

Title: PIONEER's systematic review of outcomes reported in effectiveness trials for interventions in locally advanced prostate cancer

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Introduction & Objectives: Heterogeneity in outcome reporting, definitions and measurement is a problem in the prostate cancer (PCa) evidence base. This negatively impacts clinical and patient decision making. A solution is to develop a core outcome set (COS) which consists of an agreed minimum set of outcomes to be reported in all PCa clinical trials. In the context of localised and metastatic PCa, PIONEER (an IMI2 Joint Undertaking project funded under grant agreement No. 777492 using Big Data to answer key questions in PCa) is currently updating and integrating the 'standard set' of COS from the International Consortium of Outcome Measures (ICHOM) and a COS developed using COMET's methodology. This systematic review aims to ascertain whether any new outcomes have been reported for men with locally advanced PCa, which are not already included in the already defined localised or metastatic COS.

Materials & Methods: A systematic review was conducted including randomised controlled trials (RCTs) of any intervention for men with locally advanced PCa (T3 or T4 and/or N1), published between 1st of January 2013 and 31st of March 2019. Abstract and full text screening were performed in duplicate. Verbatim outcome names, definitions and reported data were coded and categorised.

Results: Searches identified 1,611 references. Forty-seven systematic reviews were full text screened. Nine RCTs met the inclusion criteria. The identified outcomes can be found in Table 1 below, which also indicates how these outcomes correspond to the localised PIONEER COS.

Conclusions: The outcomes identified in the current systematic review are already included in PIONEER's COS for localised PCa. Discrepancies observed were related to measurement rather than underlying outcome construct. PIONEER does not recommend a specific COS for locally advanced PCa. In the future, if further treatment options for this specific population warrant new RCTs and different outcome measurements, then this recommendation may change. We propose that the outcomes reported in the PIONEER COS for localised PCa adequately cover the locally advanced PCa population and should be used for clinical trials and clinical audit in this population.

Table 1: Identified outcomes for men with localised and locally advanced PCa.

PIONEER Localised PCa COS – publication under review	Locally advanced PCa outcomes as identified in our systematic review	Locally advanced PCa outcomes standardised according to common clinical terminology
Overall survival	<ul style="list-style-type: none"> Overall Survival 	<ul style="list-style-type: none"> Overall Survival
Prostate cancer specific survival	<ul style="list-style-type: none"> Cause specific survival PCa-specific 15-yr mortality 	<ul style="list-style-type: none"> Cause specific survival
Biochemical recurrence	<ul style="list-style-type: none"> Biochemical failure (BF) Time to biochemical recurrence Biochemical recurrence-free survival PSA response Rising PSA ≥ 0.5 ng/ml 	<ul style="list-style-type: none"> Biochemical recurrence
Local disease recurrence Distant disease recurrence/metastases	<ul style="list-style-type: none"> Time to subjective progression Time to objective progression Disease-free survival (DFS) Local progression (LP) Distant metastasis Relapse-free survival Clinical relapse-free survival Metastasis free survival Progression-free survival (PFS) Time to progression (TTP) 	<ul style="list-style-type: none"> Progression Metastases
Need for salvage therapy Disease reclassification (Applicable to active surveillance) Need for curative R/ (Applicable to active surveillance) Treatment failure (Applicable to ablative procedures (cryotherapy, HIFU)) Retreatment (Applicable to ablative procedures (cryotherapy, HIFU)) Positive surgical margins (surgery)		
Bowel dysfunction	<ul style="list-style-type: none"> Adverse events Toxicity Early adverse events 	<ul style="list-style-type: none"> Adverse events Toxicity Early adverse events
Urinary dysfunction		
Sexual dysfunction		
Side effects of hormonal therapy		
Major surgical complications		
Radiation toxicity	<ul style="list-style-type: none"> Acute RT toxicities 	<ul style="list-style-type: none"> Acute RT toxicities
Overall quality of life	<ul style="list-style-type: none"> QoL 	<ul style="list-style-type: none"> QoL
Psychosocial and psychological impact	<ul style="list-style-type: none"> PSA doubling time at recurrence Safety Testosterone recovery 	<ul style="list-style-type: none"> PSA doubling time at recurrence Safety Testosterone recovery