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Patient-Reported Outcomes after Treatment for Clinically Localized Prostate Cancer: A Systematic Review and Meta-analysis.

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ABSTRACT

BACKGROUND

The aim of this systematic review is to assess the impact of primary treatments with curative intention in patients with localized prostate cancer, measured with Patient-Reported Outcomes (PROs), and to examine differences among modalities within treatments.

METHODS

We conducted a systematic literature search for January 2005-March 2017 following PRISMA guidelines, including longitudinal studies measuring disease-specific PROs in localized prostate cancer patients with a follow-up from pre- to post-treatment (≥ 1 year). Two reviewers independently extracted data and assessed risk of bias. The study is registered in PROSPERO: CRD42015019747.

RESULTS

Of 148 identified studies, 60 were included in the meta-analyses. At the 1st year, radical prostatectomy patients showed small urinary irritative-obstructive improvement (0.37SD 95%CI 0.30, 0.45), but large deterioration for sexual function and incontinence with high heterogeneity ($I^2=77\%$ and 93%). Moderate worsening in external radiotherapy patients for sexual function (-0.46SD 95%CI -0.55, -0.36), small urinary incontinence (-0.16SD 95%CI -0.23, -0.09) and bowel impairment (-0.31SD 95%CI -0.39, -0.23). Brachytherapy patients presented small deterioration in urinary incontinence (-0.29SD 95%CI -0.39, -0.19), irritative obstructive symptoms (-0.35SD 95%CI -0.47, -0.23), sexual function (-0.12SD 95%CI -0.24, -0.002), and bowel bother (-0.27SD 95%CI -0.42, -0.11). These patterns persisted up to the 5th year. High-intensity focused ultrasound and active surveillance only have results at 1st year, showing no statistically significant worsening.

CONCLUSIONS

No remarkable differences in PRO appeared between modalities within each treatment. Nowadays, available evidence supports brachytherapy as possible alternative to radical prostatectomy for patients seeking an attempted curative treatment limiting the risk for urinary incontinence and sexual dysfunction.

INTRODUCTION

Prostate cancer is currently the most common male tumor in the United States and second in the European Union (1;2). Usually diagnosed at localized stages, with low mortality rates (3), there are many treatments available with good cancer control, from radical prostatectomy to active surveillance, including various techniques of radiotherapy. Unfortunately, due to the location of the prostate, men receiving treatment may suffer side-effects which can have a long-term impact.

From the early 2000's, a growing interest in the use of Patient-Reported Outcomes (PROs) for treatment decision-making has led to the development of instruments designed specifically for localized prostate cancer patients (4) (5) (6). In parallel with this emergence of validated tools (7), the first years of the twenty-first century have been critical in terms of treatment development. This has led to the production of a great number of primary studies, culminating in the publication of the ProtecT randomized clinical trial (3;8). Therefore, the first systematic reviews have just appeared trying to synthesize the generated knowledge (9-11).

The American Agency for Healthcare Research and Quality updated in 2014 (9) a systematic review centered on patients with localized prostate cancer, including 21 studies with PRO data. In 2016 another systematic review on major treatments (10) in these patients identified 64 studies (80 treatment cohorts) measuring PROs. Also, a narrative synthesis on the PROs reported by 18 studies has been published in 2017 (11). However, none of these three systematic reviews (9-11), published in 2014-2017, included a quantitative synthesis by meta-analysis. For this reason, our main objective was to assess the impact of primary treatments in patients with localized prostate cancer, measured with PROs, by synthesizing results from longitudinal studies through a systematic review and meta-analysis. A secondary aim was to examine differences in PROs among modalities within each treatment.

METHODS

Protocol and Registration

The protocol for this review was registered in PROSPERO with the number CRD42015019747 (<http://www.crd.york.ac.uk/Prospero>). For the reporting of this systematic review and meta-analysis we followed Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) (12) and Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (13).

Information Sources and Search

Search for eligible articles was undertaken in MEDLINE database from January 2005 to March 2017. The detailed search strategy can be found in the Appendix Table A. We used both subject headings and text-word terms for 'Prostate Cancer' and 'Quality of Life'. The reference lists of previous systematic reviews were also checked, and authors were contacted by email to obtain additional information when data were missing or unclear.

Eligibility Criteria

We looked for longitudinal studies in all languages measuring PROs in localized prostate cancer. Study inclusion criteria were: participants with localized prostate cancer; primary treatments with curative intention (radical prostatectomy, external radiotherapy, interstitial brachytherapy, cryotherapy, high-intensity focused ultrasound (HIFU), and active surveillance); either prospective observational or clinical trial design; follow-up of patients from pre-treatment to 1 year post-treatment or longer; and measuring PROs with a disease-specific instrument. Studies with cross-sectional design, without PRO assessment before treatment, evaluating secondary treatments, and/or those including >25% of participants with high risk or advanced prostate cancer were excluded. High risk was defined as T3, prostate specific antigen (PSA) >20 ng/mL or Gleason >7.

Study Selection

Two members of the study team (LP and SL) independently reviewed articles found in the literature search by examining them in three consecutive phases: titles, abstracts, and full-text revision. A pilot test was performed to homogenize criteria between reviewers. Discrepancies were resolved with the assistance of an independent third party (OG).

Data Collection Process

Data were extracted using a standardized, predefined collection form. Completion of the data extraction was carried out by one author (LP or MA) with independent verification performed by other authors (AP or LC).

Data Items

The information extracted was study design, primary treatments, number of patients in each treatment cohort, patient characteristics, adjuvant hormonotherapy, PRO instrument used, and the following PRO data: mean, standard deviation (SD), and number of patients at baseline and at each point of follow-up, as well as mean of change.

Assessment of Quality in Individual Studies

The methodological quality of the studies was assessed employing a checklist developed by members of the Cochrane Non-Randomized Studies Methods group (14). The following two categories of potential biases of this checklist were used: reasons for allocation in groups (4 items), and parts of the study that were prospective (4 items). Patient withdrawal was added as a third category of potential bias due to its relevance for the methodological quality of longitudinal studies, considering the number of estimators with poor participation defined as <75% at year 1, <65% at years 2 and 3, or <60% at years 4 and 5 of follow-up. Each of these three components was classified as low risk of bias (allocation by randomization, all parts prospective, and none with poor participation), moderate, or high (no allocation information, two or more parts retrospective, and at least half the estimators with poor participation). A global rating was also obtained according to the number of components rated as high risk of bias (none, one, or more than one).

Summary Measures

The primary outcome to assess the impact of each treatment was defined as the standardized difference of PRO score means between baseline and follow-up points. As proposed by Cohen's effect size (15), the difference of means was standardized dividing it by the pooled standard deviation (SD). The latter was calculated considering SD at pre-treatment and at each follow-up. Effect size magnitude was small for 0.2 SD, moderate for 0.5 SD, and large for >0.8 SD.

Mean of change was considered the best estimator of this difference of means, and was extracted when available. Otherwise, we calculated the difference through a basic subtraction of the mean at baseline from the mean at follow-up evaluations.

Synthesis of Results

Meta-analyses were always carried out stratifying by curative treatment. We employed a random effect model (DerSimonian-Laird method), as we expected variation in effects due to differences in study populations, questionnaires, and methods. Estimators from follow-ups with poor participation rate were not included in meta-analyses. Chi square test by cohort subgroups was performed according to the treatment modalities or techniques, since it could be a relevant source of heterogeneity (for example open, laparoscopic and robot-assisted modalities for radical prostatectomy).

The results of studies with the Patient-Oriented Prostate Utility Scale (PORPUS), European Organization for Research and Treatment of Cancer Quality of Life, Prostate Specific Tool (EORTC-QLQ-PR25), and Functional Assessment of Cancer Therapy-Prostate (FACT-P) were not considered suitable to merge because they differed in measured domains (7). Conversely, results obtained with Expanded Prostate Cancer Index (EPIC), University of California, Los Angeles Prostate Cancer Index (UCLA-PCI), Prostate Cancer Quality of Life Scale (PCQoL) and Prostate Cancer Symptoms Indices (PCSI) measured very similar PRO domains (7). Almost all these instruments measured function and bother in urinary, sexual and bowel domains but varied in the number of items covering them. EPIC and PCSI also measured urinary incontinence and urinary irritative-obstructive symptoms. Therefore, the results of studies with EPIC, UCLA-PCI, PCQoL, and PCSI, which had been considered suitable to merge a priori, were included together in the meta-analyses.

Heterogeneity among studies was evaluated using I^2 statistic and categorized as follows: 25%-50% low; 50%-75% moderate; and >75% high (16). Forest plots were constructed showing the summary and 95% Confidence Interval (CI) estimated in the meta-analyses, together with results from individual studies. The forest plot was examined if $I^2 > 75\%$, to identify which trials were the possible sources of heterogeneity. The meta-analytic software program used was STATA12.

Additional Analyses

First, a sensitivity analysis was carried out by including only randomized clinical trials, since results from observational studies could be confounded by treatment selection bias. Second, meta-analyses of sexual scores in radical prostatectomy were constructed only with cohorts reporting nerve-sparing techniques in $\geq 80\%$ of the patients in order to explore the effect of this surgical approach. Finally, another sensitivity analysis was performed including only studies that used the same PRO instrument, to avoid the heterogeneity induced by the differences among the questionnaires used.

RESULTS

Study Selection

The literature search identified 5,001 articles (see Flow Diagram of Review Process in Figure 1). After screening titles and abstracts, 504 were reviewed in full text and 311 were excluded. Of the 193 articles that met the inclusion criteria, 92 were included in the meta-analyses, (8;17-107) and 101 articles (88 studies) were not. Of the latter, 63 studies because they did not provide the necessary data (mean, SD, and/or number of patients), 21 studies for providing isolated estimators which did not allow to construct a meta-analysis, and 4 studies due to lack of result stratification by treatment.

Study Characteristics

The 92 articles included describe the results from 60 studies, as 14 of these published more than one article - generally due to reporting different follow-ups. Table 1 summarizes the characteristics of the cohorts included and not included in the meta-analyses, grouped by treatments (detailed studies' characteristics in Appendix Tables B and C). Of 93 cohorts of patients treated with radical prostatectomy, 41 were included in meta-analyses and 52 were not (in both cases open surgery was the main technique evaluated); of 87 cohorts with external radiotherapy, half were included (11 stereotactic, 9 intensity modulated, 8 external beam, 7 conformational 3D, 6 proton therapy, and 3 mixing various radiotherapy techniques); 17 of the 44 cohorts with brachytherapy could be included, three of the eight that were treated with HIFU, and half of the 8 active surveillance cohorts. There were not sufficient estimators on cryotherapy to perform meta-analyses.

Number of participants in each treatment cohort included in meta-analysis varied from 16 to 1,806 (68;81), with similar variations among those cohorts not included. Age and PSA were also similar in both cases. The maximum follow-up for most of the cohorts in the meta-analysis is 12-24 months, while three studies followed patients for 5 years (44;51;85) and 2 studies during 6 years (8;22). It was similar in those cohorts not included in meta-analysis, except for the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) (108;109) and the Prostate Cancer Outcomes Study (PCOS) (110-112), which had followed patients for 10 and 15 years, respectively. Finally, regarding the PRO instrument applied, all estimators included in meta-analysis are measured with EPIC (67 cohorts) and UCLA-PCI (37 cohorts), except for 4 cohorts which used the PCSI (58;63), and 3 cohorts treated with HIFU which used FACT-P (62;75;78).

Risk of bias within studies

After methodological quality assessment, the global risk of bias was qualified as low in 34 studies, moderate in 16 and high in 10 (See Appendix Figure A). The potential bias category which was evaluated most positively was 'parts of the study that were prospective' (only high risk for 7 out of 60 studies), and 'reasons for allocation in groups' was the worst evaluated (18 out of 60 studies with high risk).

Synthesis of Results

Figures 2, 3, and 4 show results of the meta-analyses from the 1st to the 5th year (radical prostatectomy, external radiotherapy, and brachytherapy, respectively) for the following domains: A) urinary incontinence and irritative-obstructive; B) urinary function and bother; C) sexual function and bother; D) bowel function and bother. Figures of the meta-analyses constructed with summary scores, with a lower number of estimators than those of function and bother scores, are shown in Appendix Figure B. All these figures show the pooled estimators obtained by meta-analysis with the 95% confidence intervals (95%CI), the minimum and the maximum estimator for each follow-up evaluation, and heterogeneity data. Forest Plots used to construct these figures are also reported as Appendix Figure C.

Meta-analyses of cohorts treated with radical prostatectomy

Cohorts treated with three modalities of radical prostatectomy were included in meta-analyses (Figure 2): Robot-Assisted (RA), Laparoscopic Prostatectomy (LP), and Open Radical Prostatectomy (ORP). Figure 2A presents a large worsening for incontinence, without statistically significant differences among subgroups of surgery techniques at 1st year ($p=0.223$), but with high heterogeneity ($I^2>75\%$). In contrast, the urinary irritative-obstructive score showed a small increase (improvement). These results are similar throughout all evaluations, but only based on data from ORP cohorts with high heterogeneity. The meta-analysis of the urinary function (Figure 2B) showed moderate-large worsening without statistically significant differences among subgroups at 1st year ($p=0.216$), while urinary bother presented stability. Heterogeneity was also high in several meta-analyses.

Figure 2C shows large worsening for sexual function and moderate for bother. Both presented statistically significant differences among surgery technique subgroups at 1st year and high heterogeneity. Again, from this period on, most data was from ORP cohorts. Changes in bowel function and bother were negligible (Figure 2D).

Meta-analyses of cohorts treated with external radiotherapy

Cohorts treated with five modalities of external radiotherapy were included in meta-analyses (Figure 3): Proton Therapy (PT), Stereotactic (SB), Intensity Modulated (IM), External Beam (EB), and 3-Dimensional (3D) radiotherapy. Most of the meta-analyses of urinary incontinence (Figure 3A) showed a small worsening without statistically significant differences among modalities. Almost all urinary irritative-obstructive meta-analyses showed no change, though heterogeneity was high (I^2 for the global 76%-94%). Worsening of urinary function and bother were negligible in most meta-analyses (Figure 3B).

Figure 3C showed moderate worsening of sexual function at the first and second year except for stereotactic radiotherapy, with no change. High heterogeneity was found for sexual bother. Changes in bowel function and bother were small in most of the meta-analyses (Figure 3D). Moderate worsening on bowel bother was observed only for the modalities of external beam and 3D radiotherapy.

Meta-analyses of cohorts treated with brachytherapy

Cohorts treated with low- and high-dose-rate brachytherapy (LDR and HDR) were included in meta-analyses (Figure 4). A small worsening in all urinary scores (Figures 4A and 4B) was observed the 1st year, ranging between -0.16 and -0.35. After the 1st year, most pooled estimators presented high heterogeneity. Figure 4C shows a small worsening for sexual function and bother in most evaluations. A small worsening was also estimated for almost all bowel bother evaluations (Figure 4D), while changes in bowel function were mainly negligible. Differences between low- and high-dose-rate brachytherapy were not statistically significant, except for sexual function at the 3rd year.

Meta-analyses of cohorts treated with high-intensity focused ultrasound

Figure 5 shows the meta-analysis at one year after diagnosis of three cohorts treated with High-Intensity Focused Ultrasound (HIFU) with FACT-P score. No statistically significant change is appreciated (+0.08 95%CI -0.06, 0.23).

Meta-analyses of active surveillance cohorts

Figure 5 also shows the meta-analyses at one year after diagnosis for cohorts undergoing active surveillance. The meta-analyses presented no statistically significant change in urinary, sexual, and bowel scores (ranging -0.18 to +0.07).

Sensitivity analyses

First, the randomized clinical trials sensitivity analysis could be carried out only for external radiotherapy (Forest Plots are reported in Appendix Figure D). Pooled estimators obtained in the meta-analyses were very similar to those obtained when including both observational and randomized studies. For example, change at 1st year in bowel bother was -0.42 (95%CI -0.58, -0.26) among randomized clinical trials and -0.41 (95%CI -0.49, -0.32) in the meta-analysis including both study designs. Second, consistency was also observed in the nerve-sparing techniques sensitivity analysis (Forest Plots reported in Appendix Figure D). For example, change at 1st year in sexual function was -1.46 (95%CI -1.68, -1.24) among cohorts where $\geq 80\%$ of the patients underwent nerve-sparing techniques, and -1.32 (95%CI -1.48, -1.16) in the metanalysis with all cohorts of radical prostatectomy. Finally, meta-analyses constructed only with EPIC results did not greatly reduce the number of pooled estimators with high heterogeneity, compared with those constructed with EPIC and UCLA-PCI: 42.2% (27 out of 64) vs 55.4% (41 out of 74) of pooled estimators in radical prostatectomy meta-analyses; and 22.9% (19 out of 83) vs 22.7% (27 out of 119) in those evaluating external radiotherapy.

Studies not included in meta-analyses

Many of the 103 publications (90 studies) not included in meta-analyses addressed specific research questions, such as the impact of body mass index in treatment effectiveness (113), or the influence of pre-operative urinary bother on urinary symptoms after treatment (114). The two relevant projects with the longest follow-ups, PCOS and CaPSURE, are worth commenting. The PCOS (142) is a population-based cohort of men (diagnosed in 1994-1995), which administered items adapted from UCLA-PCI and EPIC instruments, but has not provided standard deviations in publications. The CaPSURE study, based on a prospective registry, has collected the UCLA-PCI (108) since its inception in 1995. Radical prostatectomy results at 2 years were included in our meta-analyses (35;41) but not for other treatments because the main CaPSURE publication (108) did not report their follow-up means.

DISCUSSION

This systematic review identified 148 studies which met the inclusion criteria. The 60 studies finally included in the meta-analyses allowed the construction of pooled estimators from the 1st to 5th year of follow-up for each treatment except for HIFU and active surveillance, limited to the 1st year. The number of patients included in meta-analyses at the 1st year, according to the treatment and outcome considered, was 2522-6314 in radical prostatectomy, 1602-3979 in external radiotherapy, 731-979 in brachytherapy, 387 in HIFU, and 316-752 in active surveillance. At the 5th year the number of patients diminished substantially, with 321-577 in prostatectomy, 407-415 external radiotherapy, and 392 brachytherapy.

Focusing on the clinical significance of results, and taking into account that 0.5 standard deviations (SD) is used to define the minimal important difference in PROs, changes of moderate and large magnitudes (around 0.5 and 0.8 SD) could be qualified as clinically relevant, meriting special attention. Meta-analyses of radical prostatectomy showed a large deterioration for sexual function and incontinence, but a small urinary irritative-obstructive improvement. Synthesis of external radiotherapy indicated moderate worsening of sexual function (except for stereotactic modality), and small worsening in urinary incontinence and bowel domains. For brachytherapy, a small deterioration in urinary incontinence, irritative-obstructive symptoms, sexual function, and bowel bother was observed in meta-analyses. Finally, HIFU and active surveillance did not show statistically significant worsening at the 1st year of follow-up.

There is considerable evidence on radical prostatectomy at short term, but scarce at medium-long term. The meta-analyses included 6-25 studies at the 1st year of follow-up, but only 2-3 studies at 4 and 5 years. Radical prostatectomy is the only treatment with side effects resulting in large magnitude impact on sexual dysfunction and urinary incontinence. The meta-analyses of sexual function presented a high heterogeneity and significant differences among technique subgroups. However, a large deterioration was observed in all the study estimators except one (107), as well as in the sensitivity analyses among cohorts where $\geq 80\%$ of the patients underwent nerve-sparing techniques. Urinary incontinence meta-analyses also presented high heterogeneity, with study estimators ranging from -0.41 to -1.33, indicating from small to large impact. No robotic cohort was included in this meta-analysis, but two included in the urinary function meta-analysis showed a large worsening (50;101), suggesting no lower urinary side effects for robotic techniques. On the other hand, it is important to mention the small improvement observed in urinary irritative-obstructive symptoms, which could be

a key factor to be considered in patients who presented obstructive symptoms at diagnosis prior to treatment, as previously highlighted (52). Findings of our systematic review are consistent with results from the PCOS (110-112) and CAPSURE (108;109), which showed that men who had undergone prostatectomy were more likely to have urinary incontinence and erectile dysfunction than those receiving external radiotherapy until 5 years of follow-up. Furthermore, their longer results showed that differences between treatments attenuated at 10 (110) and 15 years (108).

Similarly, we found considerable evidence at short term, but scarce at medium-long term, on external radiotherapy. Meta-analyses included 14-24 studies at the 1st year of follow-up, but only 1-3 studies provided data at 4th and 5th year. Pooled estimators showed moderate worsening in sexual function at the two first years without high heterogeneity. Significant differences among modalities suggest that stereotactic is the only radiotherapy producing no deterioration of sexual function, but evidence came from three studies at the 1st year (28;44;48) and only one at the 2nd year of follow-up (44). Available evidence from several studies from the 1st to 4th year after treatment described quite homogeneously that external radiotherapy produced small urinary incontinence. In general, the heterogeneity among external radiotherapy studies included in the meta-analyses of bowel domains was slightly higher for function than for bother. Evidence quite consistently shows bowel worsening of small magnitude for all modalities except external beam radiotherapy at the 1st year after treatment, for which the magnitude was moderate. It is worth highlighting that results from intensity modulated radiotherapy studies were very similar to those evaluating 3D radiotherapy, both producing moderate sexual dysfunction, and small urinary and bowel impact until the 2nd year of follow-up. There is only one study of intensity modulated radiotherapy at longer term, but it was not included in the meta-analyses since an ad-hoc PRO instrument was applied (115).

We found fewer studies on brachytherapy, 11 exclusively evaluating low-dose-rate brachytherapy (32;51;61;74;76;77;79;82;83;87;94), 3 assessing high-dose-rate (25;32;88), and 1 study evaluating both techniques (81). The meta-analyses included 6-9 studies at the 1st year of follow-up, and 1-2 studies at 4th and 5th year. In general, most urinary estimators (incontinence, irritative-obstructive, function and bother), both pooled and from individual studies, indicated small impact. However, the variability observed is noteworthy, with a few studies reporting no deterioration (61;87;94) or moderate worsening (51;74;83;107), and only one reporting large impact (76). Results showing very small worsening on sexual function and bowel bother were

notably consistent,. It is important to embark on further research to identify the sources of the heterogeneity in urinary side effects to provide reliable information to patients about this treatment option, which - on the other hand - only presents a small impact in sexual and bowel domains.

High-Intensity Focused Ultrasound is a very recent treatment, and we identified only six studies on HIFU cohorts with follow-ups of 1-3 years assessing PROs by using FACT-P (62;75;78;164) and/or EPIC urinary domains(62;75;116;163). Meta-analyses of FACT-P included 3 studies at the 1st year of follow-up, with notably consistent results that indicate stability. All studies assessing urinary change administered the EPIC domain of incontinence, except for Muto S et al. (116) that reported urinary bother and function. They also showed stability, although the estimators provided in these studies (median and interquartile range) did not allow the construction of any urinary meta-analysis. Further studies on this new treatment option should include longer follow-ups, as well as measuring all the prostate cancer-relevant domains by administering the complete EPIC, instead of just the incontinence domain.

An advantage of this systematic review is that most of the identified studies applied EPIC or UCLA-PCI to measure PRO, which allowed to obtain pooled estimates. On the other hand, the publication of varied EPIC scores (sometimes summaries, other times function and bother subscales) entails the disadvantage of having a high amount of information that cannot be synthesized or directly compared. In this sense, the adherence to consensus initiatives such as the International Consortium for Health Outcomes Measurement (ICHOM) (117) may minimize this problem in the future. The situation is even worse in the case of less widely used instruments, such as PORPUS, used only in one study evaluating radical prostatectomy (118). The EORTC-QLQ PR25 has been applied more often, and we identified nine studies which administered it to evaluate several treatments: brachytherapy (119-123), radical prostatectomy (124;125), stereotactic (126;127), intensity modulated (126;127), and 3D radiotherapy (128), active surveillance (119), and robot-assisted radical prostatectomy (119). Despite covering urinary, sexual and bowel domains, EORTC-QLQ PR25 is more centered on symptoms without measuring function and bother, unlike EPIC and UCLA-PCI. No meta-analysis could be constructed with the three studies evaluating brachytherapy because one of them evaluated patients only at 4 years after treatment (119), another only at 6 years (121;122), and the last one was excluded due to a 69% loss to follow-up rate (120). Taking into account that EORTC QLQ-PR25 was the newest specific instrument for localized prostate cancer (129), the more studies

published in coming years, the more feasible it may be to make a quantitative synthesis of their results.

Heterogeneity was high ($I^2 > 75\%$) in meta-analyses constructed with six outcomes from radical prostatectomy cohorts (urinary incontinence, function and bother, sexual function and bother, and bowel function), in five from the external radiotherapy cohorts (urinary irritative-obstructive and bother, sexual function and bother, and bowel function), and four from brachytherapy cohorts (urinary incontinence, irritative obstructive and bother, and sexual bother). This pattern suggests that treatment modalities are a source of heterogeneity. This is reasonable in external radiotherapy, where high heterogeneity concurred with statistical significant differences among modalities, which indicated better sexual outcomes for stereotactic and worse bowel ones for external beam radiotherapy. Nevertheless, some radical prostatectomy meta-analyses with high heterogeneity did not present any significant differences among surgical techniques. Despite this high heterogeneity in radical prostatectomy outcomes, it is necessary to highlight that estimators from all individual studies consistently support a side effect pattern of large incontinence, sexual dysfunction and bother. Finally, although adjuvant hormone therapy could have a role explaining the heterogeneity of sexual function, the low percentage of pooled estimators with high heterogeneity in meta-analyses of brachytherapy and external radiotherapy (35%) does not support this. Examination of forest plots also is opposite to this hypothesis; for example, studies providing the minimum and the maximum estimator of sexual dysfunction in the meta-analysis at 1st year of external radiotherapy reported very similar percentages of patients with hormone therapy: 44% (72) and 47% (28).

We identified several limitations in our review process. Firstly, 90 studies could not be included in the meta-analyses. However, most of their results were consistent with summary estimators obtained through our meta-analyses, and some of them have been commented above. Secondly, we might have failed to identify all eligible articles due to searching only in MEDLINE. We believe that this was minimized by the sensitive search strategy used (5,001 articles). On the other hand, MEDLINE is the most suitable database for our systematic review: a pilot test carried out in EMBASE for the year 2005 brought up an additional 22% of articles, but none of them met the inclusion criteria. Thirdly, the relatively few studies with follow-up beyond 2 years limited the mid- and long-term evidence available. Therefore, further PRO studies are needed with longer follow-up periods to test whether the pattern of differences among treatments persists or attenuates at long term. Fourthly, we merged results measured with

different questionnaires. This was only done for those covering similar domains, as described previously by a systematic review of prostate cancer-specific PRO instruments (7), and sensitivity analysis confirms that merging instruments does not increase heterogeneity. Fifthly, internal validity of the summary provided by a meta-analysis depends on the quality of primary studies. In our systematic review, the global risk of bias was qualified as low in 56.7% of studies, and high only in 16.7%. Furthermore, estimators with poor participation rate were not considered. Finally, secondary treatments or interventions, such as salvage radiotherapy after prostatectomy or hormonotherapy, were not considered.

In conclusion, this systematic review characterizes the PRO impact of most accepted primary treatments with curative intention for patients with localized prostate cancer. Radical prostatectomy produces large sexual and incontinence deterioration, and small improvement on urinary irritative obstructive symptoms; external radiotherapy techniques cause moderate sexual dysfunction, and small incontinence, bowel function and bother; brachytherapy produces incontinence, irritative obstructive symptoms, sexual dysfunction and bowel bother of small magnitude, and the few studies on HIFU and active surveillance show no statistically significant worsening. Our review suggests that there are no major PRO differences between modalities within each treatment, but data are still very scarce - especially beyond two years of follow-up. Nowadays, available evidence supports brachytherapy as a possible alternative to radical prostatectomy for patients with localized prostate cancer seeking an attempted curative treatment while limiting the risk for urinary incontinence and sexual dysfunction. Further PRO studies with longer follow-ups are needed, especially for HIFU and active surveillance. Our systematic review provides valuable PRO information to take into account, together with oncological outcomes, for shared clinical decision making between patients and professionals.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DISCLOSURE

All authors have approved the final article.

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FIGURE CAPTIONS

Figure 1. Flowchart of systematic literature review.

Figure 2. Summary of pooled estimators (95% CI) obtained with meta-analyses from cohorts on patients who underwent treatment with radical prostatectomy. Red diamonds represent maximum and minimum estimators from individual studies in each modality.

Footnote: **SN** Studies Number; **PN** Patients Number; **I²** and **p-value** testing heterogeneity; **χ^2** and **p-value** test by studies' subgroups; **RA** Robot-Assisted Laparoscopic Prostatectomy; **LP** Laparoscopic Prostatectomy; **ORP** Open Radical Prostatectomy; **VT** Various Techniques of Radical Prostatectomy; **All** Global Estimator.

Figure 3. Summary of pooled estimators (95% CI) obtained with meta-analyses from cohorts on patients who underwent treatment with radiotherapy. Red diamonds represent maximum and minimum estimators from individual studies in each modality.

Footnote: **SN** Studies Number; **PN** Patients Number; **I²** and **p-value** testing heterogeneity; **χ^2** and **p-value** test by studies' subgroups; **PT** Proton Therapy; **ST** Stereotactic Body Radiotherapy; **IM** Intensity Modulated Radiotherapy; **EB** External Beam Radiotherapy; **3D** 3-Dimensional Conformational Radiotherapy; **VT** Various Techniques of Radiotherapy; **All** Global Estimator.

Figure 4. Summary of pooled estimators (95% CI) obtained with meta-analyses from cohorts on patients who underwent treatment with Brachytherapy. Red diamonds represent maximum and minimum estimators from individual studies in each modality.

Footnote: **SN** Studies Number; **PN** Patients Number; **I²** and **p-value** testing heterogeneity; **χ^2** and **p-value** test by studies' subgroups; **LDR** Low-Dose-Rate Brachytherapy; **HDR** High-Dose-Rate Brachytherapy; **All** Global Estimator.

Figure 5. Forest plots of change after 1 year from cohorts of patients who underwent treatment with High-Intensity Focused Ultrasound (HIFU) and cohorts of Active Surveillance, measured in effect size.

Table 1. Characteristics of the cohorts included and not included in the systematic review, grouped by treatments.

Footnote: **PLS** Prospective Longitudinal Study; **RCT** Randomized Clinical Trial; **UCLA-PCI** University California; Los Angeles-Prostate Cancer Index; **EPIC** Expanded Prostate Cancer Index; **QLQ-PR25** European Organisation for Research and Treatment of Cancer – Quality of Life Prostate Specific Tool; **PORPUS** Patient-Orientated Prostate Cancer Utility Score; **PCSI** Prostate Cancer Symptoms Indices; **FACT** Functional Assessment of Cancer Therapy; **PCQoL** Prostate Cancer Quality of Life Scale.

Figure 1. Flowchart of systematic literature review.

Figure 2. Summary of pooled estimators (95% CI) obtained with meta-analyses from cohorts on patients who underwent treatment with radical prostatectomy (continues in next pages). Red diamonds represent maximum and minimum estimators from individual studies in each modality.

2.A URINARY INCONTINENCE

2.A URINARY IRRITATIVE-OBSTRUCTIVE

SN Studies Number; PN Patients Number; I² and p-value testing heterogeneity; X² and p-value test by studies' subgroups; RA Robot Assisted Laparoscopic Prostatectomy; LP Laparoscopic Prostatectomy; ORP Open Radical Prostatectomy; VT Various Techniques of Radical Prostatectomy; All Global estimator

Figure 2. Summary of pooled estimators (95% CI) obtained with meta-analyses from cohorts on patients who underwent treatment with radical prostatectomy (continuation). Red diamonds represent maximum and minimum estimators from individual studies in each modality.

2.B URINARY FUNCTION

2.B URINARY BOTHER

SN Studies Number; PN Patients Number; I² and p-value testing heterogeneity; χ² and p-value test by studies' subgroups; RA Robot Assisted Laparoscopic Prostatectomy; LP Laparoscopic Prostatectomy; ORP Open Radical Prostatectomy; VT Various Techniques of Radical Prostatectomy; All Global estimator

Figure 2. Summary of pooled estimators (95% CI) obtained with meta-analyses from cohorts on patients who underwent treatment with radical prostatectomy (continuation). Red diamonds represent maximum and minimum estimators from individual studies in each modality.

2.C SEXUAL FUNCTION

2.C SEXUAL BOTHER

SN Studies Number; PN Patients Number; I² and p-value testing heterogeneity; χ² and p-value test by studies' subgroups; RA Robot Assisted Laparoscopic Prostatectomy; LP Laparoscopic Prostatectomy; ORP Open Radical Prostatectomy; VT Various Techniques of Radical Prostatectomy; All Global estimator

Figure 2. Summary of pooled estimators (95% CI) obtained with meta-analyses from cohorts on patients who underwent treatment with radical prostatectomy (continuation). Red diamonds represent maximum and minimum estimators from individual studies in each modality.

2.D BOWEL FUNCTION

2.D BOWEL BOTHER

SN Studies Number; PN Patients Number; I² and p-value testing heterogeneity; χ² and p-value test by studies' subgroups; RA Robot Assisted Laparoscopic Prostatectomy; LP Laparoscopic Prostatectomy; ORP Open Radical Prostatectomy; VT Various Techniques of Radical Prostatectomy; All Global estimator

Figure 3. Summary of pooled estimators (95% CI) obtained with meta-analyses from cohorts on patients who underwent treatment with radiotherapy (continues in next pages). Red diamonds represent maximum and minimum estimators from individual studies in each modality.

3.A URINARY INCONTINENCE

3.A URINARY IRRITATIVE-OBSTRUCTIVE

SN Studies Number; PN Patients Number; I² and p-value testing heterogeneity; χ² and p-value test by studies' subgroups; PT Proton Therapy; ST Stereotactic Body Radiotherapy; IM Intensity Modulated Radiotherapy; EB External Beam Radiotherapy; 3D 3-Dimensional Conformational Radiotherapy; VT Various Techniques of Radiotherapy; All Global estimator

Figure 3. Summary of pooled estimators (95% CI) obtained with meta-analyses from cohorts on patients who underwent treatment with radiotherapy (continuation). Red diamonds represent maximum and minimum estimators from individual studies in each modality.

3.B URINARY FUNCTION

3.BURINARY BOTHER

SN Studies Number; PN Patients Number; I² and p-value testing heterogeneity; χ² and p-value test by studies' subgroups; PT Proton Therapy; ST Stereotactic Body Radiotherapy; IM Intensity Modulated Radiotherapy; EB External Beam Radiotherapy; 3D 3-Dimensional Conformational Radiotherapy; VT Various Techniques of Radiotherapy; All Global estimator

Figure 3. Summary of pooled estimators (95% CI) obtained with meta-analyses from cohorts on patients who underwent treatment with radiotherapy (continuation). Red diamonds represent maximum and minimum estimators from individual studies in each modality.

3.C SEXUAL FUNCTION

3.C SEXUAL BOTHER

SN Studies Number; PN Patients Number; I² and p-value testing heterogeneity; χ² and p-value test by studies' subgroups;
 PT Proton Therapy; ST Stereotactic Body Radiotherapy; IM Intensity Modulated Radiotherapy; EB External Beam Radiotherapy;
 3D 3-Dimensional Conformational Radiotherapy; VT Various Techniques of Radiotherapy; All Global estimator

Figure 3. Summary of pooled estimators (95% CI) obtained with meta-analyses from cohorts on patients who underwent treatment with radiotherapy (continuation). Red diamonds represent maximum and minimum estimators from individual studies in each modality.

3.D BOWEL FUNCTION

3.D BOWEL BOTHER

SN Studies Number; PN Patients Number; I² and p-value testing heterogeneity; χ² and p-value test by studies' subgroups; PT Proton Therapy; ST Stereotactic Body Radiotherapy; IM Intensity Modulated Radiotherapy; EB External Beam Radiotherapy; 3D 3-Dimensional Conformational Radiotherapy; VT Various Techniques of Radiotherapy; All Global estimator

Figure 4. Summary of pooled estimators (95%CI) obtained with meta-analyses from cohorts on patients who underwent treatment with Brachytherapy (continues in next page). Red diamonds represent maximum and minimum estimators from individual studies.

4.A URINARY INCONTINENCE

4.A URINARY IRRITATIVE-OBSTRUCTIVE

SN Studies Number; PN Patients Number; I² and p-value testing heterogeneity; X² and p-value test by studies' subgroups; LDR Low-Dose-Rate Brachytherapy; HDR High-Dose-Rate Brachytherapy; All Global estimator.

Figure 4. Summary of pooled estimators (95%CI) obtained with meta-analyses from cohorts on patients who underwent treatment with Brachytherapy (continuation). Red diamonds represent maximum and minimum estimators from individual studies.

4.B URINARY FUNCTION

4.B URINARY BOTHER

SN Studies Number; PN Patients Number; I² and p-value testing heterogeneity; X² and p-value test by studies' subgroups; LDR Low-Dose-Rate Brachytherapy; HDR High-Dose-Rate Brachytherapy; All Global estimator.

Figure 4. Summary of pooled estimators (95%CI) obtained with meta-analyses from cohorts on patients who underwent treatment with Brachytherapy (continuation). Red diamonds represent maximum and minimum estimators from individual studies.

4.C SEXUAL FUNCTION

4.C SEXUAL BOTHER

SN Studies Number; PN Patients Number; I² and p-value testing heterogeneity; X² and p-value test by studies' subgroups; LDR Low-Dose-Rate Brachytherapy; HDR High-Dose-Rate Brachytherapy; All Global estimator.

Figure 5. Forest plots of change after 1 year from cohorts of patients who underwent treatment with High-Intensity Focused Ultrasound (HIFU) and cohorts of Active Surveillance, measured in effect size.

HIGH-INTENSITY FOCUSED ULTRASOUND (HIFU): Change in FACT-P score

ACTIVE SURVEILLANCE

URINARY INCONTINENCE

URINARY IRRITATIVE-OBSTRUCTIVE

SEXUAL FUNCTION

BOWEL FUNCTION

BOWEL BOTHER

Table 1. Characteristics of the cohorts included and not included in the systematic review grouped by treatments.

TREATMENT	Study Design/ Number of cohorts		Number of patients Median (range)		Age Median (range)		PSA (ng/mL) Median (range)		Follow-up (months) Median (range)		Specific PRO instrument/ Number of cohorts	
	Included	Not I	Included	Not I	Included	Not I	Included	Not I	Included	Not I	Included	Not I
PROSTATECTOMY	41	52										
Robot Assisted Laparoscopic	PLS=7	PLS=15	90 (45-361)	129 (21-945)	61 (58-65)	61 (47-66)	7.2 (5-9)	6.4 (5-10.5)	15 (12-36)	18 (12-48)	EPIC=3 UCLA-PCI=4	UCLA-PCI=6 EPIC=5 QLQ-PR25=3 PCQoL=1
Laparoscopic Prostatectomy	PLS=3	PLS=3	161 (105-210)	122 (93-229)	62 (58-66)	61 (58-68)	7.6 (5.7-8.6)	6 (5.7-7.7)	12 (12-36)	12 (12-12)	EPIC=2 UCLA-PCI=2	EPIC=2 UCLA-PCI=1
Open Radical Prostatectomy	PLS=26 RCT=2	PLS=32	122 (24-1806)	166 (22-3706)	64 (58-70)	63 (53-71)	8 (4.2-16.9)	7.3 (4.8-12.4)	24 (12-72)	24 (12-72)	UCLA-PCI=14 EPIC=12 PCQoL=1	UCLA-PCI=12 EPIC=10 QLQ-PR25=4 PCSI=1 PORPUS=1
Various surgery techniques	PLS=3	PLS=2	627 (170-1670)	315 (140-290)	63 (60-64)	61 (59-63)	5.9 (3.1-8.6)	6.1 (5.6-6.7)	36 (12-36)	36 (12-60)	EPIC=3	EPIC=2
RADIOTHERAPY	44	43										
Proton Therapy	PLS=4 RCT=2	PLS=3	91 (33-262)	226 (65-1243)	65 (56-68)	66 (63-66)	5.2 (5.2-5.2)	4.7 (4.5-4.8)	24 (24-72)	24 (24-24)	EPIC=5 PCSI=2	EPIC=3
Stereotactic Body Radiation Therapy	PLS=7 RCT=4	PLS=8 RCT=3	102 (30-864)	75 (28-912)	69 (66-70)	69 (66-71)	5.7 (3.4-7.0)	6.9 (5.8-8.2)	36 (12-60)	24 (12-72)	EPIC=11	EPIC=8 QLQ-PR25=3 UCLA-PCI=1
Intensity Modulated Radiation Therapy	PLS=4 RCT=5	PLS=4 RCT=2	153 (16-692)	87 (20-204)	69 (64-71)	69 (65-73)	7.7 (5.3-11.9)	9 (9-9)	24 (12-36)	24 (14-60)	EPIC=9 PCSI=1	EPIC=2 QLQ-PR25=2
External Beam Radiation Therapy	PLS=8	PLS=13 RCT=1	126 (26-598)	122 (27-491)	65 (62-68)	68 (60-72)	11.9 (8.2-14.6)	14.2 (9-24)	36 (12-52)	36 (12-180)	EPIC=3 UCLA-PCI=8 PORPUS=1 PCSI=1	UCLA-PCI=4 EPIC=2 PCSI=3 FACT-P=1
3D-Conformational Radiation Therapy	PLS=6 RCT=1	PLS=3	60 (54-153)	153 (149-153)	70 (67-71)	67 (67-68)	7.3 (7-7.5)	11.8 (11.8-11.8)	24 (16-72)	60 (12-60)	EPIC=6	QLQ-PR25=3
Various Radiation Therapy	PLS=3	PLS=1	118 (78-292)	60	71 (67-75)	65	13.6 (9.1-29.4)	4.5	24 (24-36)	36	EPIC=1 UCLA-PCI=2	EPIC=1
EBRT+BT		PLS=5		95 (75-1010)		67 (66-67)		8 (8-8)		12 (12-120)		EPIC=3 UCLA-PCI=2
BRACHYTHERAPY	17	27										
	PLS=15 RCT=2	PLS=27	85 (27-306)	92 (12-684)	67 (62-70)	66 (64-69)	6.8 (5-10.6)	7.2 (6-11.2)	24 (12-60)	36 (11-120)	EPIC=12 UCLA-PCI=6	QLQ-PR25=10 EPIC=6 UCLA-PCI=54 PCSI=3 FACT-P=2
HIFU	3	5										
	PLS=3	PLS=3 RCT=2	41 (20-326)	45 (29-118)	63 (60-68)	66 (20-326)	7.3 (6.6-12.7)	6.8 (5.4-7.6)	12 (12-24)	12 (12-36)	FACT-P=3 EPIC=2	UCLA-PCI=2 FACT-P=2 EPIC=1
ACTIVE SURVEILLANCE	4	8										
	PLS=2 RCT=2	PLS=8	77 (77-545)	187 (50-314)	65 (65-66)	67 (64-73)	5.1 (4.0-6.3)	5.2 (3.3-5.8)	36 (12-72)	30 (24-120)	EPIC=3 UCLA-PCI=1	EPIC=4 UCLA-PCI=2 QLQ-PR25=1 PCSI=1
CRYOTHERAPY		2										

PLS Prospective Longitudinal Study; RCT Randomized Clinical Trial; **UCLA-PCI** University California; Los Angeles-Prostate Cancer Index; **EPIC** Expanded Prostate Cancer Index; **QLQ-PR25** European Organisation for Research and Treatment of Cancer – Quality of Life Prostate Specific Tool; **PORPUS** Patient-Orientated Prostate Cancer Utility Score; **PCSI** Prostate Cancer Symptoms Indices; **FACT** Functional Assessment of Cancer Therapy; **PCQoL** Prostate Cancer Quality of Life Scale.

HIGHLIGHTS

Many PRO studies but data still very scarce beyond two years of follow-up

Surgery produces sexual and incontinence deterioration but improves urinary symptoms

External radiotherapy has moderate sexual yet small incontinence & bowel side effects

Brachytherapy causes small incontinence and urinary, sexual and bowel side effects

The few studies on high-intensity focused ultrasound and active surveillance show no statistically significant worsening