Q test and chi-square tests were usedtoverify the heterogeneity between the included works ofliterature.If $I^2 > 50\%$, the differences between theliteraturewere considered significant[13]. We used a bivariate model tocalculatethe pooled sensitivity, specificity, positive andnegativelikelihood ratios (PLRs and NLRs), diagnostic odds ratio(DOR) andthe 95% confidence interval (CI)[14]. We calculated the area under thereceiveroperator characteristic curve (SROC, AUC). AUC varied from0.5 to1. If the area was equal to 1, then a diagnostic test wasextremelyvaluable. If the area was 0.5, then the diagnostic abilitywasconsidered as poor[15]. Deeks's funnel plot was used to assessthepublication bias, and Fagan plots showed the relationshipbetweenthe prior probability, the likelihood ratio, and theposterior testprobability[16].$P < 0.05$ was considered to bestatistically significant.

Results

Study selection and study characteristics

The literature search selection steps retrievalinFig. 1. Initially,weretrieved a total of 324 articles in the selected databaseandmanually retrieved 22 articles by referring to relevantliteraturecitations. In these studies, we excluded 134 duplicatesrecords. Byanalyzing titles, abstracts, and topics, 142 articleswere alsoexcluded. Through full-text analysis and assessment ofeligibility,42 articles that were not related to diagnostic value,12 articlesthat were no related to LN staging, and 6 studies thathad noaccess data. Finally, we included 10 studies inourmeta-analysis[2, 9, 10,17–23].

In Table 1, wepresentedthe basic data of the articles included in themeta-analysis of ^{68}Ga-PSMA PET/CT for LN staging of PCapreoperative.These articles were published between 2016 and 2019. Atotal of 701sample individuals were included in our analysis. Mostof them aresingle-center retrospective studies in regions includingAsia(China, India, and Turkey), Europe (Germany) and Australia. Atthesame time, we also display the age, PSA and other informationofpatients included in each study.

Quality assessment

Based on the evaluation results of the QUADAS-2 scale,wereflected the quality evaluation results of each articleinTable 1. The final scoreofeach article was 11 or better, and 7 of them received quitehighscores.

Pooled diagnostic values

After statistical tests, the value of I^2 isgreaterthan 50%, it can be considered that the included documentshavehigh heterogeneity. Therefore, a random effect model is usedtocombine sensitivity and specificity, thereby obtainingmoreconservative results. The diagnostic value is showninTable 2. Thepooledsensitivity and specificity were recorded as 0.84 (95%CI:0.55–0.95) and 0.95 (95% CI: 0.87–0.98, Fig. 2), respectively. The Youden index was0.79.The pooled PLR and NLR was 17.19 (95% CI: 6.27–47.17) and 0.17(95%CI: 0.05–0.56), and DOR was 4.60 (95% CI: 2.91–6.03). TheoverallSORC curve is presented in Fig. 3, with an AUC of 0.97 (95% CI:0.95–0.98).Figure 4 is shownin theFagan plot. The prior probability was 20%, and thepost-testprobability was 81% for LR-positive and 4% forLR-negative. Thediagnostic accuracy for detecting^{68}Ga-PSMA PET/CT forLN staging in PCa was found to begenerally better.

Publication bias

The publication bias (P = 0.02, Fig. 5) was shown in Deek's funnel plot.

Heterogeneity and sensitivity analysis

According to the results of the forest plot, the heterogeneityof^{68}Ga-PSMA PET/CT was high in both sensitivity(I^2 = 97.25%) and specificity(I^2 = 95.12%).Due to the small number of studies weincluded (n = 10) thatprevented meta-regression from beingimplemented, a random-effectsmodel was used to pool the data of^{68}Ga-PSMA PET/CT.

Discussion

To our knowledge, this is the first meta-analysis ofthediagnostic efficacy for ^{68}Ga-PSMA PET/CT in aprostatecancer patient with pelvic LN metastasis risk. We foundthat theindicators and results of ^{68}Ga-PSMA PET/CT showasatisfactory diagnostic efficacy.

In previous treatments, LN staging of prostate cancerpatientscan only be determined by performing PLND according tothesituation during the operation. However, this method is notalwaysfeasible [24].Clinically, the use of PLND is not alwaysfeasible, beingrestricted for the following reasons: not everypatient willreceive PLND, limited anatomical locations performed,andconsideration regardingcomplications[25–27], resulting in suboptimal lymphnodestaging. 68 Ga-PSMA PET/CT is a more accurate methodtodetermine the LN stage of PCa patientsbeforesurgery[28],which can be incorporated into clinicalpractice.

Our meta-analysis included 10 studies from differentcountriesand regions, involving a total of 701 patients. Thepooledspecificity of 0.95 (95% CI: 0.87–0.98) for^{68}Ga-PSMAPET/CT. But pooled sensitivity was recorded as0.84 (95% CI:0.55–0.95), which is not enough to convince us to giveup theremaining 20% of the patient. The Youden index

was 0.79. AUCwas0.97 (95% CI: 0.95–0.98), which was in line with ourinitialpredictions. Through these comprehensive indicators, we canthinkthat ^{68}Ga-PSMA PET/CT has better diagnosticefficacy inpreoperative LN staging in patients with prostatecancer. In thepast few decades, CT and MRI have been used todetermine the LNstaging before radical prostatectomy, but theiraccuracy rate isstill low compared to the goldstandard[6].Hovels et al. Performed ameta-analysis of 24 studies to assessCT/MRI for preoperativeevaluation of LN staging. In his research,for CT, pooledsensitivity and specificity was 0.42 (95% CI:0.26–0.56) and 0.82(95% CI: 0.8–0.83) respectively. For MRI, pooledsensitivity andspecificity was 0.39 (95% CI: 0.22–0.56) and 0.82(95% CI:0.79–0.83)[29].From this point of view, the performanceof CT and MRI in judgingLN staging is not satisfactory. Ifclinicians rely on CT or MRI,they will easily make the wrongdecision on the patient'scondition. In our analysis, we could seethat two studies havelower sensitivity, 0.38(95%: 0.28–0.48) and0.33 (95% CI:0.24–0.43) respectively[10, 22]. The reason for this analysis was that,dueto the technical level of the test, the sample size, andbiasbetween the samples, it might have lead to different finalresults.The specificity value provided in one study issignificantlylower[17]. Wethought that the main reason is thatthe patients included inHerlemann's[17]study received different PLNDs. Among them,20 received primaryPLND and 14 received secondary PLND, which maybe the main reasonfor the lower specificity. Multi-parametermagnetic resonance(mpMR) also plays a large role in thepreoperative evaluation ofprostate cancer, especially in judgingextraprostatic extension(EPE) of the tumor, invasion of the seminalvesicle(SVI)[20]. In aretrospective study by Van Leeuwen atal. They also compared thediagnostic accuracy of mpMR and^{68}Ga-PSMA PET/CT for LNmetastasis in a patient withintermediate high-risk PCa. Thesensitivity was 14% and 53%,respectively, and the specificity was99% and 88%,respectively[2].All of these indicated that68 Ga-PSMA PET / CT has betterdiagnostic efficacy and wasexpected to be popularized and used inclinical.

The higher the value of DOR, the better the diagnostic valueofthis diagnostic method. In our study, The DOR value was 4.60(95%CI: 2.91–6.30), indicating that the overall accuracy washigh.Pooled PLR and NLR value was 17.19 (95% CI: 6.27–47.17) and0.17(95% CI: 0.05–0.56), respectively. This can be understood astheprobability of ^{68}Ga-PSMA PET/CT correctly judgingLNmetastasis is 17 times that of misjudging, and the probabilityofcorrectly judging LN non-metastasis is 0.17 times thatofmisjudging. At the same time, we also noticed that thepublicationbias shown by Deek's funnel plot (Fig. 5) has a P-value of 0.02. Itisunderstandable that most of the articles we includedwereretrospective trials and were not included in relatedstudiesbefore 2016, which led to the results. From the dataresults, it isworth trying to use 68 Ga-PSMA PET / CT todiagnose LN stagingin patients with PCa.

We perform this meta-analysis strictly according toPRISMguidelines[30].However, there are still some limitationsin our meta-analysis.First, most of the studies we included weresingle-centerretrospective studies, and the existence of selectionbias mayaffect our judgment. Second, the sample populationsincluded inthese articles are only Asia, Europe, and Australia, sopopulationbias is unavoidable. Third, the sample size is too small.Due tothe clinical application of ^{68}Ga-PSMA PET/CT inthefuture, there is not a sufficiently large sample size tobeincluded in our meta-analysis. Compared with PLND,although^{68}Ga-PSMA PET/CT has only moderate sensitivityandbetter specificity, it can perform relatively accurate LNstagingof detected PCa patients. At this point,^{68}Ga-PSMAPET/CT is due to any other imagingexaminations, but due to manylimitations, our conclusions stillrequire a larger sample size,multi-center prospective randomizedcontrolled trial to verify.

Conclusion

In summary, ^{68}Ga-PSMA PET / CT was potentiallyaeffective and appropriate imaging modality to predict theLNmetastasis prior to a surgery strategy. Further studiesin^{68}Ga-PSMA PET / CT are needed, and efforts arewarrantedto improve understanding and intervention of thesediagnosticdeviations and effectiveness.

Declarations

Compliance with Ethics Standards

Not applicable.

Funding

This study was funded by National Natural Science FoundationofChina, grant number: 81900617, application code: H0503,relyingunit code: 63700708A0140-0268

Conflict of Interest

The authors declare that they have nocompetinginterests.

Research involving human participantsand/oranimals

This article does not contain any studies with humanparticipantsor animals performed by any of the authors.

Informed consent

There are no details on individuals reported withinthismanuscript, and no consent for publication was collected.

Availability of data and materials

All data generated and analysed during this study are includedinthis published article.

Authors' contributions

Conceived and designed the experiments: Yunxiang Li. Analysedthedata: Lei Peng, Jinze Li, Chunyang Meng.Contributedreagents/materials/analysis: Jinming Li, Chengyu You,Dandan Tang,Tangqiang Wei and Wei xiong. Wrote the manuscript: LeiPeng, andJinze Li. All authors have read and approved thefinalmanuscript.

Acknowledgements

The authors thank Ms Xinnan Gou for providingcontinuousencouragement to Dr Lei Peng to pursue his career inmedicine.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, TorreLA,Jemal A. Global cancer statistics 2018: GLOBOCAN estimatesofincidence and mortality worldwide for 36 cancers in 185countries.CA Cancer J Clin. 2018;68(6):394–424.
2. van Leeuwen PJ, Donswijk M, Nandurkar R, Stricker P, HoB,Heijmink S, Wit EMK, Tillier C, van Muilenkom E, Nguyen Q, etal.Gallium-68-prostate-specific membrane antigen ((68)Ga-PSMA)positron emission tomography (PET)/computed tomography(CT)predicts complete biochemical response from radicalprostatectomyand lymph node dissection in intermediate- andhigh-risk prostatecancer. BJU Int. 2019;124(1):62–8.
3. Gandaglia G, Fossati N, Zaffuto E, Bandini M,Dell'OglioP, Bravi CA, Fallara G, Pellegrino F, Nocera L,Karakiewicz PI, etal. Development and Internal Validation of aNovel Model toIdentify the Candidates for Extended Pelvic LymphNode Dissectionin Prostate Cancer. Eur Urol.2017;72(4):632–40.

4. Hovels AM, Heesakkers RA, Adang EM, Jager GJ, StrumS,Hoogeveen YL, Severens JL, Barentsz JO. The diagnostic accuracyofCT and MRI in the staging of pelvic lymph nodes in patientswithprostate cancer: a meta-analysis. ClinRadiol.2008;63(4):387–95.
5. Fossati N, Willemse PM, Van den Broeck T, van denBerghRCN, Yuan CY, Briers E, Bellmunt J, Bolla M, Cornford P, DeSantisM, et al. The Benefits and Harms of Different Extents ofLymph NodeDissection During Radical Prostatectomy for ProstateCancer: ASystematic Review. Eur Urol.2017;72(1):84–109.
6. Mottet N, van den Bergh RCN, Briers E, Bourke L,CornfordP, De Santis M, Gillessen S, Govorov A, Grummet J, HenryAM, et al:**EAU** - **ESTRO** - **ESUR** - **SIOGGuidelines onProstate Cancer 2018**. In: *European Associationof UrologyGuidelines* 2018 *Edition. Volume presented at theEAUAnnual Congress Copenhagen 2018*, edn. Arnhem, TheNetherlands:European Association of Urology GuidelinesOffice;2018.
7. Luiting HB, van Leeuwen PJ, Busstra MB, Brabander T,vander Poel HG, Donswijk ML, Vis AN, Emmett L, Stricker PD, RoobolMJ.**Use of gallium-68 prostate-specific membraneantigenpositron-emission tomography for detecting lymph nodemetastases inprimary and recurrent prostate cancer and location ofrecurrenceafter radical prostatectomy: an overview of thecurrentliterature**. *BJU Int* 2019.
8. Bouchelouche K, Choyke PL. J C: Prostate specificmembraneantigen- a target for imaging and therapy withradionuclides. DiscovMed. 2010;9(44):55–61.
9. Zhang Q, Zang S, Zhang C, Fu Y, Lv X, Zhang Q, DengY,Zhang C, Luo R, Zhao X, et al. Comparison of (68)Ga-PSMA-11PET-CTwith mpMRI for preoperative lymph node staging in patientswithintermediate to high-risk prostate cancer. J TranslMed.2017;15(1):230.
10. Yaxley JW, Raveenthiran S, Nouhaud FX, SamartungaH,Yaxley AJ, Coughlin G, Delahunt B, Egevad L, McEwan L, WongD.Outcomes of Primary Lymph Node Staging of Intermediate andHighRisk Prostate Cancer with (68)Ga-PSMA PositronEmissionTomography/Computerized Tomography Compared toHistologicalCorrelation of Pelvic Lymph Node Pathology. JUrol.2019;201(4):815–20.
11. Afshar-Oromieh A, Holland-Letz T, Giesel FL, KratochwilC,Mier W, Haufe S, Debus N, Eder M, Eisenhut M, Schafer M, etal.Diagnostic performance of (68)Ga-PSMA-11 (HBED-CC) PET/CTinpatients with recurrent prostate cancer: evaluation in1007patients. Eur J Nucl Med MolImaging.2017;44(8):1258–68.
12. Afshar-Oromieh A, Haberkorn U, Eder M, EisenhutM,Zechmann CM. [68Ga]Gallium-labelled PSMA ligand as superiorPETtracer for the diagnosis of prostate cancer: comparisonwith18F-FECH. Eur J Nucl Med MolImaging.2012;39(6):1085–6.
13. Higgins JP, Thompson SG, Deeks JJ, Altman DG.Measuringinconsistency in meta-analyses.Bmj.2003;327(7414):557–60.
14. Reitsma JB, Glas AS, Rutjes AW, Scholten RJ, BossuytPM,Zwinderman AH. Bivariate analysis of sensitivity andspecificityproduces informative summary measures in diagnosticreviews. J ClinEpidemiol. 2005;58(10):982–90.
15. Hamza TH, Arends LR, van Houwelingen HC, StijnenT.Multivariate random effects meta-analysis of diagnostic testswithmultiple thresholds. BMC medical researchmethodology.2009;9:73.
16. Song F, Khan KS, Dinnes J, Sutton AJ. Asymmetricfunnelplots and publication bias in meta-analyses of diagnosticaccuracy.Int J Epidemiol. 2002;31(1):88–95.
17. Herlemann A, Wenter V, Kretschmer A, ThierfelderKM,Bartenstein P, Faber C, Gildehaus FJ, Stief CG, Gratzke C,FendlerWP. (68)Ga-PSMA Positron Emission Tomography/ComputedTomographyProvides Accurate Staging of Lymph Node Regions Prior toLymph NodeDissection in Patients with Prostate Cancer. EurUrol.2016;70(4):553–7.

18. Obek C, Doganca T, Demirci E, Ocak M, Kural AR,YildirimA, Yucetas U, Demirdag C, Erdogan SM, Kabasakal L, et al.Theaccuracy of (68)Ga-PSMA PET/CT in primary lymph node staginginhigh-risk prostate cancer. Eur J Nucl Med MolImaging.2017;44(11):1806–12.
19. Gupta M, Choudhury PS, Hazarika D, Rawal S. AComparativeStudy of (68)Gallium-Prostate Specific Membrane AntigenPositronEmission Tomography-Computed Tomography and MagneticResonanceImaging for Lymph Node Staging in High Risk ProstateCancerPatients: An Initial Experience. World J NuclMed.2017;16(3):186–91.
20. Yilmaz B, Turkay R, Colakoglu Y, Baytekin HF, ErgulN,Sahin S, Tugcu V, Inci E, Tasci AI, Cermik TF. Comparisonofpreoperative locoregional Ga-68 PSMA-11 PET-CT and mp-MRIresultswith postoperative histopathology of prostate cancer.Prostate.2019;79(9):1007–17.
21. Maurer T, Gschwend JE, Rauscher I, Souvatzoglou M,HallerB, Weirich G, Wester HJ, Heck M, Kubler H, Beer AJ, etal.Diagnostic Efficacy of (68)Gallium-PSMA PositronEmissionTomography Compared to Conventional Imaging for Lymph NodeStagingof 130 Consecutive Patients with Intermediate to High RiskProstateCancer. J Urol. 2016;195(5):1436–43.
22. Budaus L, Leyh-Bannurah SR, Salomon G, Michl U, HeinzerH,Huland H, Graefen M, Steuber T, Rosenbaum C. Initial Experienceof(68)Ga-PSMA PET/CT Imaging in High-risk Prostate CancerPatientsPrior to Radical Prostatectomy. EurUrol.2016;69(3):393–6.
23. van Leeuwen PJ, Emmett L, Ho B, Delprado W, Ting F,NguyenQ, Stricker PD. Prospective evaluationof68Gallium-prostate-specific membrane antigen positronemissiontomography/computed tomography for preoperative lymph nodestagingin prostate cancer. BJU Int. 2017;119(2):209–15.
24. Abdollah F, Karnes RJ, Suardi N, Cozzarini C, GandagliaG,Fossati N, Bianchi M, Boorjian SA, Sun M, Karakiewicz PI, etal.Predicting survival of patients with node-positive prostatecancerfollowing multimodal treatment. EurUrol.2014;65(3):554–62.
25. Abdollah F, Sun M, Thuret R, Budäus L, Jeldres C,GraefenM, Briganti A, Perrotte P, Rigatti P, Montorsi F, et al.Decreasingrate and extent of lymph node staging in patientsundergoingradical prostatectomy may undermine the rate of diagnosisof lymphnode metastases in prostate cancer. Europeanurology.2010;58(6):882–92.
26. Galper SL, Chen MH, Catalona WJ, Roehl KA, RichieJP,D'Amico AV. Evidence to support a continued stage migrationanddecrease in prostate cancer specific mortality. The Journalofurology. 2006;175(3 Pt 1):907–12.
27. Kawakami J, Meng MV, Sadetsky N, Latini DM, DuchaneJ,Carroll PR. Changing patterns of pelvic lymphadenectomyforprostate cancer: results from CaPSURE. The Journal ofurology.2006;176(4 Pt 1):1382–6.
28. Mandel P, Tilki D, Chun FK, Pristupa E, GraefenM,Klutmann S, Budaus L, Steuber T: **Accuracyof(68)Ga-Prostate-specific MembraneAntigenPositron Emission Tomography for the Detection of LymphNodeMetastases Before Salvage Lymphadenectomy**. *EurUrolFocus* 2018.
29. Hövels AM, Heesakkers RA, Adang EM, Jager GJ, StrumS,Hoogeveen YL, Severens JL, Barentsz JO. The diagnostic accuracyofCT and MRI in the staging of pelvic lymph nodes in patientswithprostate cancer: a meta-analysis. ClinRadiol.2008;63(4):387–95.
30. Moher D, Liberati A, Tetzlaff J, Altman DG.PreferredReporting Items for Systematic Reviews and Meta-Analyses:ThePRISMA Statement. PLoS Medicine. 2009;6(7):e1000097.

Tables

Table 1: Characteristics of the included studies in themeta-analysis

Author(year)	Country	StudyDesign	StudyPopulation	RecruitingTime	Uptake Time(min)	Lymphade-nectomy	Age Median(Range) Median(IQR[])	PSA[] median(Range) Median(IQR)	Quality of eachstudies
Budaus 2016	Germany	Retrospective	Single center	June. 2014 to Mar. 2015	NA	ePLND[]	63 (44-75) -	8.8 (1.4-376) -	11
Gupta 2017	India	Retrospective	Single center	Dec. 2014 to Dec. 2015	Nearly 60	ePLND	NA	NA	10
Herlemann 2016	Germany	Retrospective	Single center	Jan. 2014 to Aug. 2015	60	PLND[]	70.5(59-80)[]	70.5(59-80)[]	12
Maurer 2016	Germany	Retrospective	Single center	Dec. 2012 to Nov. 2014	59.8±17.8[]	PLND	66 (45-84) -	66 (46-84) -	11
Obek 2017	Turkey	Retrospective	Single center	July. 2014 to Oct. 2015	45-60	ePLND	64±6.0[]	26.5±21.4[]	10
Yaxley 2019	Australia	Retrospective	Single center	July. 2014 to Sep. 2017	45-60	PLND	68 (44-80) -	7.6 (1.5-51) -	11
VanLeeuwen 2017	Australia	Prospective	Single center	Apr. to Oct. 2015	60	ePLND	- 65 (60-71)	- 65 (55-82)	11
VanLeeuwen 2018	Australia	Retrospective	Single center	Feb. 2015 to Oct. 2017	60	ePLND	NA	9.4 -	10
Yilmaz 2019	Turkey	Retrospective	Single center	May. 2016 to Apr. 2018	Approximately 60	rLND[]	62.8(49-73)[]	12 (2.4-32)[]	10
Zhang 2017	China	Retrospective	Single center	Mar. to July. 2017	60	PLND	69 (55-82) -	37.25 (7.2-348) -	11

[]Mean±SD;[]Mean (Range); []rLND, regional lymph nodedissection; []PSA: prostate specificantigen[]IQR: interquartile range; []ePLND:extend pelvic lymph node dissection; []PLND: pelvic lymphnode dissection.

Table 2: Summary estimated ofdiagnostic performance of the ^{68}Ga-PSMAPET/CT[a]for lymph node staging in patient with ProstateCancer

Author(year)	Samplesize	TP[b]	FP[c]	FN[d]	TN[e]
Budaus2016	30	33	0	67	100
Gupta2017	12	100	20	0	80
Herlemann2016	34	91	33	9	67
Maurer2016	130	66	1	34	99
Obek2017	51	53	14	47	86
Yaxley2019	208	38	6	62	94
Van Leeuwen2017	30	64	5	62	94
Van Leeuwen2018	140	60	12	40	88
Yilmaz2019	24	38	6	62	94
Zhang2017	42	93	4	7	96
Pooledanalysis	Inconsistency (I^2) (95%CI)	99% (98-99)			
	Sample Size	701			
	SEN[f] (95%CI)	0.84 (0.55, 0.95)			
	SPE[g] (95%CI)	0.95 (0.87, 0.98)			
	PLR[h] (95%CI)	17.2 (6.3, 47.2)			
	NLR[i] (95%CI)	0.17 (0.05, 0.56)			
	DOR[j] (95%CI)	100 (18, 545)			
	Youden Index	0.79			

[a]^{68}Ga-PSMAPET/CT, ^{68}Gallium-PSMA positron emissiontomography/computerized tomography; [b]TP, true positive,[c]FP, false positive, [d]FN, false negative,[e]TN, true positive, [f]SEN, Sensitivity;[g]SPE, Specificity; [h]PLR, Positive LikelihoodRatio; [i]NLR, Negative Likelihood Ratio, [j]DOR,Diagnostic Odds Ratio

Figures

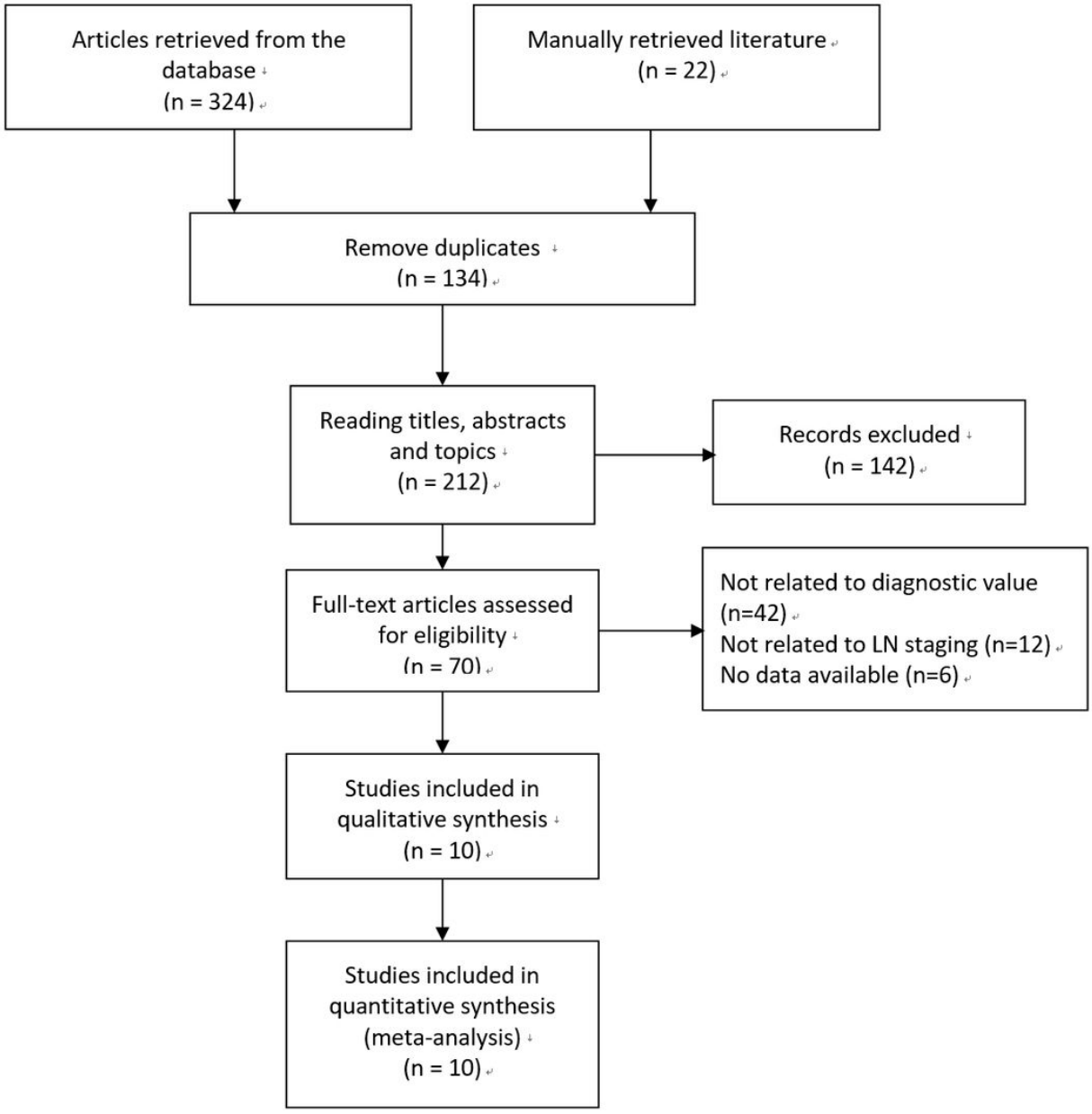

Figure. 1 Flow diagram of studies selection process.

Figure 1

Flow diagram of studies selection process.

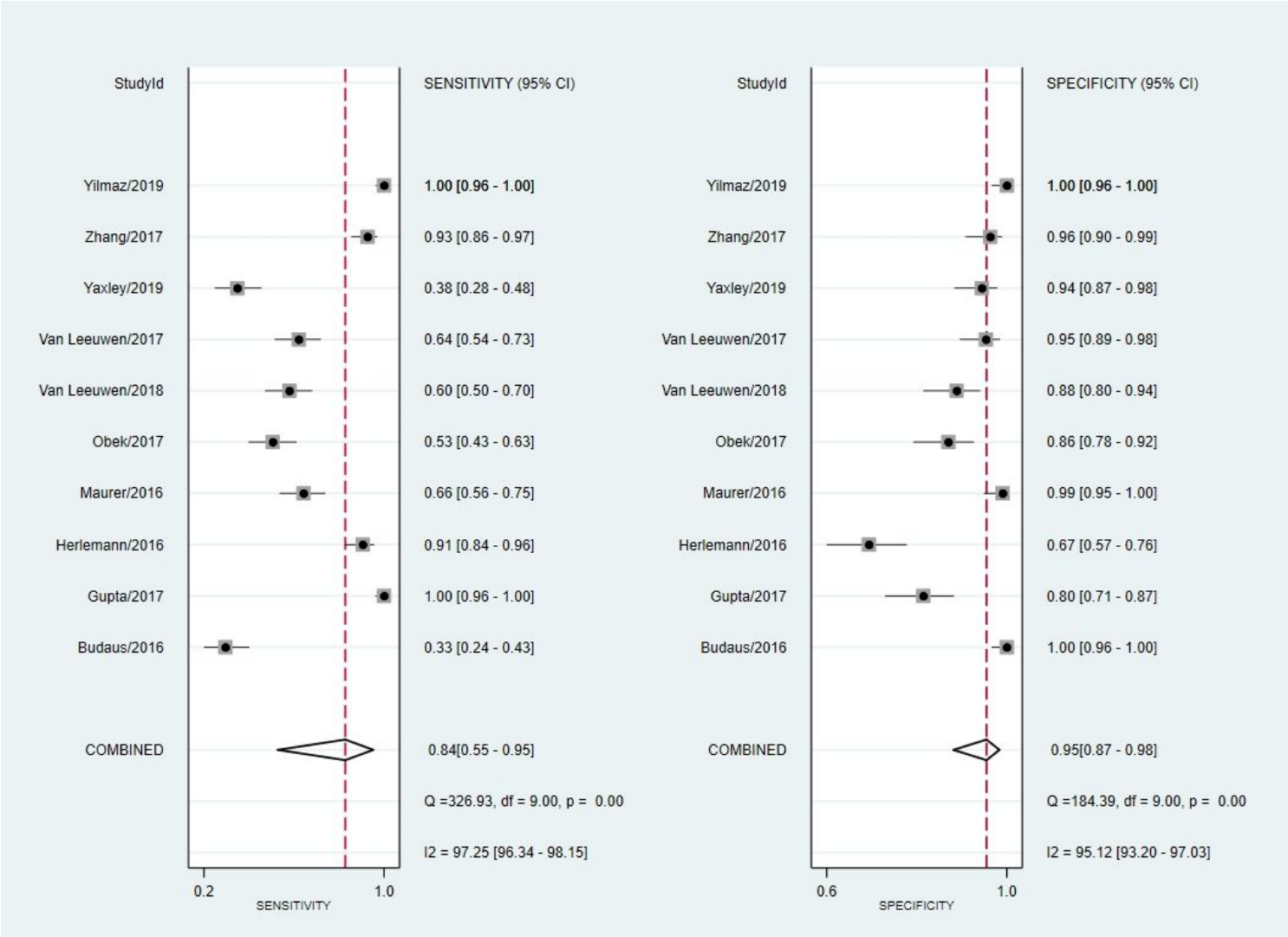

Figure 2

Forest plot of pooled sensitivity and specificity of 68Ga-PSMA PET/CT for lymph node staging in patient with prostate cancer

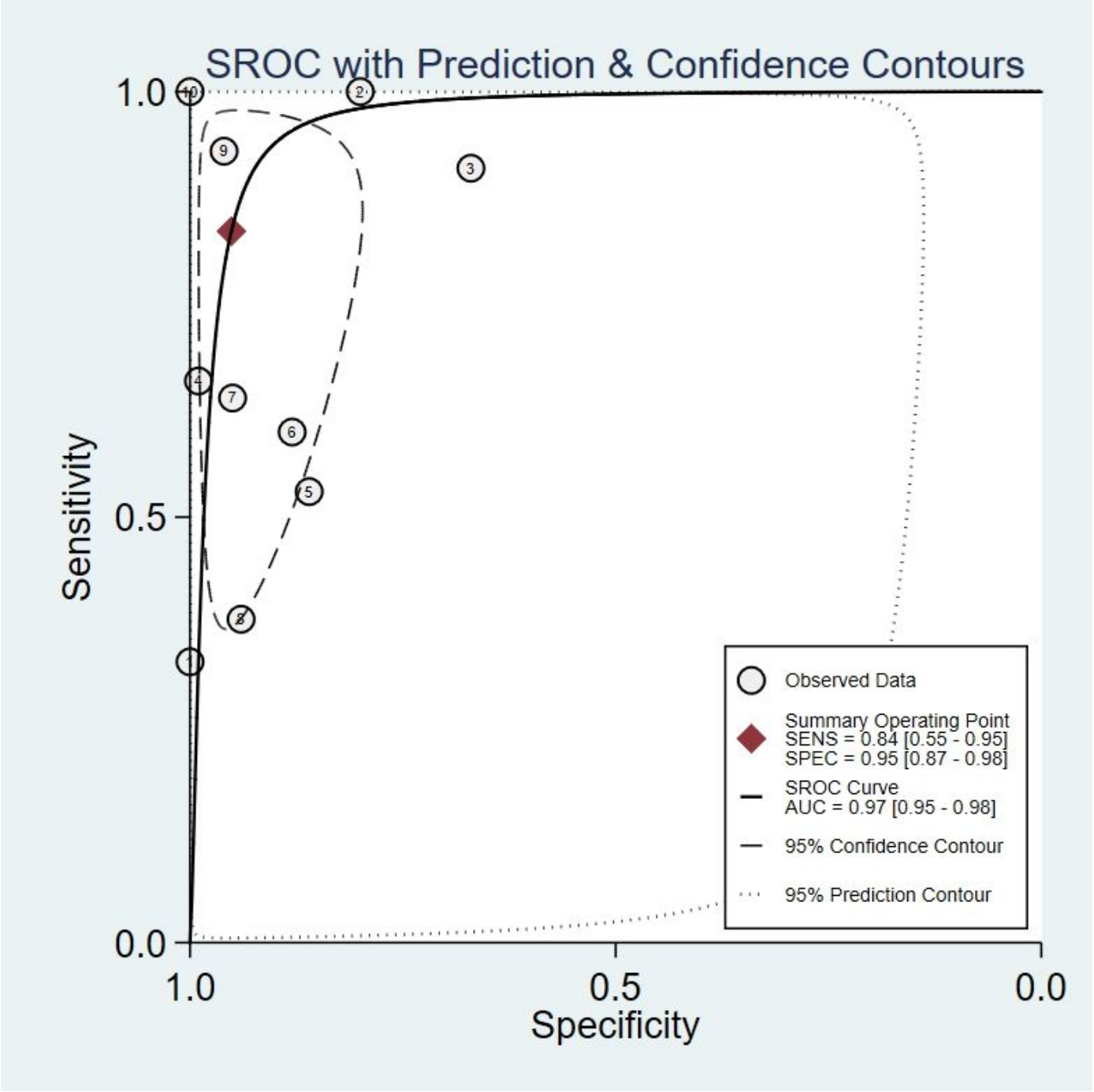

Figure 3

The SORC curve of 68Ga-PSMA PET/CT for lymph node staging in patient with prostate cancer

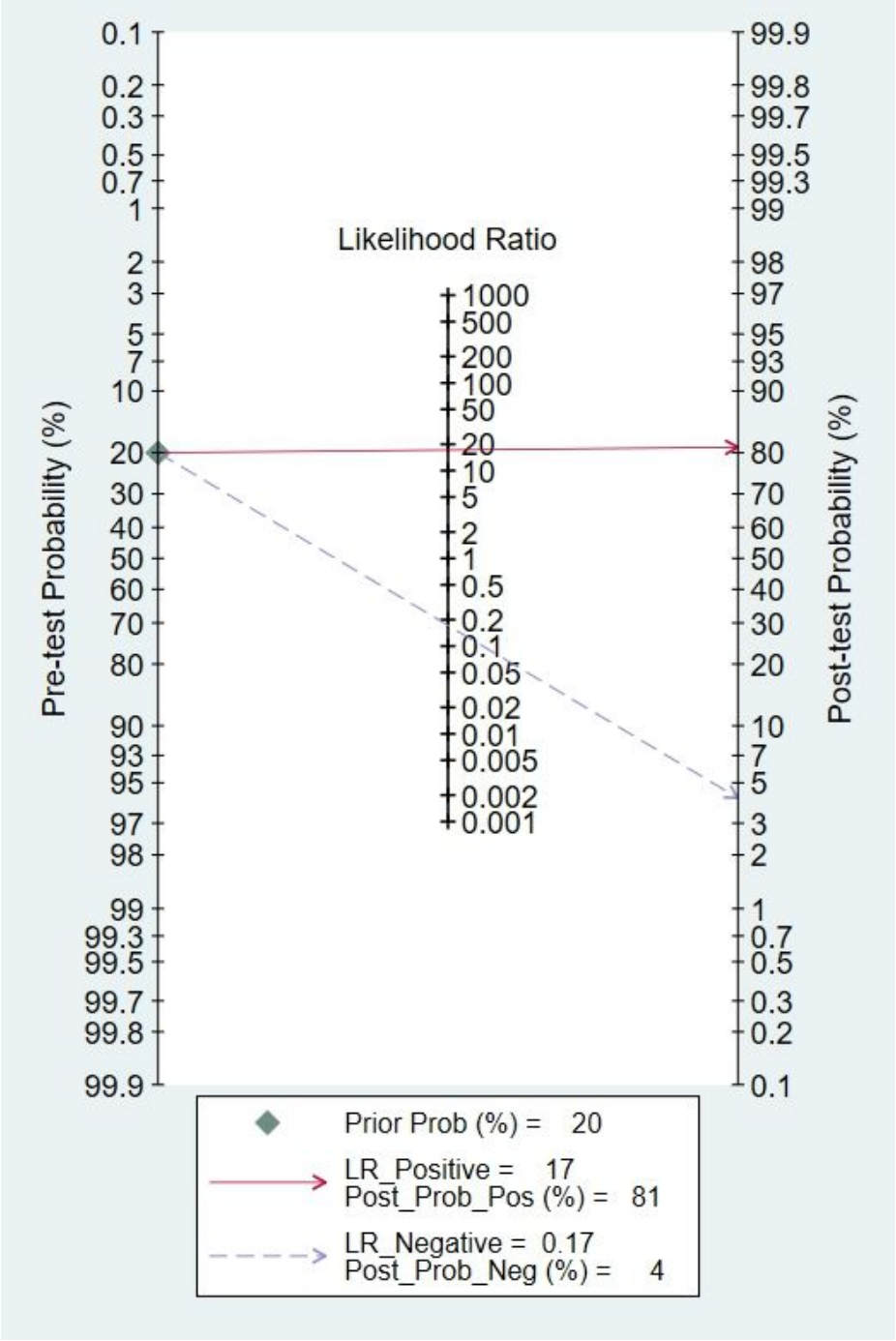

Figure 4

Fagan diagram evaluating the overall diagnostic value of 68Ga-PSMA PET/CT for lymph node staging in patient with prostate cancer

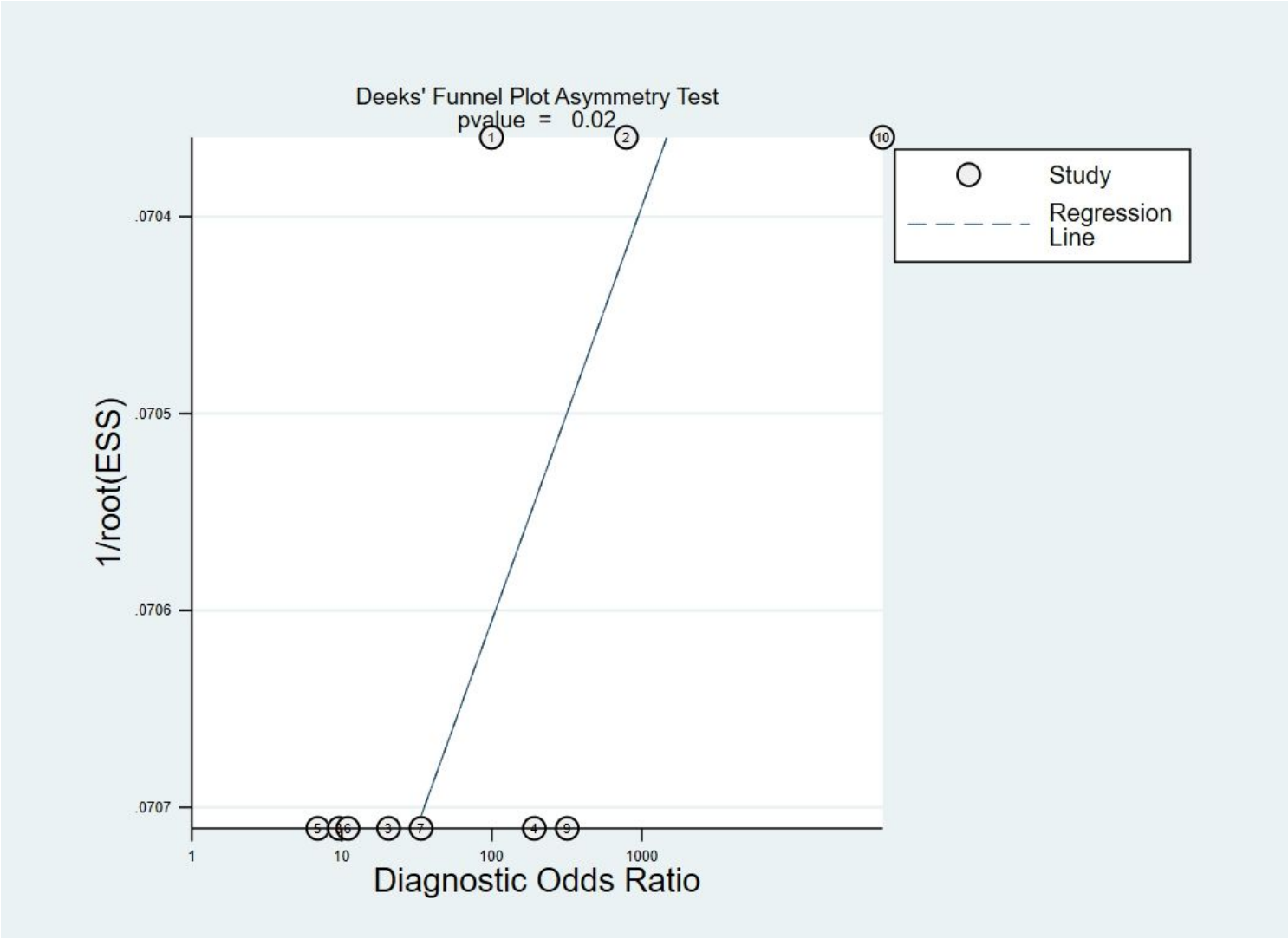

Figure 5

Deek's funnel plot to evaluate the publication bias.