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Quality of Life Outcomes after Primary Treatment for Clinically Localised Prostate Cancer: a Systematic Review

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Abstract

Context: Current evidence-based management for clinically localised prostate cancer includes active surveillance, surgery, external beam radiotherapy (EBRT) and brachytherapy. The impact of these treatment modalities on quality of life (QoL) is uncertain.

Objective: To systematically review comparative studies investigating disease-specific QoL outcomes as assessed by validated cancer-specific Patient Reported Outcome Measures with at least 1 year of follow-up after primary treatment for clinically localised prostate cancer.

Evidence acquisition: Medline, Embase, AMED, PsycINFO and the Cochrane Library were searched to identify relevant studies. Studies were critically appraised for risk of bias. A narrative synthesis was undertaken.

Evidence synthesis: Of 11,486 articles identified, 18 studies were eligible for inclusion including 3 RCTs (follow-up range: 60-72 months) and 15 non-randomised comparative studies (follow-up range: 12-180 months) recruiting a total of 13,604 patients. Two RCTs recruited small cohorts and only one was judged as low risk of bias. The quality of evidence from observational studies was low to moderate. For a follow-up of up to six years, active surveillance was found to have the lowest impact on cancer-specific QoL, surgery had a negative impact on urinary and sexual function when compared to active surveillance and EBRT, while EBRT had a negative impact on bowel function when compared to active surveillance and surgery. Data from one small RCT reported that brachytherapy has a negative impact on urinary function 1 year post treatment, but no significant urinary toxicity were reported at 5 years.

Conclusions: This is the first systematic review comparing the impact on cancer- specific QoL of different primary treatments for men with clinically localised PCa, using validated cancer-specific PROMs only. There is robust evidence that choice of primary treatment for localised prostate cancer has distinct impacts on patients' QoL. This should be discussed in detail with patients during pre-treatment counselling.

Patient Summary: Our review of the current evidence suggests that for a period of up to six years after treatment, men with localised prostate cancer who were managed with active surveillance reported high levels of QoL. Men treated with surgery reported mainly urinary and sexual problems, while men treated with external beam radiotherapy reported mainly bowel problems. Men eligible for brachytherapy reported urinary problems up to a year after therapy, but then their QoL returned gradually to as it was before treatment.

1. Introduction

Since the introduction of PSA testing, there has been a substantial shift to a more favourable stage in newly-diagnosed prostate cancer (PCa), with approximately 81% of cases being diagnosed as clinically localised [1]. Currently, evidence-based management for clinically localised PCa includes active surveillance (AS), surgery, external beam radiotherapy (EBRT) and brachytherapy (BT) [2]. Knowledge of the adverse events of different management options is critical for making informed treatment decisions, considering that the survival benefit is uncertain, especially in men with favourable-risk PCa [3].

The adverse effects of primary treatments for localised disease can negatively impact on disease-specific quality of life (QoL) [4]. The concept of 'quality of life' is subjective, however, in cancer cohorts, specific tools or Patient Reported Outcome Measures (PROMs) have been developed and validated. These questionnaires assess common issues that affect men after PCa diagnosis and treatment and generate scores, which reflect the impact on perceptions of health-related quality of life (HRQoL). It is currently unclear which primary treatment for localised disease offers superior disease-specific QoL outcomes. The primary objective of this systematic review was to compare cancer-specific QoL data as measured by PROMs for intermediate (1-10 years) to long-term (>10 years) follow-up, among competitive treatments.

2. Evidence acquisition

2.1 Search strategy

The review was performed according to Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines [5] and Cochrane review principles [6]. An experienced research librarian performed the search strategy in consultation with a multi-disciplinary panel of expert clinicians and patient representative (EAU Prostate cancer guideline panel). The database searched were EMBASE, MEDLINE, AMED, PsycINFO, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials. Searches were limited to studies published from the year 2000 onwards. No language restrictions were imposed. Full details of the search strategies used are described in Appendix 1.

All abstracts and full text articles were screened by two independent reviewers (MIL, MAL). Disagreement was resolved by discussion; if no agreement was reached, a third independent party acted as an arbiter (LB).

2.2 Types of study design included

Prospective randomised and non-randomised comparative studies with a sample size of at least 10 patients per arm, reporting cancer-specific QoL outcomes measured by validated PROMs with at least 12 months of follow-up, were eligible for inclusion.

2.3 Types of participants included

The study population was adult men (≥18 years of age) diagnosed with clinically localised PCa (T1-T2c) that had not undergone any previous treatment prior to their primary treatment for PCa (with the exception of neoadjuvant Androgen Deprivation Therapy [ADT] preceding radiotherapy).

2.4 Types of interventions included

The following interventions were eligible for inclusion:

(1) Active surveillance/monitoring (as defined by primary authors)
(2) Radical prostatectomy (Open or Laparoscopic or Robot-Assisted)
(3) Radiotherapy (3D conformal or Intensity Modulated [IMRT] or Stereotactic radiotherapy [SBRT]) +/- brachytherapy boost (Low Dose Rate [LDR] or High Dose Rate [HDR]); or Radiotherapy delivered with or without neoadjuvant/concurrent/adjuvant ADT for the treatment of localised PCa
(4) Brachytherapy alone (LDR or HDR)

Studies reporting comparisons between any of the above treatments were included. Studies reporting within treatment comparisons only (e.g. radiotherapy vs radiotherapy in combination with ADT) were excluded.

2.5 Types of outcome measures included

The primary outcome of this review was specified a priori and included cancer-specific QoL after primary cancer treatment, assessed by a validated PROM as defined by authors. In addition, a list of validated PROMs was used to identify potentially relevant studies and incorporated into the search strategy [7]. Studies using non-cancer specific PROMs or studies reporting cancer specific QoL using a non-validated tool were excluded, as were those studies reporting incomplete data from sub-domains of QoL PROMs. Secondary outcomes were sub-domains of QoL PROMs related to PCa QoL e.g. sexual function, urinary function and bowel function.

2.6 Assessment of risk of bias and confounding

Randomised controlled trials (RCTs) risk of bias (RoB) assessment was undertaken using the recommended tool in the Cochrane Handbook for Systematic Reviews of Interventions [6].

In non-randomised comparative studies (NRCSs), RoB was assessed using additional domains to assess the risk of confounders, which were developed a priori with clinical content experts (EAU Prostate Cancer Guideline Panel). This is a pragmatic approach informed by methodological literature pertaining to assessing RoB in NRCSs [8, 9]. The main confounding factors identified, included baseline QoL score, age, co-morbidities (any classification) and baseline Gleason score.

2.7 Data analysis

A data extraction form was developed a priori to collect information on study design, participant demographics, characteristics of interventions, and outcome measures. Two reviewers independently extracted data relating to the pre-specified outcomes. Descriptive statistics were used to summarise baseline characteristic data. For studies with more than two intervention groups, only the intervention groups relevant to the review were selected. If relevant data could be extracted and it was appropriate to do so, a meta-analysis of RCT data was planned. For studies with multiple publications, only the most up-to-date or complete data for each outcome was utilized. If meta-analyses of RCTs were inappropriate, a narrative synthesis of the evidence was performed. A narrative synthesis was undertaken for NRCSs [10].

3. Evidence synthesis

3.1 Quantity of evidence identified

The study selection process is outlined in Figure 1. A total of 18 studies were eligible for inclusion: 3 RCTs [11-13] and 15 NRCSs [14-30] of which one NRCS [23, 24, 26] had multiple publications. Ultimately, a total of 13,604 patients were recruited (2,011 from RCTs and 11,593 from NRCSs).

3.2 Characteristics of the included studies

Tables 1 and 2 present the baseline study characteristics for the 3 RCTs and 15 NRCSs, respectively. Due to heterogeneity of study PROMs data, a meta-analysis was not performed and consequently, data were summarised narratively instead.

3.3 Risk of bias and quality assessment of the included studies

Figures 2a and 2b present the RoB summary and confounder assessment for the three RCTs [11-13] and fifteen NRCSs [14-30]. As it was not possible to blind the participant to their intervention, all RCTs [11-13] had a high risk of bias for blinding of participants but we did not judge that this necessarily compromised study quality. One RCT [11] was also judged to have high selection bias (as only 19% of patients were randomly assigned to treatment arms), high bias due to closing prematurely and unclear detection bias, while another [13] was judged to have unclear selection and funding bias.

The NRCSs had a high risk of selection, performance, and detection biases. The risks of reporting bias were low, while risks of attrition bias were moderate. All confounders were measured and corrected for, in five studies [17, 21, 26, 28, 30].

3.4 Comparisons of interventions results

3.4.1. Data from RCTs

Statistically significant differences, for QoL outcomes between or within treatment groups at the latest follow-up of each RCT [11-13] are shown in Table 3. The complete summary of the outcome results can be found in Supplementary Table 1.

3.4.1.1 RP vs EBRT vs Active monitoring

Data were obtained from the recently published study ProtecT trial [12], where 1643 men randomised to active monitoring, RP or EBRT. The trial predominantly enrolled men with low-risk PCa. Trial retention and completion of follow-up assessments were higher than 85% for most outcome measures. Analyses were performed according to an intent-to-treat basis.

Approximately 50% (291) of men who initially underwent active monitoring had either surgery or radiotherapy by the end of November 2015.

Importantly, the study reported no difference in EORTC QLQ-C30 assessed global quality of life, up to 5 years of follow-up. However, Expanded Prostate Cancer Index Composite (EPIC) urinary summary scores were worse in men treated with RP compared to active monitoring or EBRT (88.7 vs 89.0 vs 91.4, respectively) as were urinary incontinence (80.9 vs 85.8 vs 89.4, respectively) and sexual summary, function and bother scores (32.3 vs 40.6 vs 41.3 for sexual summary, 23.7 vs 32.5 vs 32.7 for sexual function and 51.4 vs 57.9 vs 60.1 for sexual bother, respectively) at 6 years of follow-up. For men receiving EBRT, EPIC bowel scores deteriorated initially and although they improved after the first year, they were still poorer compared to active monitoring and RP at 6 years post-treatment in all domains: function (90.8 vs 92.3 vs 92.3, respectively), bother (91.7 vs 94.2 vs 93.7, respectively) and summary (91.2 vs 93.2 vs 93.0, respectively).

3.4.1.2 RP vs BT

For the comparison of RP vs BT, data were obtained from two RCTs. The SPIRIT trial [11] enrolled 168 men with low-risk PCa who received either RP or LDR BT. The investigators using the EPIC tool, found a statistically significant difference in the urinary and sexual domain, favouring men treated with LDR BT at a mean follow up of 5.2 years. These results should be interpreted with caution since only a minority of patients were randomly assigned to treatment arms (19%) and the trial was closed prematurely due to poor accrual.

Another RCT [13] that recruited 200 patients with low-risk PCa, reported that urinary irritation was statistically significantly worse in the LDR BT arm when compared with pre-treatment values, while urinary incontinence was more common - although not statistically significantly different - in the nerve-sparing RP (NSRP) arm, at 1 year of follow up. However, there were no significant differences in EORTC-QLQ-C30/PR25 scores at 5 years of follow up. It is notable that only within group tests were reported in this trial.

3.4.2. Data from NRCSs

Statistically significant differences, for QoL outcomes between or within treatment groups at the latest follow-up of each NRCS [14-30] are shown in Table 4. The complete summary of the outcome results can be found in Supplementary Table 2.

3.4.2.1 RP vs EBRT vs BT

An observational study [25] compared men undergoing NSRP vs non-NSRP vs EBRT vs BT using the University of California, Los Angeles (UCLA) Prostate Cancer Index (PCI) tool. The study was characterised by poor participant retention at 5 and 10 years. However, at 2 years of follow-up (81% cohort retention), authors using NSRP as a reference value, reported that men treated EBRT were more likely to have a clinically significant decline [(CSD) at least half standard deviation from baseline] in bowel function and bother score, while men treated with BT were more likely to have a CSD in bowel bother score. Conversely, men were less likely

to have a CSD in urinary and sexual function for BT and EBRT. These results are analogous with results from two other studies [14, 21]. The first [14] used the UCLA-PCI tool and for a follow up of up to five years reported that patients treated with EBRT had better sexual and urinary but worse bowel function than those treated with RP. BT patients had better sexual function, sexual bother and urinary function compared with RP patients, however, they had worse bowel function, bowel bother and urinary bother. The second study [21] assessed QoL scores at 3 years using the EPIC questionnaire. In comparison with NSRP, EBRT and BT caused significantly worse urinary irritative/obstructive adverse effects but less urinary incontinence and sexual dysfunction. EBRT also caused worse bowel and hormonal adverse effects.

Sanda et al [27] using the EPIC tool, compared CSDs in QoL scores within treatment groups only, from baseline to 2 years post treatment. Patients in the RP group reported CSDs in urinary continence and sexual function, however urinary irritation/obstruction scores significantly improved after surgery. EBRT was also associated with improvement in urinary irritation/obstruction scores but with reduced QoL related to bowel function and vitality. Patients treated with EBRT plus ADT also reported CSD in sexual function. Surprisingly, patients in the BT group reported significant reduction in all QoL subdomain scores except vitality.

3.4.2.2 RP vs EBRT or AS

Four studies [23, 24, 26, 28-30] reported QoL outcomes in men with localised PCa undergoing RP or EBRT, however in one [29], authors did not compare differences in QoL scores between treatments. In the most recent update of the Prostate Cancer Outcomes Study (PCOS) [26], the authors compared QoL scores at 2, 5 and 15 years after primary therapy. Although men undergoing RP had significantly higher rates of incontinence and erectile dysfunction and lower rates of bowel urgency at 2 and 5 years, these rates were similar to those in the EBRT group at 15 years. Barocas et al [30] using the EPIC questionnaire, reported that RP was associated with a greater decrease in sexual function and urinary incontinence than EBRT at 3 years of follow up. No clinically meaningful differences existed in bowel function beyond 12 months. The fourth study [28] had a limited follow up and reported that men who underwent RP experienced significant declines in urinary and sexual function when compared to EBRT.

Regarding comparison of QoL outcomes between RP and AS, Jeldres et al [17] in a cohort of patients with low-risk PCa reported similar results to ProtecT trial [12], as at 3 years of follow up, patients who underwent surgery had significantly poorer urinary, sexual function and sexual bother scores.

3.4.2.3 BT vs RP or EBRT

Four studies assessed QoL outcomes in patients with localised PCa after BT or RP [15, 18-20]. The investigators in two studies [18, 20] included a small number of patients with a limited follow up of 12 months and using the UCLA-PCI questionnaire, reported statistically worse sexual function for patients in the RP arm. Namiki et al [20] also reported significantly better urinary function scores for patients treated with BT. Another small study [15] reported that at

12 months sexual function was impaired significantly in patients after non-NSRP but not after NSRP when compared to patients treated with BT. In the largest prospective study [19], authors compared patients treated with RP, brachytherapy and cryotherapy. Statistical comparison for QoL outcomes between RP and BT cannot be made (as cryotherapy is not included in this review), nevertheless at 3 years of follow up BT patients tended to have better sexual and urinary scores.

Only 2 studies [16, 22] compared QoL after BT and EBRT using the EPIC questionnaire. Pinkawa et al [22] reported that BT was associated with statistically significantly higher urinary toxicity at 16 months. Evans et al [16] reported similar results, however SBRT was associated with lower bowel toxicity than BT at 2 years.

3.5 Discussion

3.5.1 Principal findings

The current review synthesises the existing evidence regarding cancer-specific QoL outcomes, of competitive treatments for clinically localised PCa. QoL is an important endpoint in PCa treatment and recently the COMPACTERS Study group, which developed a core outcome set for trials of effectiveness, identified QoL as an outcome which should be measured in all clinical trials of localised PCa [31]. Outcomes were measured by PROMs and the three most mainly used among the included studies were: EPIC, UCLA-PCI and EORTC QLQ-C30.

The ProtecT trial [12] provides level 1 evidence for the different effects of PCa treatments on disease-specific QoL**.** No difference was found among treatment modalities in global quality of life at 5 years. However, surgery had a negative effect on urinary continence and sexual function, EBRT was associated with a negative effect in bowel function which was more intense the first year after treatment, while active monitoring had the lowest impact on disease-specific QoL at 6 years. The PCOS 5-year results [26], confirm that men who underwent RP had a higher prevalence of urinary incontinence and erectile dysfunction, while men treated with EBRT had a higher prevalence of bowel dysfunction. Results from ProtecT trial are also comparable with the findings of the PIVOT Trial [32] as authors reported that at 2 years, urinary incontinence and erectile dysfunction were significantly more common among men who were assigned to RP when compared to men managed with observation.

Most other observational studies provide similar, consistent intermediate-term results for RP and EBRT. However, in a recently published study [30], investigators reported that although EBRT was associated with a negative effect in bowel function, the difference in bowel domain score was below the threshold for clinical significance 12 months after treatment. As 81% of patients in the EBRT arm of the study received IMRT, these data suggest that the risk of side effects in contemporary treatments may be slightly less. Another discrepancy noted, is that while some studies report worse declines in urinary function after surgery [14, 25, 28], others report that surgery resulted in more incontinence but less irritating/obstructive symptoms than EBRT [21, 27, 30]. This variation could be explained by the use of different PROMs. Studies reporting urinary function decline after RP use the UCLA-PCI tool which focuses primarily on urinary incontinence, while studies reporting less irritative/obstructive symptoms use the EPIC tool. EPIC addresses irritative and obstructive voiding symptoms and provides a more

comprehensive assessment of urinary QoL [33]. Urinary irritation symptoms are sometimes said to be worse with EBRT, however, this was not confirmed by ProtecT trial [12].

Regarding the effect of AS on QoL, as recently highlighted [34] there is a lack of data. We were able to identify only one NRCS [17] including patients undergoing AS, which similarly to ProtecT trial [12] reported no major perturbations to their cancer-specific QoL.

With respect to BT cancer-specific QoL outcomes, the best available evidence come from one small RCT [13]. The authors compared post-treatment QoL scores for patients undergoing BT and NSRP with their baseline scores only (there is no comparison between groups available), and they reported that at 1 year, BT had a negative impact on urinary irritative symptomatology. This result is consistent among all observational studies that use the EPIC tool, which addresses irritative-obstructive symptomatology [16, 21, 22, 27]. Unexpectedly, authors also reported that both BT and NSRP had no significant impact on QoL 5 years after treatment. Conversely, the SPIRIT trial [11], which directly compared QoL outcomes for BT and RP found a statistically significant difference in favour of BT in the urinary and sexual domains. In that trial though, the small difference in the overall mean scores in the urinary domain may have questionable clinical significance.

As only a small proportion of patients with early stage PCa progress to metastatic disease and die from cancer within 10–15 years [35], understanding the long term impact of treatment on disease-specific QoL is critical. This systematic review revealed an important knowledge gap in the evidence base, as we were able to identify only one NRCS [26] that reported QoL outcomes at a follow up of more than 10 years. Interestingly, data from the PCOS [26], showed that there were no significant differences in the adjusted odds of urinary incontinence, bowel dysfunction or erectile dysfunction between RP and EBRT at 15 years. PCOS provided two further important observations; firstly, at the end of follow up, the prevalence of erectile dysfunction was very high (≥80%) in both treatment arms and secondly patients had significant declines in sexual and urinary function over the duration of follow up. These observations have also been reported for patients undergoing RP and watchful waiting (WW), in the most recent publication of the SPCG-4 trial, regarding HRQoL outcomes [36], for a median follow up of 12.2 years. While it would be difficult to determine whether these declines are the consequence of treatment, advancing age or both, data from PLCO Trial comparing a sample of screened PCa survivors to a sample of screened noncancer controls, suggested that these persistent symptoms were due to treatment [37].

3.5.2 Strength and limitations of the review

The strengths of this review are the systematic, transparent, and robust approach taken to examine the evidence base, including the use of Cochrane review methodology, RoB and confounding assessment and adherence to PRISMA guidelines. The clinical question was prioritised by a multidisciplinary panel of clinical experts, methodologists, and patient representatives (EAU Prostate Cancer Guideline Panel), and the work was undertaken as part of the panel's clinical practice guideline update for 2017. The inclusion criteria restricted the review to studies reporting data on cancer-specific QoL outcomes, measured by validated PROMs only. This approach ensured a comprehensive review of the literature, while maintaining methodological rigour.

It is important for the authors of this review to acknowledge several limitations. The number of RCTs providing level 1 evidence is limited (i.e. three) two of which recruited small cohorts. The quality of the evidence obtained from observational studies is problematic in relation to high risk of selection, performance, and detection biases and the minority of the studies accounting for our a priori identified confounders. There is large methodological heterogeneity among studies (as different PROMS being used to measure the same outcome, along with outcomes being measured at different time points), as well as heterogeneity regarding outcome reporting. An additional limitation is the fact that treatment arms in many included studies differ from contemporary care (i.e IMRT), as newer interventional techniques, especially newer EBRT techniques, may result in a lower risk and severity of side effects.

3.5.3 How does this systematic review compare with other systematic reviews?

To our knowledge, this is the first systematic review comparing the impact on cancer- specific QoL of different primary treatments for men with clinically localised PCa, using outcomes measured by validated cancer-specific PROMs only. The most recent systematic review [38] including mostly single treatment cohorts, is over four years out of date (searches up to January 2013) and highlighted the lack of sufficient quality data to make recommendations to patients about QoL outcomes. Similar were the results of two previous reviews, which concluded that there was a paucity of clinically important information from high-quality RCTs on this topic [39, 40]. In another review by Chou et al [41], that included not only HRQoL outcomes, the authors reported that RP was associated with increased risk for urinary incontinence and erectile dysfunction, while EBRT was associated with increased risk for erectile and bowel dysfunction when compared with WW. Our systematic review differs from others with regards to the methodology, the strict inclusion and exclusion criteria and the robust methods used to synthesise the evidence and analyse the data. These are the principal strengths of our study.

4. Conclusion

Based on currently available evidence, choice of primary treatments for clinically localised PCa have a distinct impact on cancer-specific QoL, for a period of up to 6 years following treatment. Men managed with AS have good overall QoL scores, which are comparable or better than those of patients undergoing radical treatments. Surgery has a more pronounced negative impact on urinary and sexual function when compared to AS and EBRT, while EBRT has a more pronounced negative impact on bowel function when compared to AS and RP. Data from one small RCT including patients with low-risk disease reported that brachytherapy has a negative impact on urinary function at 1 year, but there are no significant differences in cancer-specific QoL 5 years after treatment. The review findings support the assertion that AS provides a good alternative to radical treatments in patients in whom it is desirable to prioritise QoL outcomes. The findings provide a basis for informing patients and clinicians regarding the impact of radical treatments on QoL.

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