REVIEW PAPER

UROLOGICAL ONCOLOGY

Effectiveness of extended pelvic lymphadenectomy in the survival of prostate cancer: a systematic review and meta-analysis

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Citation: García-Perdomo HA, Correa-Ochoa JJ, Contreras-García R, Daneshmand S. Effectiveness of extended pelvic lymphadenectomy in the survival of prostate cancer: a systematic review and meta-analysis. Cent European J Urol. 2018; 71: 262-269.

Article history
Submitted: April 17, 2018
Accepted: Aug. 6, 2018
Published online: Aug. 20, 2018

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Introduction To determine the effectiveness and safety of extended pelvic lymphadenectomy compared with standard lymphadenectomy in the overall, cancer-specific survival and biochemical recurrence-free survival of patients with localized prostate cancer who underwent radical prostatectomy.

Material and methods Clinical trials and cohort studies were included without language restrictions with the following participants: men older than 40 years of age diagnosed with localized prostate cancer who received radical prostatectomy plus pelvic lymphadenectomy. Standard vs. extended pelvic lymphadenectomy were compared. The primary outcomes were overall and cancer-specific survival. A search strategy in MEDLINE, EMBASE, CENTRAL, LILACS, and other databases was conducted to obtain published and unpublished literature. The risk of bias was evaluated with the Cochrane Collaboration tool. The statistical analysis was performed in STATA 14.

Results Six studies were included, of which only one was experimental; the other studies were cohort studies. The surgical technique was robot-assisted in three studies. Two studies only had information concerning the adverse effects. It was not possible to include one clinical trial that met the criteria because an erratum was published in which falsification of the experimental data was proven. There was a biochemical recurrence-free survival hazard ratio (HR) = 0.62 and a 95% confidence interval (CI) (0.36 to 0.87).

Conclusions According to current literature, a mild difference was evident favoring the extended lymphadenectomy in biochemical recurrence-free survival. Additionally, there was no evidence to draw a conclusion regarding the overall survival since we did not find any studies concerning this outcome.

Key Words: lymph node dissection ‹› prostate neoplasm ‹› lymphadenectomy ‹› systematic review ‹› meta-analysis

INTRODUCTION

Prostate cancer is the most frequent neoplasm in men worldwide and a major public health issue in countries where there is a large proportion of elderly men, it has shown a substantial increase in the last decade regarding the costs related to the disease. It is estimated that the total economic costs of prostate cancer exceed 8.4 billion euros and 7% of overall cancer costs [1].

The widespread use of screening with prostate-specific antigen (PSA) and digital rectal examination (DRE) has enabled early detection, with a notable migration in the stage at diagnosis. Approximately 90% of cases are detected in clinically localized states, but the challenge for those who treat patients with prostate cancer is the choice of an effective treatment for patients for whom treatment is necessary [2, 3]. In this scenario (clinically localized disease),

treatment is perhaps one of the topics of greatest concern and controversy today because multiple variables (tumor polymorphism, staging inaccuracy, life expectancy, degree of impact on the quality of life, fears, and patient preference) are making it almost impossible to define a single treatment as optimal [4].
Radical prostatectomy was the first treatment used for clinically localized prostate cancer and has been used for over 100 years. The main goal is to eradicate the disease while functionally preserving continence and sexual potency. The anatomical definition of pelvic lymph node dissection (PLND) distinguishes a standard pelvic lymphadenectomy (sPLN) from an extended or expanded pelvic lymphadenectomy (ePLN). sPLN is restricted to the obturator fossa or a standard variant, which also includes the external iliac vessels. Performing a sPLN includes the removal of the nodes that line the external iliac vessels, the nodes located within the cranial obturator fossa and caudally to the obturator nerve and the nodes medial and lateral to the internal iliac artery. Some lymphatic mapping studies have advised extending the dissection template to the common iliac vessels, where approximately 75% of all metastatic sites can be removed with this modification [5, 6].
The role of PLND in patients with prostate cancer continues to be controversial. PLND during radical prostatectomy is the most suitable process for disease staging. In this sense, extended PLND has been demonstrated to significantly improve the detection of lymphatic involvement compared with limited PLND; however, its therapeutic role and impact on oncological outcomes are uncertain [7–10].
In patients with prostate cancer treated with radical prostatectomy plus pelvic lymphadenectomy, the histopathological evidence of lymphatic node involvement is one of the strongest predictors of poor outcomes. Therefore, defining the extent of the PLND is of crucial interest for optimizing staging and removing all areas of lymphatic metastasis [5].
Data from the first randomized clinical trial published in 2012 showed the benefit of extended pelvic lymphadenectomy during radical prostatectomy on biochemical progression-free survival with seventy- four months of follow-up. The data was received with great enthusiasm by the urological community, but unfortunately, this publication was recently withdrawn due to academic misconduct and falsification of data by one of the authors [11].
Moreover, observational studies have not yet managed to fully demonstrate the beneficial impact of extended pelvic lymphadenectomy on survival and/or biochemical recurrence. This lack is important because any therapeutic benefit associated with surgical treatments for prostate cancer should be tested using an appropriate surgical approach in an adequately selected population [9].
Given the evidence to date, which suggests the benefit of sPLN (entirely retrospective), it is necessary to conduct a systematic review and meta-analysis with the objective of determining the effectiveness and safety of extended pelvic lymphadenectomy in the overall, cancer-specific survival and biochemical recurrence-free survival of patients with localized prostate cancer who have undergone radical prostatectomy.

MATERIAL AND METHODS

This study was conducted according to the recommendations of the Cochrane Collaboration following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement. The protocol was registered in the international prospective register of systematic reviews (PROSPERO): CRD42016043658.

Selection criteria

Randomized clinical trials and cohort studies performed were included. Open and crossover trials and studies with simultaneous interventions were excluded. No language restriction was imposed.
Participants: Men older than 40 years of age with a histological diagnosis of prostate cancer with a localized clinical stage received with radical prostatectomy plus pelvic lymphadenectomy.
Interventions: Standard vs. extended pelvic lymphadenectomy.
Exclusion criteria: 1. Radical prostatectomy not performed; 2. No description of pelvic lymphadenectomy; 3. Metastatic patients; and 4. Patients with locally advanced disease. Primary outcomes: 1. Overall survival and 2. Cancer-specific survival.
Secondary outcomes: 1. Biochemical progression-free survival; 2. Biochemical recurrence; 3. Clinical progression-free survival; and 4. Adverse effects.

Information sources and search strategy

A search strategy was designed for controlled clinical trial publications in MEDLINE via Ovid, CENTRAL, LILACS, and EMBASE. The search strategy was specific for each database and included a combination of medical headings and free text terms for lymphadenectomy, prostate cancer, and type of study. A specific search was performed with indexed terms and free writing for sources of conference abstracts, clinical trials in progress (www.clinicaltrials.gov), literature published in non-indexed

journals and other sources of gray literature. A generic search strategy was designed for Google Scholar. No language restrictions or restrictions on article publication statuses were considered. Articles published from inception to nowadays were included. The full search strategy for each database is listed in the supporting Appendix 1.

Study selection

Two researchers reviewed the titles and abstracts independently and blindly to determine the potential usefulness of the articles within the systematic review. The eligibility criteria were applied during the review of the full text of potentially eligible articles. Discrepancies were resolved in consensus by the two researchers. In cases with no consensus, a third reviewer made the final decision.

Data Collection

The data was collected by two researchers using a standardized extraction tool that contained the study designs, participants, interventions, comparators and final outcomes. The reviewers confirmed the data in duplicate. There was no need to contact the authors because the data was complete.

Risk of bias

The risk of bias assessment was conducted by two reviewers independently. In case of discrepancies, a discussion was needed to arrive at a consensus. The tool used was described by the Cochrane Collaboration for experimental studies which included the following items: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective reporting and other bias. A modified Cochrane tool for the evaluation of analytical observational studies was used which included the following issues: selection of participants; comparability between groups; conflict of interest; confounding control; statistical methods; selective reporting; assessment of the outcome; follow-up long enough and those lost to follow-up. Each one of the tools was classified as low, unclear or high risk of bias.

Summary measures and synthesis of results

The analysis was performed in STATA 14. The measures of effect for both the primary and secondary outcomes were the risk difference (RD) and hazard ratio (HR) with their corresponding confidence intervals (95% CI). A meta-analysis of the random effects

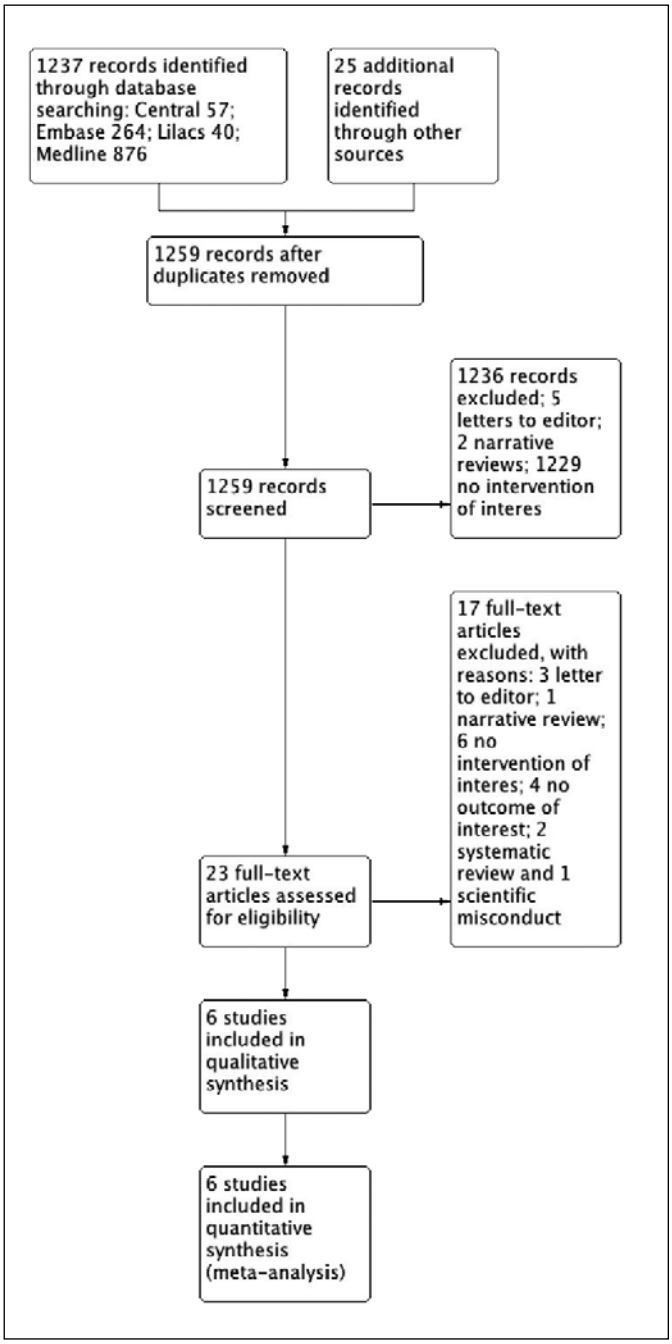

Figure 1. *Flow chart.*

was performed due to the statistical heterogeneity found in the included studies. We calculated HR for the biochemical recurrence-free survival, based on Tierney et al. [12] for those studies where this association measure was not explicitly described. Heterogeneity was evaluated with the I2 index. An I2 value greater than 50% was considered high heterogeneity in accordance with Higgins et al. The results were reported in forest plots, which showed the magnitude of the effect with the corresponding confidence

Table 1. *Characteristics of included studies*

Study	Country SC/MC	Design	Follow-up time (years)	Outcome	Mean age (years)	N (patients)	Mean PSA level (ng/ml)	Risk according to D´Amico classification	Procedure
Kim et al., 2013	Korea	Cohort, single site	5	Biochemical recurrence-free survival, biochemical recurrence, complications	65	282	12.4	Intermediate and High	Robotic
Yuh et al., 2013	Italy	Cohort, single site	4	Complications	64	406	5.5	Intermediate and High	Robotic
Bivalacqua et al., 2013	USA	Cohort, single site	11	Biochemical recurrence-free survival, biochemical recurrence	57	4265	16.5	Low, intermediate and high	Open
Liss et al., 2013	USA	Cohort, single site	5	Biochemical recurrence, complications	61	285	8.5	Intermediate and High	Robotic
Lestingi et al., 2015	Brazil	Randomized clinical trial, single site	2	Biochemical recurrence, complications	NA	216	NA	Intermediate and High	Open
Matsumoto et al., 2011	Japan	Cohort, single site	2	Biochemical recurrence-free survival, biochemical recurrence	67	100	9.9	Low, intermediate and high	Open

Table 2. *Risk of bias.* **A.** *Non-randomized studies.* **B.** *Randomized studies*

A

Author, year	Selection of participants (Selection bias)	Comparability between groups (selection bias)	Conflict of interest	Confounding control	Statistical methods	Selective reporting (Information and detection bias)	Assessment of the outcome	Follow-up long enough	Lost to follow-up
Kim et al., 2013	Low risk	High risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Yuh et al., 2013	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Bivalacqua et al., 2013	Unclear risk	High risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk
Liss et al., 2013	Low risk	High risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk
Matsumoto et al., 2011	High risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

B

Author, year	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Lestingi et al., 2015	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk

intervals. No additional analysis or meta- regression was performed.

Sensitivity analysis

A sensitivity analysis was performed based on the exclusion of each of the studies, but no differences were found [13].

Publication bias

Publication bias was not assessed due to the small number of studies included in the systematic review [14].

RESULTS

Study selection: A total of 1,237 records were found with the designed search strategies, including a clinical trial with proven research misconduct [15]. Six studies were included in the qualitative and quantitative analyses [16–21] (Figure 1).

Characteristics of the included studies: Six studies were included at the end of the review, which comprised 5,554 patients (54–2,279). Five studies evaluated biochemical recurrence-free survival as the primary outcome. Three of these studies also reported the rate of complications inherent to the procedures in the evaluation, and one study ana-

lyzed metastasis-free survival and cancer-specific survival (Table 1).
Characteristics of the excluded studies: The reasons for exclusion were as follows: no intervention or outcome of interest, letters to the editor, systematic/narrative reviews, and research misconduct.
Risk of bias in the studies: generally, a low risk of bias was observed. However, there were some high-risk elements in the comparability between groups in the studies of Kim et al. (2013), Bivalacqua et al. (2013) and Liss et al. (2013). Bivalacqua et al. (2013) had an unclear risk in the selection of the participants and in the control of confounders because it did not clearly describe how the groups in the cohort were formed and did not describe the variables used as the control. Liss et al. (2013), had an unclear risk in the statistical methods because they were not described (Table 2).

Results of the studies according to the outcome

Biochemical recurrence-free survival

Regarding the primary outcome (biochemical recurrence-free survival), we included Kim et al. (2013), Bivalacqua et al. (2013), and Matsumoto et al. (2011), and found an HR = 0.62, 95% CI (0.36, 0.87), and an I2 = 5.8%, favoring the ePLN (Figure 2).

Biochemical recurrence

Regarding one of the secondary outcomes (biochemical recurrence), we included Kim et al. (2013), Bivalacqua et al. (2013), Matsumoto et al. (2011) and Lestingi et al. (2015). The recurrence presented an RD = -0.102, 95% CI (-0.234, 0.03) and an I2 = 92%, with no evidence of significant differences (Figure 3).

Risk of complications

Only Kim et al. (2013), Liss et al. (2013), Yuh et al. (2013) and Lestingi et al. (2015) reported the outcome of complications. We found an RD = 0.04, 95% CI (-0.02, 0.09), and an I2 = 48% was observed, with no evidence of significant differences (Figure 4).

DISCUSSION

Extrapolated studies of other types of cancer have demonstrated a distinct therapeutic value in performing a more thorough pelvic lymphadenectomy. However, the evidence for benefits in prostate cancer has been inconsistent and has suffered from methodological biases. Although the routine use of pelvic lymphadenectomy at the time of radical prostatectomy has decreased in the last decade partially due to a shift towards earlier stages of the disease and the ability to better predict the likelihood of nodal disease using tools such as Partin tables, it is important to recognize that a more extensive nodal

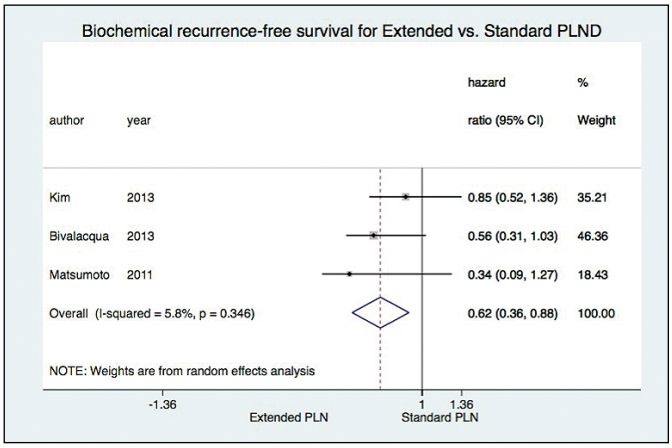

Figure 2. *Biochemical recurrence-free survival.*

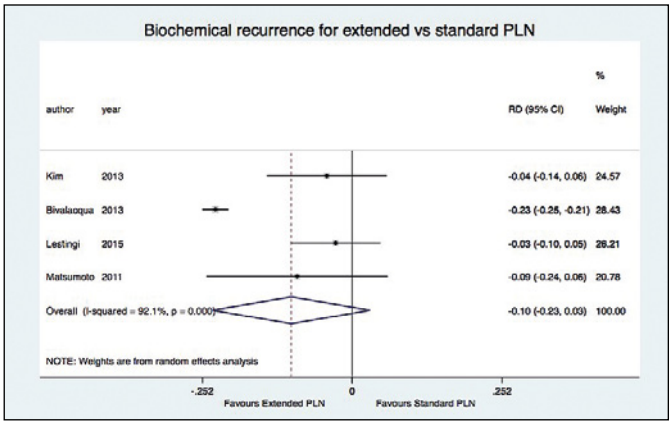

Figure 3. *Biochemical recurrence.*

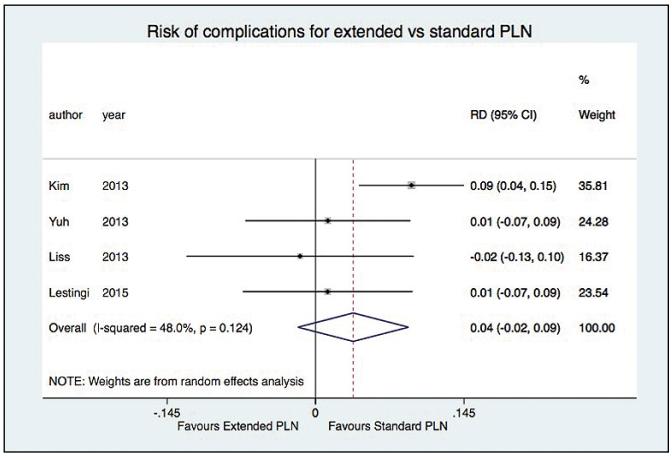

Figure 4. *Risk of complications.*

dissection may be imperative in patients with an increased risk of nodal metastasis [22, 23].

In this sense, Joniau et al. confirmed that a template that included the areas of the external and internal iliac vessels and the obturator fossa was capable of correctly staging 94% of patients. Even if a dissection known as super-extended (extended pelvic lymphadenectomy limits plus presacral nodes and common iliac vessels) is performed, correct staging of up to 97% of the patients can be achieved. It is recommended that the nodes from each resected region be sent in separate containers for histopathological analysis because this approach is usually associated with a diagnostic gain by the uropathologist [24].

This systematic review and meta-analysis of 6 studies, including a total of 5,454 patients, without highlighting the results from the staging perspective of the disease (given the nature of the included studies), revealed that there were no significant differences between performing a standard or extended pelvic lymphadenectomy at the time of radical prostatectomy compared with oncologic outcomes of importance, such as biochemical recurrence and complications. A marginal difference was found in biochemical recurrence-free survival according to the inclusion of three cohort studies. In this case, we did not have the information from the only clinical trial included.

Similar to other oncological entities (i.e., muscle-invasive bladder cancer) where there has been increasing evidence that ePLN improves recurrence-free survival in patients with little nodal involvement, the question to be answered is whether the eradication of all metastatic sites or micro-metastases improves survival in patients with prostate cancer and nodal involvement [25].

Although the beneficial effect of PLND on cancer outcomes has not been documented through prospective studies to date, more recent results of retrospective studies in patients with positive nodes report the best cancer-specific survival rates in patients who have undergone more node extractions, reaching up to 97.9% for patients with 45 nodules removed [9]. However, these results should be treated with caution because retrospective studies have an increased number of biases that can increase or decrease the magnitude of the effect according to the bias present.

In contrast to the above results, Kim et al. investigated a cohort of 905 patients with intermediate and high D'Amico risks and found that although performing the extended pelvic lymphadenectomy increased the detection of nodal metastases, this intervention did not alter the biochemical results after 3 years compared with the performance of a standard lymphadenectomy. The biochemical recurrence-free survival was 77.8% and 73.5% in the ePLN and sPLN groups, respectively, with no significant difference (ePLN vs. sPLN (HR = 0.85, 95% CI 0.52–1.36, p = 0.497) [16].

In some series, the number of nodes resected during the lymphadenectomy was significantly correlated with the time of progression of the disease. Bader et al. found that patients in a population study with ten years of follow-up who underwent excision of at least 10 nodes had a lower risk of death from prostate cancer at 10 years than those who did not undergo excision. However, these results should be confirmed with prospective studies [9, 26]. Classifying, staging, or diagnosing nodes is not the same as improving survival in prostate cancer; this issue was one of the main reasons that we conducted this systematic review. Despite the limitations encountered, it is up to researchers to conduct clinical trials of better methodological quality so that we can perform the procedures that improve the overall survival of patients with prostate cancer with certainty.

It is generally believed that the extended pelvic lymphadenectomy can remove more lymphatic tissue and thus find more positive nodes and increase the trauma and complication rates. This finding was evaluated by Briganti et al., who found that a higher overall percentage of complications (20%) was shown by patients who underwent the extended pelvic lymphadenectomy compared to patients who underwent standard PLN (9%) ($p < 0.001$). However, these results did not translate into major complications because the main complications were the occurrence of a lymphocele and a longer hospital stay [27, 28].

The results of our meta-analysis can offer relief from this non-negligible concern. Our results showed that there were no significant differences in the groups of patients who underwent extended pelvic lymphadenectomy compared with those who underwent a standard procedure RD = 0.04, 95% CI (−0.02, 0.09)].

Recently, we found a systematic review conducted by Choo 2017 [29]. They followed a relevant methodology, but with some important flaws: they included and pooled all comparative studies (case control, cohort and clinical trials studies) and when detailing each of the studies, we found that some of them were only descriptive, retrospective and even, they included information from another systematic review. Some other studies did not accomplish our outcomes and so we did not include them in our review. Therefore, there are some important issues that make these standard reviews not comparable with our standard review.

Finally, several limitations should be taken into account when analyzing our review. There was only

one clinical trial available to include in our study, and we could not find information for biochemical recurrence- free survival. The most important issue was a high heterogeneity found when analyzing the main oncological outcomes, with few studies available for their analysis; perhaps two of them [Matsumoto et al. (2011) and Bivaclaqua et al. (2013)] included also people with low risk prostate cancer and the follow-up had a wide range (2 to 11 years) which could increase heterogeneity. Considering the outcomes shown in the rate of complications, we clarify that although they were not significant, they could be influenced by the experience of the surgeon, their level of training, and the bias that might exist when reporting an adverse outcome.

As a conclusion, according to current literature, a mild difference was evident favoring the extended lymphadenectomy in biochemical recurrence-free survival. Additionally, there is no evidence to draw a conclusion regarding overall survival since we did not find any studies about this outcome. Subsequent randomized studies are needed to confirm or refute these findings.

SUPPORTING INFORMATION

Appendix 1. Search strategy

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

Appendix 1

Search strategy MEDLINE via OVID

1. exp Prostatic Neoplasms/
2. exp prostatic intraepithelial neoplasia/
3. (prostatic adj2 malignanc$).mp
4. (prostatic adj2 cancer).mp
5. or/
6. exp Lymph Node Excision/
7. exp Lymph Nodes/
8. (lymph adj2 node adj2 dissection).mp.
9. (lymph adj2 node adj2 excision).mp.
10. Lymphadenectom$.mp
11. or/
12. exp randomized controlled trial/
13. (randomi*ed adj2 controlled adj2 trial).mp.
14. exp clinical trial/
15. (clinical adj2 trial).mp.
16. exp double-blind method/
17. Exp cohort studies/
18. (cohort adj2 stud$).mp
19. or/
20. 5 and 11 and

EMBASE earch

1. 'Prostate Tumor'/exp
2. 'prostatic intraepithelial neoplasia'/exp
3. (prostatic NEXT/2 malignanc*):ti,ab
4. (prostatic NEXT/2 cancer):ti,ab
5. (organ NEXT/2 confined NEXT/2 disease):ti,ab
6. or/
7. 'lymph node dissection'/exp
8. 'lymph node'/exp
9. (lymph NEXT/2 node NEXT/2 excision):ti,ab
10. Lymphadenectom*:ti,ab
11. or/
12. 'randomized controlled trials'/exp
13. (randomi*ed NEXT/2 controlled NEXT/2 trial):ti,ab
14. 'clinical trials'/exp
15. (clinical NEXT/2 trial):ti,ab
16. 'double blind procedure'/exp
17. 'cohort analysis'/exp
18. or/
19. 6 and 11 nd 18 LILACS Search

[mh:('neoplasias de la prostata')] OR [mh:('Neoplasia Intraepitelial Prostática')] OR [tw:('Cáncer de próstata')] OR [tw:('Cáncer prostático')] AND [mh:('Escisión del Ganglio Linfático')] OR [tw:('linfadenectomia')] OR [tw:('Disección del Nódulo Linfático')] AND [mh:('Ensayo clinico')] OR [tw:('Experimento clinico')] OR [tw:('doble ciego')] OR [mh:('Estudios epidemiológicos')] OR [mh:('estudios observaciones')] OR (mh:('estudios de cohortes')]

CENTRAL Search

1. exp Prostatic Neoplasms/
2. exp prostatic intraepithelial neoplasia/
3. (prostatic next/3 malignanc*):ti,ab,kw
4. (prostatic next/3 cancer):ti,ab,kw
5. or/
6. exp Lymph Node Excision/
7. exp Lymph Nodes/
8. (lymph next/3 node next/3 dissection) :ti,ab,kw
9. (lymph next/3 node next/3 excision) :ti,ab,kw
10. Lymphadenectom*:ti,ab,kw
11. or/
12. 5 and 11

References

1. Luengo-Fernandez R, Leal J, Gray A, Sullivan R. Economic burden of cancer across the European Union: a population-based cost analysis. Lancet Oncol. 2013; 14: 1165-1174.

2. Mottet N, Bellmunt J, Briers E, et al. EAU – ESTRO – ESUR – SIOG Guidelines on Prostate Cancer. [Internet]. 2014 [cited 2018 Mar 20]. Available from: https://uroweb.org/guideline/prostate-cancer/

3. Ilic D, Neuberger MM, Djulbegovic M, Dahm P. Screening for prostate cancer. Cochrane database Syst Rev. 2013; 1: CD004720.

4. Bianco FJ, Scardino P, Eastham J. Radical prostatectomy: long-term cancer control and recovery of sexual and urinary function ('trifecta'). Urology. 2005; 66: 83-94.

5. Heidenreich A, Varga Z, Von Knobloch R. Extended pelvic lymphadenectomy in patients undergoing radical prostatectomy: high incidence of lymph node metastasis. J Urol. 2002; 167: 1681-1686.

6. Mattei A, Fuechsel F, Bhatta Dhar N, et al. The template of the primary lymphatic landing sites of the prostate should be revisited: results of a multimodalitymapping study. Eur Urol. 2008; 53: 118-125.

7. Heck M, Retz M, Bandur M, et al. Topography of Lymph Node Metastases in Prostate Cancer Patients Undergoing Radical Prostatectomy and Extended Lymphadenectomy: Results of a Combined Molecular and Histopathologic Mapping Study. Eur Urol. 2014; 66: 222-229.

8. Schiavina R, Bertaccini A, Franceschelli A, et al. The Impact of the Extent of Lymph-node Dissection on Biochemical Relapse after Radical Prostatectomy in Node-negative Patients. Anticancer Res. 2010; 30: 2297-2302.

9. Abdollah F, Gandaglia G, Suardi N, et al. More extensive pelvic lymph node dissection improves survival in patients with node positive prostate cancer. Eur Urol. 2015; 67: 212-219.

10. Wagner M, Sokoloff M, Daneshmand S. The Role of Pelvic Lymphadenectomy for Prostate Cancer Therapeutic? J Urol. 2008; 179: 408-413.

11. Briganti A, Giannarini G, Karnes R, Gandaglia G, Ficarra V, Montorsi F. What Evidence Do We Need to Support the Use of Extended Pelvic Lymph Node Dissection in Prostate Cancer? Eur Urol. 2015; 67: 597-598.

12. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials. 2007; 8: 16.

13. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986; 7: 177-188.

14. Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. The Cochrane Collaboration; 2011.

15. Ji J, Yuan H, Wang L, Hou J. Is the impact of the extent of lymphadenectomy in radical prostatectomy related to the disease risk ? A single center prospective study. J Surg Res. 2012; 178: 779-784.

16. Kim K, Lim S, Kim H, et al. Extended vs standard lymph node dissection in robot-assisted radical prostatectomy for intermediate- or high-risk prostate cancer: a propensity- score-matching analysis. BJU Int. 2013; 112: 216-223.

17. Yuh B, Ruel N, Mejia R, Novara G, Wilson T. Standardized comparison of robot-assisted limited and extended pelvic lymphadenectomy for prostate cancer. BJU Int. 2013; 112: 81-88.

18. Lestingi J, Pontes J, Borges L, et al. Extended vs limited pelvic lymphadenectomy during radical prostatectomy for intermediate and high-risk prostate cancer: A prospective randomized trial. Eur Urol suppl. 2015; 14: e904.

19. Bivalacqua TJT, Pierorazio PPM, Gorin MAM, Allaf MME, Carter HB, Walsh PCP. Anatomical Extent of Pelvic Lymph Node Dissection: Impact on Long-Term Cancer-Specific Outcomes in Men with Positive Lymph Nodes at Time of Radical Prostatectomy. Urology. 2013; 82: 653-659.

20. Liss M, Palazzi K, Stroup S, Jabaji R, Raheem O, Kane C. Outcomes and complications of pelvic lymph node dissection during robotic-assisted radical prostatectomy. World J Urol. 2013; 31: 481-488.

21. Matsumoto R, Sakashita S. Prospective study of extended versus limited lymphadenectomy in patients undergoing radical prostatectomy with localized prostate cancer. Hinyokika Kiyo. 2011; 57: 359-362.

22. Joslyn S, Konety B. Impact of extent of lymphadenectomy on survival after radical prostatectomy for prostate cancer. Urology. 2006; 68: 121-125.

23. Partin A, Kattan M, Subong E. Combination of prostate-specific antigen, clinical stage, and Gleason score to predict pathological stage of localized prostate cancer: a multi-institutional update. JAMA. 1997; 277: 1445-1451.

24. Joniau S, Van den Bergh L, Lerut E, et al. Mapping of Pelvic Lymph Node Metastases in Prostate Cancer. Eur Urol. 2013; 63: 450-458.

25. Gakis G, Boorjian S, Briganti A, et al. The Role of Radical Prostatectomy and Lymph Node Dissection in Lymph Node–Positive Prostate Cancer: A Systematic Review of the Literature. Eur Urol. 2014; 66: 191-199.

26. Bader P, Burkhard F, Markwalder R, U S. Is a limited lymph node dissection an adequate staging procedure for prostate cancer? J Urol. 2002; 168: 514-518.

27. Briganti A, Blute ML, Eastham JH, et al. Pelvic lymph node dissection in prostate cancer. Eur Urol. 2009; 55: 1251-1265.

28. Briganti A, Chun F, Salonia A, et al. Complications and Other Surgical Outcomes Associated with Extended Pelvic Lymphadenectomy in Men with Localized Prostate Cancer. Eur Urol. 2006; 50: 1006-1013.

29. Choo MS, Kim M, Ku JH, Kwak C, Kim HH, Jeong CW. Extended versus standard pelvic lymph node dissection in radical prostatectomy on oncological and functional outcomes: a systematic review and meta-analysis. Ann Surg Oncol. 2017; 24: 2047-2054.