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Aims and Scope

European Urology Oncology is the new sister journal to *European Urology* and *European Urology Focus*, and the first official publication of the EAU fully devoted to the study of genitourinary malignancies.

The journal aims to deliver high quality research while implementing a multi-disciplinary approach to incorporate Urology, Medical Oncology, Radiation Therapy, Imaging, Pathology and Basic Research with the ultimate goal of improving patient care.

European Urology Oncology will include original articles, opinion piece editorials and invited reviews covering clinical, basic and translational research and it will be published six times a year in electronic format.
All submitted manuscripts will be peer-reviewed by a panel of experts before being considered for publication.

Welcome to European Urology Oncology

Your new journal, where multiple disciplines meet to improve care of patients with genito-urinary cancers

Alberto Briganti, Laurence Albiges, Gianluca Giannarini, Ashish M. Kamat, Paul L. Nguyen

Over recent years, we have seen a real revolution in the management of genito-urinary (GU) cancers, involving all disciplines, including urology (surgery), radiation oncology, medical oncology, imaging and pathology. None of these advances would have occurred without close collaboration between different specialists and health professionals. Nowadays, such cooperation represents one of the pillars of modern treatment of patients with cancer, aimed at individualizing pathways of care with the ultimate goal to improve patient survival and quality of life. With the increased incidence of cancer worldwide and the growing complexity of contemporary cancer patients, the role of a multi-disciplinary approach is paramount. This approach has been rapidly embraced in our field, where recent advances in imaging, novel technologies and biomarkers, as well as availability of more and more effective systemic therapies coupled with enhanced programmes of early diagnosis have allowed patients with GU malignancies to be presented with a personalized state of treatment options for their disease. The complexity of patient care is also increasing, and requires continuous evidence-based updates; only once a collaboration among multiple disciplines is envisioned can such levels of complexity be managed and advances in the management of our patients be reached. This will have a beneficial impact not only in clinical practice, but also in the setting of clinical research, paving the way to design and conduct groundbreaking, practice-changing trials.

It is with enthusiasm that we would like to introduce our (your!) new journal, *European Urology Oncology*, which is the first official publication of the European Association of Urology entirely devoted to the study of urological cancers. The journal was officially launched last November as a sister Journal to *European Urology*. Our journal aims to deliver high-quality research while pursuing the goal of a multi-disciplinary approach. Urology, Medical Oncology, Radiation Oncology, Imaging, Pathology, and Basic and Translational Research working together to reach the final aim: improving patient care.

The journal will be published six times a year in electronic format and will feature varying article formats such as: original articles, invited reviews, commentaries, debates and editorials covering the whole spectrum of GU Cancers (clinical, basic and translational research). The manuscripts can be directly submitted to our Journal via the link: https://ees.elsevier.com/euonco. On occasion, selected manuscripts submitted to European Urology will also be given the opportunity to be published in European Urology Oncology. For all submitted manuscripts, we guarantee a fast and rigorous peer-review process by a panel of worldwide experts before being considered for publication. Additional and detailed information about the Journal can be found at our website: www.europeanurology.com/euoncology. Please follow along on Twitter at @EUOncology and on Facebook at https://www.facebook.com/EuropeanUrologyOncology. *European Urology Oncology* thus represents an important addition to the editorial landscape of modern urologic oncology, and we invite all of you to join us in this endeavor and contribute your high-quality original research. This is your journal and with your help we are sure *European Urology Oncology* will soon be the reference journal in the field of genitourinary cancers.

We would like to take this opportunity to share with you a selection of papers accepted in March 2018, which will be published in the first issue of the journal. We hope you will find these articles of interest and we hope you can contribute to the journal in the future.

European Urology Oncology: multiple disciplines, one goal.

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Optimizing the Timing of Salvage Postprostatectomy Radiotherapy and the Use of Concurrent Hormonal Therapy

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Abstract

Context: Currently, salvage radiotherapy (SRT) is the only known curative intervention for men with recurrent disease following prostatectomy. Critical issues in the optimal selection and management of men being considered for SRT include the threshold prostate-specific antigen (PSA) value at which to initiate treatment (ie, pre-SRT PSA) and the role of concurrent hormonal therapy (HT).

Objective: To review the published evidence pertaining to the optimal timing for SRT and the role of concurrent HT.

Evidence acquisition: MEDLINE (via PubMed), EMBASE, the Cochrane Central Register of Controlled Trials, and guideline statements from professional organizations were queried from January 1, 2000 through January 10, 2018.

Evidence synthesis: Thirty-three independent reports, including two randomized trials evaluating HT with SRT, were identified. Retrospective data suggest that SRT initiation at lower pre-SRT PSA levels is associated with better clinical outcomes. Prospective data suggest an overall survival benefit with concurrent HT that manifests during long-term follow-up, with the caveat that hypothesis-generating subgroup analyses suggest that this benefit may be limited to patients with higher pre-SRT PSA levels. Patients with adverse risk factors, such as Gleason grade group 4–5 disease, are likely to benefit the most from earlier SRT initiation and/or the use of HT.

Conclusions: Given the limitations of the available data, it is imperative that physicians participate in shared decision-making, with the recommendation tailored for each man's desire to maximize oncologic benefit (with a risk of overtreatment) versus potential quality-of-life optimization (with a risk of undertreatment). Within that framework, a significant body of retrospective data supports initiation of SRT at low pre-SRT PSA values, without an arbitrary absolute threshold. Prospective data suggest a benefit of HT, but this benefit may be greatest in patients with a pre-SRT PSA that is higher than the typical level in most patients receiving "early" SRT. Further research is necessary before absolute recommendations can be made.

Patient summary: Two ways to potentially improve outcomes following salvage radiotherapy for prostate cancer that recurs after prostatectomy are to start treatment at a lower prostate-specific antigen level and to use concurrent hormonal therapy. Our review suggests that the available evidence is imperfect, but highlights that both measures are likely to improve clinical outcomes in general, but perhaps not uniformly and/or consistently for all patients. Physician-patient shared decision-making and further research are critical.

1. Introduction

Prostate cancer (PCa) is the second leading cause of cancer-related death in the USA [1] and the third leading cause of cancer-related death in Europe [2]. Among men who ultimately die from their PCa, nearly 50% have potentially curable, localized disease at diagnosis that ultimately recurs after upfront treatment [3]. Therefore, effective management of men with biochemically recurrent PCa is integral in ultimately minimizing PCa-specific mortality (PCSM). Nearly 30% of men undergoing radical prostatectomy (RP) will ultimately experience a biochemical recurrence (BCR), defined as two consecutive prostate-specific antigen (PSA) levels >0.2 ng/ml [4,5]. In such patients, the only known curative intervention is salvage radiotherapy (SRT), which—on the basis of compelling but retrospective data—can offer a relative reduction in PCSM of up to 68% [6]. Unfortunately, patterns of care data indicate that SRT utilization rates can be as low as 42% among patients with PSA >0.2 ng/ml after RP [7]. This underutilization is reflective of a mix of practice philosophies that place varying weight on toxicity and oncologic benefit [8]. Critical issues in the optimal selection and management of men being considered for SRT include the threshold

PSA value at which to initiate treatment (ie, pre-SRT PSA) and the role of concurrent hormonal therapy (HT). In this systematic review, we explore the rationale for and evidence pertaining to (1) the optimal timing for SRT and (2) the role of concurrent HT. We emphasize that further research is desperately needed to improve the efficacy of SRT and lessen the burden of PCSM among men with BCR after RP.

2. Evidence acquisition

2.1. Search strategy

The methods for this systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [9]. MEDLINE (via PubMed), EMBASE, the Cochrane Central Register of Controlled Trials, and guideline statements from professional organizations were queried to identify manuscripts available from January 1, 2000 through January 10, 2018. The initial search strategy included the following different terms: "(<radiotherapy> OR <radiation>) AND <prostatectomy> AND (<salvage> OR <recurrent>)". This yielded 1443 results.

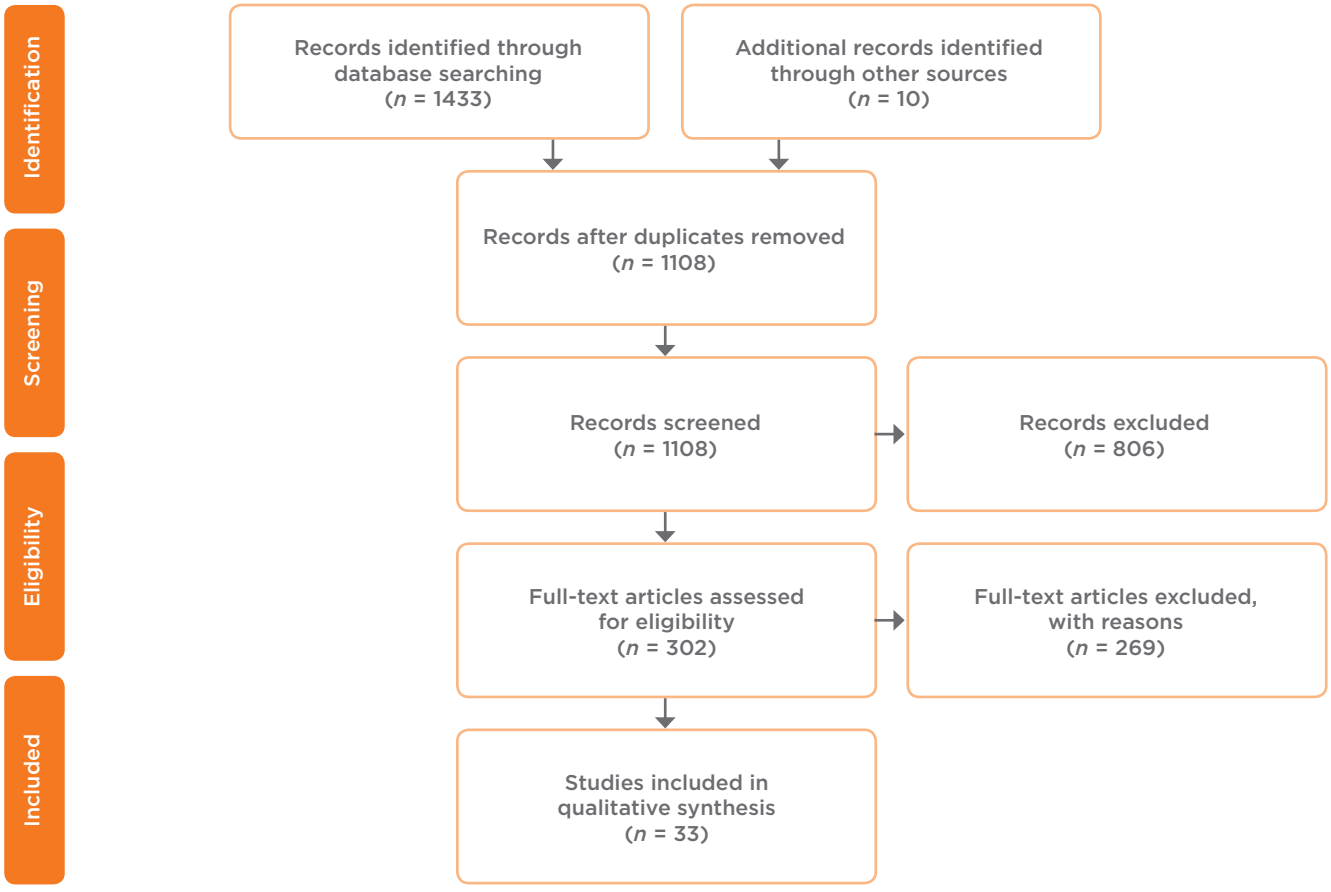
2.2. Inclusion and exclusion criteria

The 1443 abstracts identified were further analyzed according to the PRISMA approach, as depicted in Figure 1. Inclusion criteria included identification based on (1) the additional search term "<PSA>", which yielded 706 results, and (2) the additional search term "(<androgen deprivation> OR <hormonal>)", which yielded 402 results. Further screening of manuscript abstracts to remove erroneous identification and abstracts without a cognate manuscript revealed 302 articles for review. These articles were then screened in detail by a single investigator (A.U.K.) against the following exclusion criteria: (1) did not present primary data; (2) did not specifically analyze the association between pre-SRT PSA and the use of HT and SRT outcomes; (3) included 50 or fewer patients; (4) reported outcomes for a patient population for which a subsequently updated report was available; (5) were not written in English; or (6) did not have full text available. Ultimately, this yielded 16 manuscripts specifically analyzing the importance of the pre-SRT PSA level and 17 manuscripts specifically reporting the impact of concurrent HT with SRT. Outside of two randomized trials evaluating the role of HT, all other reports were retrospective in nature.

2.3. Data extraction

Patient characteristics extracted from each study included a proxy indicator of pre-SRT PSA distribution (generally median PSA), the percentage of patients with pathologic Gleason grade group (GG) 4–5 disease, the percentage of patients with pT3b or pT4 disease, and the percentage of patients with negative margins. Information on the SRT dose and field design was also extracted, along with median HT duration. Outcomes data were obtained for all reported outcomes, including BCR, progression-free survival, distant metastasis (DM)-free survival, PCSM, and overall survival (OS). No statistical tests were performed; findings were interpreted as statistically significant if reported as such, provided the p value was <0.05.

Figure 1 Flow diagram for inclusion of studies in the systematic review.



2.4. Assessment of risk bias

The risk of bias for the two randomized controlled trials included in this review was assessed using the Cochrane risk of bias assessment tool for randomized controlled trials [10].

3. Data synthesis

3.1. Timing of SRT

3.1.1. Rationale for early salvage

The European Association of Urology/European Society for Radiotherapy and Oncology/International Society of Geriatric Oncology guidelines emphasize the importance of early SRT, defined as SRT initiated at PSA <0.5 ng/ml [11], while the 2013 American Society for Radiation Oncology/American Urological Association guidelines state that "patients should be informed that the effectiveness of RT for PSA recurrence is greatest when given at lower levels of PSA" [12]. These recommendations are in large part driven by a systematic review of 41 studies that identified an average 2.6% decrement in BCR-free survival for each increment of 0.1 ng/ml in PSA at the time of SRT [13]. However, the optimal pre-SRT PSA remains unclear. Theoretically, PSA is a proxy for disease burden and thus a low pre-SRT PSA suggests a low-volume curable disease burden that is potentially still localized. Alternatively, it is possible that the magnitude of the pre-SRT PSA itself is less important, and instead treating at lower pre-SRT PSAs simply "selects" for men with longer PSA doubling times (PSADTs), with PSADT known as a predictor of adverse clinical outcomes following RP and SRT [14–18]. However, pre-SRT PSA and PSADT appear to be independent predictors of BCR-free survival following SRT [14], suggesting that the importance of pre-SRT PSA is likely to be independent from that of PSADT. In either scenario, treating at a lower pre-SRT PSA would probably be more effective than treating at a higher pre-SRT PSA, whether directly or indirectly. Conversely, delaying SRT may allow for improved functional recovery. Some data do indicate that prolonging the interval between RP and SRT is associated with better erectile function and continence outcomes [19,20], but these findings are not uniform and others have reported no significant impact of SRT timing on the quality of outcomes [21,22]. It is possible that advances in RT, such as intensity-modulated RT and image guidance, may lead to better toxicity outcomes [23–25]. A detailed discussion of the toxicity profile and quality-of-life effects of postoperative RT is beyond the scope of this review, so our discussion of the evidence for early SRT will instead focus on oncologic, rather than functional, outcomes.

While no prospectively obtained data are yet available, numerous retrospective studies have investigated the importance of SRT timing, specifically focusing on pre-SRT PSA as a critical variable. In the next section, we summarize and critically review these studies. Of note, patients with persistently elevated PSA after RP are known to constitute a distinct high-risk subset of patients [26,27]. For the purposes of this review, studies including such patients were still considered for inclusion.

3.1.2. Retrospective evidence: a review

Key findings from 16 studies evaluating the importance of pre-SRT PSA are presented in Table 1. The importance of pre-SRT was originally highlighted in the widely adopted Stephenson nomogram, which was developed on the basis of outcomes for 1540 patients treated with SRT across 17 North American centers [14]. The authors found that along with other now canonical risk factors (eg, GG), pre-SRT PSA was a statistically significant predictor of PFS, with 6-yr PFS rates of 48% versus 26% for pre-SRT PSA of ≤0.5 ng/ml versus >0.5 ng/ml. Tendulkar et al [28] recently developed an updated nomogram based on 2460 patients treated with SRT across ten institutions, with median follow-up of 5.0 yr. The median pre-SRT PSA was 0.5 ng/ml, and 18% had pre-SRT PSA between 0.01 and 0.2 ng/ml. The median SRT dose was 66 Gy. Overall, the 5-yr BCR-free survival rate was 56%; there was evidence of a clear relationship with pre-SRT PSA, and freedom from BCR decreased from 71% for PSA of 0.01–0.2 ng/ml to 63%, 54%, 43%, and 37% for PSA of 0.21–0.4, 0.51–1.0, 1.01–2.0, and >2.0 ng/ml, respectively. Similarly, the 10-yr DM rates were 9%, 15%, 19%, 20%, and 37% across the same strata. Importantly, the nomogram suggests that pre-SRT PSA would be best used as a risk factor along with (rather than instead of) other canonical risk factors. That is, higher pre-SRT PSA values may have more influence on outcomes in the presence of other risk factors.

Stish et al [29] examined pre-SRT PSA in a cohort of 1106 patients treated with SRT at the Mayo Clinic, with median follow-up of 8.9 yr. Each doubling of pre-SRT PSA was associated with an 18% increase in the relative risk of BCR and a 32% increase in the relative risk of DM. The 10-yr rate of PSCM was 10.4%, and overall 22.7% of the patients died by 10 yr. The relative risk of PCSM and all-cause mortality increased by 40% and 12%, respectively, for each doubling of pre-SRT PSA. The authors also dichotomized pre-SRT PSA using 0.5 ng/ml as the cutoff point. The 10-yr BCR rate was 60% versus 68%, while the 10-yr DM and PCSM rates were 13% versus 25%, and 6% versus 13%, respectively; all of these differences were statistically significant in favor of early SRT. All-cause mortality rates were not significantly different (17% vs 27%).

Fossati et al [30] reported outcomes for 925 patients who received SRT at seven institutions, with median follow-up of 8.0 yr. The study included patients with PSA persistence (≥0.1 ng/ml at 1 mo after RP; 24% of patients). The investigators found that pre-SRT PSA was a significant predictor of DM on multivariable analysis (hazard ratio [HR] 1.06 per 0.1-ng/ml increment). Using a regression tree approach, five risk categories were developed with regard to DM risk. Pre-SRT PSA was significantly associated with DM outcomes in all but the very low-risk and very high-risk groups (characterized by GG ≤3, tumor stage ≤pT3a disease with undetectable PSA after RP, and PSA persistence after RP with GG ≥4). The relationship between pre-SRT PSA and outcome was not linear and the most significant change in outcomes was seen for PSA <1 ng/ml. Of note, 30% of patients received HT. However, this finding was concordant with a prior study of patients from the same institutions in which patients receiving concurrent HT were omitted [31].

Finally, Abugharib et al [32] recently evaluated biochemical and clinical outcomes in a cohort of 657 men treated with SRT at the University of Texas Southwestern and the University of Michigan, with median follow-up of 9.8 yr. The authors operationally defined early SRT as either the time from RP to SRT (<9, 9–21, 22–47, or >48 mo) or the pre-SRT PSA (0.01–0.2, 0.2–0.5, or >0.5 ng/ml). Higher pre-SRT levels were correlated with worse outcomes, and 10-yr PCSM rates were 7%, 11%, and 20% for pre-SRT PSA of 0.01–0.2, 0.2–0.5, and >0.5 ng/ml, respectively. The

corresponding 10-yr DM-free survival rates were 86%, 79%, and 66%. Intriguingly, on multivariable analysis, SRT delivery at PSA values between 0.2 and 0.5 ng/ml was associated with a higher risk of BCR (HR 1.97) and DM (HR 1.95) compared to SRT at PSA of 0.01–0.2 ng/ml, though SRT in either stratum would be considered early. SRT at PSA >0.5 versus ≤0.2 ng/ml was associated with a higher risk of BCR (HR 3.48), DM (HR 4.45), and PCSM (HR 4.07). Importantly, when SRT was defined by time to SRT rather than pre-SRT PSA, no significant relationships were identified. This specifically addresses concerns about lead-time bias [33]. That is, if follow-up is measured from the time of SRT rather than from the time of RP, patients receiving SRT would by definition have better time-to-event outcomes than patients receiving late SRT simply because SRT was delivered at a chronologically earlier time point. By also evaluating outcomes based on time from RP, the authors obviated that concern.

3.1.3. Synthesis and recommendation

These studies, in addition to the numerous smaller studies reviewed in Table 1, suggest at least a DM benefit of SRT delivery at lower PSA values, and possibly a PCSM benefit as well. An important caveat is that the majority of patients in these studies did not receive concurrent HT, which, as reviewed below, may improve SRT outcomes. Regardless, there does appear to be a benefit to initiating SRT at PSA values below 0.5 ng/ml (and potentially below 0.2 ng/ml). Overall, in the absence of prospective data to guide management, we recommend that physicians participate in shared decision-making with their patients in order to understand any given patient's relative prioritization of potential oncologic benefit (with a risk of overtreatment) versus potential quality-of-life optimization (with a risk of undertreatment). If maximizing oncologic benefit is the primary goal, we recommend strongly considering SRT when two consecutive rising PSA values have been identified, and recommend against delaying SRT until PSA has exceeded an arbitrary absolute threshold. However, we submit that certain factors, such as the kinetics of the PSA rise, the possibility of persistent benign tissue, the patient's life expectancy, and, most importantly, the patient's preferences, must be incorporated into any final treatment recommendation. We suggest that there a spectrum of benefit probably exists, with SRT offering better outcomes if delivered at PSA values <0.2 ng/ml than if performed when PSA is between 0.2 and 0.5 ng/ml. The absolute benefit of such an intervention is likely to be highly dependent on other disease factors [28]. For example, in a patient with GG 1–2 disease and a positive margin, SRT could be reasonably delayed despite a rising pre-SRT PSA above 0.2 ng/ml to aid in functional recovery. However, in patients with multiple high-risk features, such as negative margins and/or GG 4–5 disease, SRT should be considered for consecutive rising PSA values, regardless of the absolute value of the pre-SRT PSA. It should be acknowledged that in this latter scenario, the competing risk of synchronous out-of-field disease is higher than in the former, which might limit the benefit of SRT. Again, however, we recommend shared decision-making to understand whether the patient is willing to risk potential overtreatment (ie, SRT if micrometastatic disease is present) for a potential cure. In order to discuss the baseline risk of metastasis after BCR, we strongly encourage use of the aforementioned nomogram published by Tendulkar et al [28].

The interplay between SRT timing and SRT target volumes has not been rigorously evaluated, and a detailed analysis is beyond the scope of this review. However, we acknowledge that inclusion of elective nodal radiation and/or the integration of advanced imaging techniques, such as positron emission tomography/computed tomography scans with 18F-fluciclovine or 68Ga-labeled prostate-specific membrane antigen (PSMA) ligands, may allow improvement of SRT outcomes, regardless of pre-SRT PSA. For example, it was shown that whole-pelvis RT (WPRT) improves BCR-free survival outcomes only in patients with pre-SRT PSA ≥0.4 ng/ml, and not in those with lower PSA [34]. However, data from a larger study showed that WPRT offered a significant BCR-free survival benefit on multivariable analysis that included pre-SRT PSA as a covariate [35]. Part of the variability in outcomes could reflect that the incidence of occult nodal metastases is high and difficult to predict. A recent study of 270 patients who underwent PSMA-based imaging found that data from the PSMA scan would have changed SRT field delineation significantly in nearly 20% of patients [36]. In this study, 30.5% of patients had PSMA-positive pelvic lymph nodes and another 3.5% had extrapelvic PSMA-positive lymph nodes. Similarly, a randomized trial of 96 patients evaluating the impact of 18F-fluciclovine imaging on target volume reported an essentially uniform increase in treatment volume following incorporation of information from the advanced imaging study [37]. A conceptually attractive, although unproven, strategy would be to defer SRT initiation until advanced imaging is able to identify recurrent disease. At the current time, however, this strategy cannot be endorsed outside of a clinical protocol, as the wealth of available evidence (albeit retrospective) supports early initiation of SRT.

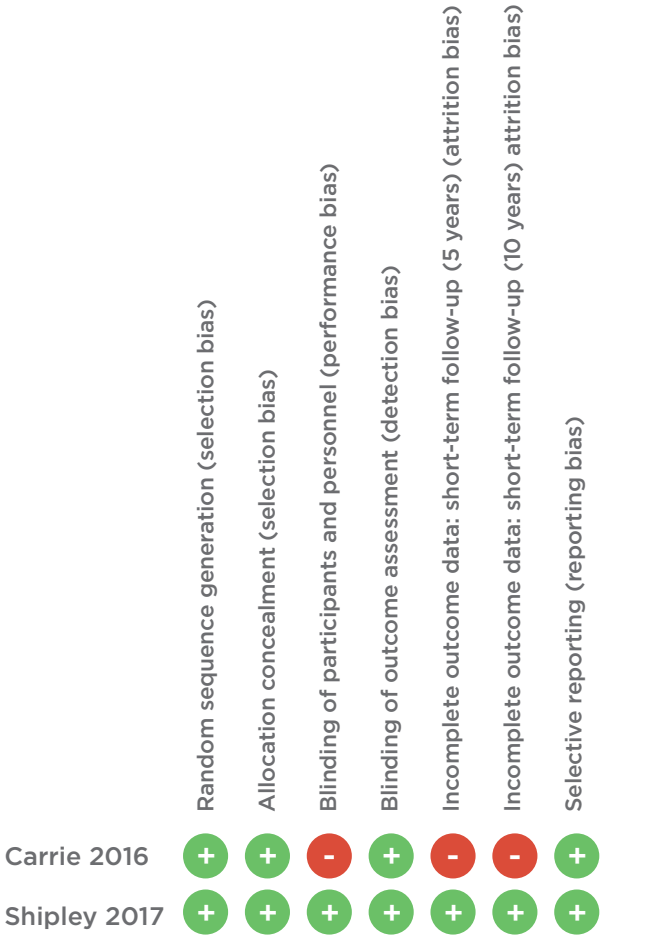
3.2. Importance of HT

Multiple randomized studies have shown an OS benefit for concomitant HT with RT in definitive treatment of localized PCa [38]. While the precise pathophysiological basis of this benefit remains an active area of study, recent data have identified a direct radiosensitizing action of HT [39,40], raising the possibility that concurrent HT has both local control benefits and benefits in terms of controlling micrometastatic disease. Adjuvant HT may also be important to suppress the induction of androgen receptor–mediated signaling by RT [41]. However, HT is associated with multiple effects, including bone loss, altered metabolism, diminished muscle mass, gynecomastia, hot flashes, possibly increased cardiovascular events, renal events, and cognitive-psychological disorders [42–45]. Emerging data do suggest an additive, rather than redundant, negative functional impact of RT and HT in the postoperative setting [46]. Therefore, the integration of HT with SRT must be considered carefully. In the next section, we summarize and critically review both the randomized and retrospective evidence on the use of HT with SRT.

3.2.1. An overview of the randomized evidence: RTOG 9601 and GETUG-16

Two randomized trials, RTOG 9601 and GETUG-16, have compared outcomes following SRT with or without concurrent HT (Table 2) [47,48]. The risk-of-bias assessment for these trials is presented in Figure 2. Overall, the risk of selection, detection,

Figure 2 Risk of bias assessment for the two randomized controlled trials.



and reporting bias was low for both trials, and the risk of attrition bias and performance bias was low for RTOG 9601 but high for GETUG-16, as the follow-up is relatively short and participants were not blinded. The first trial, RTOG 9601, randomized 840 men between 1998 and 2003 to receive SRT of 64.8 Gy to the prostate bed with or without 24 mo of 150 mg/d bicalutamide (a nonsteroidal androgen receptor antagonist). Ultimately, following postrandomization screening, 760 patients were eligible for analysis. Patients were required to have either pT3 disease or pT2 disease with a positive margin, as well as PSA of 0.2–4.0 ng/ml (initially, the lower threshold for pre-SRT PSA was 0.5 ng/ml, but as PSA assays became more sensitive, this was gradually lowered to 0.2 ng/ml). Of note, 11.8% of the patients had PSA persistence after surgery and 46.7% had pre-SRT PSA levels >0.7 ng/ml at trial entry. At the time of final publication, the median follow-up was 13 yr [47]. Significant improvements were seen in OS, PCSM, DM, and BCR, with 12-yr OS of 76.3% versus 71.3% for patients with versus without HT. Importantly, no significant difference was seen in the risk of non–disease-specific death, including the rate of cardiovascular deaths. The rate of hot flashes was similar between the groups, but the rate of gynecomastia was significantly higher in patients receiving HT (69.7% vs 10.9%).

The investigators conducted a number of subgroup analyses and reported that the OS benefit seen in the overall study population was also seen in patients with GG 2–3 disease, pre-SRT PSA of 0.7–1.5 ng/ml and >1.5 ng/ml, and positive margins; the event rate was too low in the GG 4–5 group to demonstrate a statistically significant difference in OS. Of note, however, interaction tests failed to identify a significant differential benefit in subgroups, with the exception of PSA level, suggesting that the relative benefit is similar regardless of GG or margin status. While provocative, the results for the PSA subgroup analysis should be considered primarily as hypothesis-generating rather than definitive, as the PSA threshold and direction of benefit were not prespecified [49].

The second trial, GETUG-16, randomized 743 patients between 2006 and 2010 to receive SRT with or without two 10.8-mg injections (ie, 3-mo) of goserelin (a luteinizing hormone–releasing hormone agonist). Patients were required to have pT2–4a disease (bladder neck involvement) with initial PSA of <0.1 ng/ml after RP for at least 6 mo, followed by consecutive rises to between 0.2 and 2 ng/ml. Patients with PSA persistence were thus expressly excluded, and the median PSA at inclusion was 0.3 ng/ml; 75% of the men had PSA <0.5 ng/ml. Patients received 66 Gy to the prostate bed, and pelvic radiation to 46 Gy was permitted for patients with a Partin table–defined risk of pN+ disease of >15% (ultimately, 16% of patients received pelvic RT). The primary endpoint was PFS, defined to reflect biological progression or clinical progression (or both), death from any cause, or censoring at date of last follow-up. The initial intention-to-treat analysis focused on 742 patients with median follow-up of 5.25 yr [48]. A significant PFS benefit was seen with 6 mo of HT (5-yr PFS 80% vs 62%). The majority of patients with disease progression (83%) had a local progression event with or without biochemical progression. Grade 1–3 hot flashes were more common in patients receiving HT (46% vs <1%), as was hypertension (6% vs <1%). The rate of grade 1–3 gynecomastia was <5% in both groups. Patient-reported quality-of-life outcomes, including global quality-of-life scores, sexual activity, and sexual function scores, were similar at 5 yr in both groups, although at an intermediate time point of 1 yr, sexual activity and sexual function scores were numerically lower among patients receiving HT. Notably, quality of life was not assessed at 6 mo, which is ostensibly when the peak negative effect of HT would occur.

Two protocol-specified subgroups were selected for analysis: low risk, defined as patients with GG <4, positive margins, PSADT > 6 mo, and no T3b disease; and high risk, defined as GG 4–5, negative margins, PSADT <6 mo, and T3b disease. There was no evidence of significant heterogeneity of effect size between the two subgroups, with HR of 0.40 and 0.51 for the low-risk and high-risk groups, respectively. Post hoc subgroup analyses identified a benefit in patients with PSA ≤0.5 ng/ml and >0.5 ng/ml, but not specifically in patients with PSA ≥1 ng/ml or GG 4–5 disease (although only a minority of patients fell in the latter groups). As with the RTOG study, these subgroup analyses should be considered hypothesis-generating rather than definitive.

In contrast to the RTOG study, no differences in DM or PCSM rates were seen in the GETUG-16 study (crude incidence rates of 3.5% vs 5.1% for DM and 1% vs 2% for PCSM for HT vs no HT, respectively), probably because of the short follow-up. Overall, the GETUG-16 trial enrolled a patient population with significantly

lower risk than the RTOG 9601 trial, as evidenced by the median pre-SRT PSA and inclusion of patients with PSA persistence in the RTOG study. In addition, clinical outcome differences may only appear after longer follow-up. Notably, the RTOG trial had identified a DM-free survival benefit at median follow-up of 7.1 yr [50]. It has also been noted that the kinetics of testosterone recovery alone may explain the difference in PFS seen in the GETUG-16 trial, particularly when outcomes were defined using time from randomization and the majority of events are presumed to be from biochemical progression [51]. Therefore, the updated results for the GETUG-16 trial, which are likely to be reported within a year, are eagerly anticipated.

3.2.2. Review of the retrospective evidence

Numerous retrospective studies have investigated the association between HT and SRT, as summarized in Table 3. All of these studies are limited by significant selection bias, as in any retrospective setting HT is likely to have been used preferentially in patients with adverse disease characteristics.

The study with the longest follow-up was recently reported by Gandaglia et al [52] and included 525 patients (178 of whom received HT) treated across six institutions with median follow-up of 8.7 yr. The authors developed a multivariable model for DM-free survival based on verified prognostic factors and then calculated the 10-yr DM risk for each patient in both the HT and no-HT cohorts. They found that the effect of HT on the 10-yr risk of DM varied according to the model-predicted risk. Specifically, HT was only associated with a significant benefit in patients with pT3b/4 and GG ≥4 or pT3b/4 and PSA ≥0.4 ng/ml. The SRT dose was also associated with the DM risk, and it is possible that the absence of a specific benefit of HT among patients with positive margins in this study (compared to RTOG 9601) reflects inherent better control from a higher SRT dose (median 66 Gy). In the setting of escalated SRT doses, the benefit of HT may be predominantly related to systemic control. In addition, the aforementioned multi-institutional study by Tendulkar et al [28] reported a significant DM benefit for concurrent HT (HR 1.41 for omission of HT).

Notably, two other large retrospectives studies investigating concurrent HT did not reveal a statistically significant DM benefit. A recent multi-institutional study by Ramey et al [35] included 1861 SRT patients (267 patients with HT) and found only a trend towards statistical significance (p = 0.09) for the association between HT use and DM outcomes, despite a BCR-free survival benefit. A prior report from the University of Michigan, which included 680 patients receiving postoperative RT (including adjuvant RT, with 144 receiving HT), also found no significant association between HT and DM outcomes, although longer HT durations were associated with better DM outcomes among patients receiving HT [53]. Of note, 67% of patients treated with HT had at least one particularly high-risk feature (GG 4–5, pT3b, or pre-RT PSA ≥1 ng/ml) compared to only 48% of patients not receiving HT. Of the studies designed to examine BCR outcomes, those with subset analyses similarly found HT to be most beneficial in the subset of patients with higher-risk features (Table 2). The large retrospective series by Stish et al [29] from the Mayo Clinic (discussed above in the context of the pre-SRT PSA level) included 180 patients treated with HT. Despite the long follow-up and an improvement in BCR outcomes, HT was not significantly associated with improved DM. The study cohort may have had less enrichment of patients with negative margins and/or high-GG tumors when compared to the studies showing a DM benefit. Alternatively, if the benefit of HT stems mainly from augmenting local control, then the high median SRT dose in this study of 68 Gy may explain the relative lack of benefit from HT.

Thus far, retrospective studies have not reported evidence of a PCSM benefit from the use of HT [53]. A large study of men with recurrent PCa managed at Johns Hopkins University included 238 men who received SRT (78 with HT) with median follow-up of 6 yr. Men receiving concurrent HT were more likely to have GG 4–5 disease, higher pathologic T stage, negative margins, and shorter PSADTs. Despite this, PCSM outcomes were no different (crude rates of 11.3% and 11.5% without and with HT, respectively), while the rate of DM was lower (27.2% vs 19.5%).

Finally, PSADT following BCR may be an important factor with regard to the use of HT with SRT. As briefly mentioned in the context of pre-SRT PSA, PSADT is associated with poor prognosis following RP and SRT [14–18]. In general, patients with shorter PSADTs are likely to have more aggressive disease (whether local or systemic), and in fact SRT may be more likely to provide a PCSM benefit in patients with shorter PSADTs, even if the overall prognosis for such patients is inferior to that for men with longer PSADTs [6]. Whether HT has a differential benefit according to PSADT is unknown, but PSADT is considered a high-risk feature for enrollment in the FORMULA-509 trial and is a stratification factor for the SALV-ENZA trial (Table 4).

3.2.3. Synthesis and recommendations

Concurrent HT with SRT has not been consistently linked to better survival outcomes aside from the RTOG 9601 trial. While that study does provide high-level evidence to support the use of concurrent HT, the median pre-SRT PSA among patients enrolled in that study was significantly higher than what might be encountered among patients presenting for SRT under an "early SRT" paradigm (ie, with pre-SRT PSA <0.5 ng/ml). However, although subgroup analyses from that trial do suggest a potential interaction between PSA level and the benefit of HT, those analyses should be regarded as hypothesis-generating rather than conclusive. While the GETUG-16 trial did identify a PFS benefit in a population with a lower median pre-SRT PSA, this benefit largely stemmed from biochemical events given the relatively short follow-up. Thus, the role of HT in the setting of early SRT remains an open question, and this constitutes an area in which further research is sorely needed. Until definitive conclusions are available, we suggest that physicians consider enrolling patients in open clinical trials. If clinical trials are not an option, we recommend shared decision making with the patient, highlighting the paucity of available data and sharing the conclusions that can be gleaned from all of the evidence, including the hypothesis-generating subgroup analyses and retrospective data. As with discussing the benefits and risks of treating at a lower pre-SRT PSA level, the decision ultimately rests on the patient's desire to maximize oncologic benefit versus minimizing the risk of overtreatment.

With those caveats, the retrospective data along with the subgroup analyses of RTOG 9601 suggest that the clinical benefit of concurrent HT may be greatest in patients with a higher a priori risk of SRT failure. Adverse risk factors include elevated pre-SRT PSA, GG 4–5

disease, and negative margin status. The aforementioned RTOG 9601subgroup analysis provocatively suggests that the survival benefit conferred by HT may be reserved for patients with pre-SRT PSA >0.7 ng/ml. In addition, retrospective data have thus far not consistently identified a clinical benefit (ie, DM or PCSM) from HT use, whereas nearly all retrospective studies with sufficient follow-up have identified a benefit from early SRT for these outcomes. However, the subgroup analysis must be regarding as hypothesis-generating rather than conclusive, and the available retrospective data focusing on HT use are likely to have been subject to selection bias, wherein the patient populations receiving HT were enriched for adverse risk features. Nonetheless, we believe it is reasonable to discuss with patients that concurrent HT may be of relatively lower added value for men with pre-SRT PSA <0.5 ng/ml. We suggest that in shared decision-making with the patient, physicians should highlight that this is an area ripe for further investigation.

It has been shown in the RTOG 9601 trial and in multiple retrospective series that high-GG lesions benefit from HT. While GETUG-16 did not show a benefit in this group, that subgroup analysis was underpowered and central pathology was not performed. Therefore, concurrent HT should be strongly considered in patients with GG 4–5 disease. The influence of margin status is unclear. RTOG 9601 did show a robust benefit from HT among patients with positive margins, but historically, negative margins have been considered to portend a higher risk of adverse outcomes following SRT, and the overall interaction test for a significant differential effect of benefit based on margin status was negative. It is possible that HT enhances local control (with the SRT dose of 64.8 Gy otherwise less likely to control residual disease) and/or that the negative margin subgroup in RTOG 9601 study was simply too small to observe a significant difference. GETUG-16 identified an adverse prognostic significance for negative margins, but did not specifically analyze the effect of margin status on the benefit of HT. We therefore recommend concurrent HT in patients with GG 4–5 disease and suggest that margin status is not necessarily an independent factor to influence decisions on the use of concurrent HT.

Finally, the prolonged timeframe needed to identify the survival benefit in RTOG 9601, despite the baseline high risk in the patient population, underscores the need to personalize decisions regarding the benefit of HT, with careful consideration of the patient's age and other comorbidities. Patients with life expectancy of <13 yr (the median follow-up in RTOG 9601) may not live to see the survival benefit of HT and could be spared its morbidity.

Overall, these recommendations are largely in accordance with a framework recently reported by Spratt et al [51]. It should be noted that the optimal HT duration is not clear; thus far, only retrospective data are available, and these do suggest a benefit of longer-term HT. Once more, these data are influenced by selection bias, as patients receiving longer-term HT were more likely to have other adverse prognostic features. The ongoing RADICALS trial on RT and androgen deprivation therapy for patients who have undergone surgery for PCa will randomize patients receiving either adjuvant RT or SRT to receiving no HT, 6 mo of HT, or 24 mo of HT (Table 4), and will provide prospective evidence regarding the optimal HT duration. Several other trials are investigating the additional benefit of other systemic agents in addition to conventional HT with SRT (Table 4).

The interplay between SRT dose and target volumes and the role of HT has not been rigorously evaluated, and a detailed analysis is beyond the scope of this review. In the definitive setting, multiple randomized trials have demonstrated a clear biochemical benefit of dose-escalated RT, but none have shown a survival benefit; in contrast, multiple randomized trials have shown a survival benefit of HT [38]. It is unclear whether this is related to a greater relative benefit of HT than dose escalation or a mixed effect of HT on both local and distant disease. Regardless, the benefit of HT in the context of dose-escalated SRT is likely to be more modest than the benefit with lower SRT doses, as any benefit for local control would be less profound. Regarding radiation volume, only a minority of patients in the GETUG-16 trial received pelvic RT, and no patient in RTOG 9601 received this. The available retrospective data suggest a synergistic rather than a redundant role for pelvic RT [35]. The ongoing RTOG 0534 trial on short-term androgen deprivation with pelvic lymph node or prostate bed–only RT will provide prospective data to guide field design.

4. Conclusions

Nearly half of patients who ultimately die of PCa initially presented with curative disease and underwent local therapy. Thus, optimizing the management of patients who have recurrent disease is critical to ultimately improve PCSM outcomes. SRT constitutes the only known curative intervention following post-RP BCR, but it is widely appreciated that outcomes following SRT can be quite variable. Established nomograms can assist greatly in risk stratification based on readily available clinicopathologic data. Only retrospective data are available regarding the interplay of pre-SRT PSA and SRT outcomes. However, data from prospective, randomized studies are available to guide the use of HT with SRT, but the most mature data pertain to a population with median pre-SRT PSA of 0.5 ng/ml (ie, whereby many patients were treated with late SRT). Given the uncertainties, we underscore that this is an area ripe for future research and strongly suggest that when clinical trials are not an option, physicians should participate in shared decision-making with patients in which they disclose the imperfect nature of the available information. With these caveats in mind, we note that the preponderance of data suggests that delivering SRT at low PSA values (ie, early SRT) is associated with better outcomes in most groups, although the absolute benefit may be more limited in patients with an overall low risk of adverse outcomes. Similarly, we suggest that the greatest benefit of concurrent HT is likely to be for patients with a higher baseline risk of treatment failure, and particularly those who are undergoing pre-SRT at higher PSA values (ie, late SRT). Certain high-risk groups, such as those with GG 4–5 disease, may still benefit from concurrent HT at lower PSA values. An exciting area of future research involves the use of genomic tools, such as the 22-gene Decipher genomic classifier, to better predict outcomes in patients who have undergone RP [54,55]. The PAM50 classifier [56] and the PORTOS signature [57] are emerging tools that may serve as predictive biomarkers for response to HT and SRT, respectively. As these tools are being validated and more prospective data are gathered, our recommendation is to highlight the importance of early SRT and the judicious use of concurrent HT, with an emphasis on shared decision-making and the relative importance of maximizing oncologic benefit and minimizing overtreatment.

Table 1 – Timing of SRT and the importance of pre-SRT PSA: a retrospective synthesis

Reference	Patients (*n*)	Primary outcome	Median FU (yr)	Patient risk profile	Median RD (Gy)	Median HTD (mo)	Conclusions
European multi-institutional study [30]	925 (30% with HT)	DM	8	Median PSA: 0.3 ng/ml GG ≥4: 24% pT3b/4: 33% NMs: 56% 24% with persistent PSA elevation	68 (no WPRT)		pre-SRT PSA significantly associated with DM (HR 1.06 per 0.1 ng/ml) and remained significant in three risk categories: Low-risk: GG 3 and ≥pT3b Intermediate-risk: GG 4 High-risk: PSA persistence with GG 1–3
Mayo Clinic [29]	1106 (180 with HT)	BCR DM PCSM ACM	8.9	Median PSA: 0.6 ng/ml GG ≥4: 16.2% pT3b/4: 16% NMs: 48.7%	68 (WPRT 4%)	60% ≤12 40% >12	HT associated with lower BCR risk (HR 0.59for ≤12 mo and 0.26 for >12 mo), but not associated with DM or mortality Pre-SRT PSA (continuous) was associated with BCR; each pre-SRT PSA doubling associated with 32% increase in DM risk, 40% increase in PCSM risk, and 12% increased in ACM risk These relationships held true for pre-SRT PSA as a dichotomous variable (>0.5 vs ≤0.5 ng/ml)
US multi-institutional study [14,28]	2460 (390 with HT)	BCR DM	5	Median PSA: 0.5 ng/ml GG ≥4: 19% pT3b/4: 18% NMs: 40%	66 (WPRT 17%)	6	HT significantly reduced the risk of BCR and DM (HR 1.85 and 1.41) Freedom from BCR decreased with increasing PSA 0.01–0.2 ng/ml: 71% 0.21–0.5 ng/ml: 63% 0.5–1.0 ng/ml: 54% 1.0–2.0 ng/ml: 43% >2.0 ng/ml: 37% DM rate increased with PSA 0.01–0.2 ng/ml: 9% 0.21–0.5 ng/ml: 15% 0.5–1.0 ng/ml: 19% 1.0–2.0 ng/ml: 20% >2.0 ng/ml: 37% Freedom from BCR and DM significantly associated with increasing pre-SRT PSA (HR 1.88 BCR, 2.23 DM)
University of Texas Southwestern and University of Michigan [32]	657 (154 with HT)	BCR DM PCSM ACM	9.8	Median PSA: 0.4 ng/ml GG ≥4: 28% pT3b/4: NR NMs: 39%	68.4 WPRT NR)	6	HT significantly reduced the risk of BCR (HR 0.63) SRT at PSA 0.2–0.5 vs ≤0.2 ng/ml was associated with higher risk of BCR (HR 1.97) and DM (HR 1.95) SRT at PSA >0.5 vs ≤0.2 ng/ml was associated with higher risk of BCR (HR 3.48), DM (HR 4.45), and PCSM (HR 4.07)
European multi-institutional study [31]	716 (0 with HT)	BCR	4.75	Median PSA: 0.2 ng/ml (all <0.5 ng/ml) GG ≥4: 14% pT3b/4: 15% NMs: 46%	66 (no WPRT)		pre-SRT PSA was significantly associated with BCR (HR 4.89), but only among patients with ≥2 risk factors (pT3b–4, GG ≥4,NMs) In the high-risk group, BCR increased by 10% per 0.1 ng/ml increase in PSA, compared to 1.5% in the lower-risk group
Sydney [58]	189 (62 with HT)	BCR	4.17	Median PSA: 46% <0.2, 37.8% 0.2–1 ng/ml GG ≥4: 23.9% pT3b/4: 22.8% NMs: 39.7%	69.8 (WPRT NR)		Rates of 5-yr BCR varied by pre-SRT PSA <0.2 ng/ml: 28.3% ≥0.2 to <1.0 ng/ml: 44.3% ≥1.0 ng/ml: 73.7% Compared to PSA <0.2 ng/ml, BCR was significantly more common for PSA ≥0.2 to <1.0 (HR 1.73) and >1.0 ng/ml (HR 3.1)
University of Tokyo [59]	76 (12 with HT)	BCR	5.833	Median PSA: 26% <0.2, 53% 0.2–0.5, 21% >0.5 ng/ml GG ≥4: 20% pT3b/4: 5% NMs: 39.7%	Median NR, most 66 Gy (WPRT NR)		pre-SRT PSA <0.2 ng/ml was significantly associated with lower BCR than SRT at PSA ≥0.2 ng/ml; however, this may have been driven by comparing PSA <0.2 vs. >0.5 ng/ml, and not PSA 0.2–0.5 ng/ml
Charité Universitäts-medizin [60]	301 (0 with HT)	BCR	2.5	Median PSA: 0.28 ng/ml GG ≥4: NR pT3b/4: 17.9% NMs: 33.2%	Median NR, most 66.6 Gy (WPRT 0%)		Higher pre-SRT PSA (dichotomized as >0.28 vs ≤0.28 ng/ml) was significantly associated with higher BCR (OR 2.771) 2-yr BCR 22% for pre-SRT PSA ≤0.28 ng/ml vs 39% for >0.28 ng/ml
French multi-institutional study [61]	201 (0 with HT)	"Treatment failure"	3.691	Median PSA: 0.48 ng/ml GG ≥4: 14.9% pT3b/4: 21.4% NMs: 32.3%	NR		Higher pre-SRT PSA associated with higher risk of treatment failure (HR 1.8 for >0.5 vs ≤0.5 ng/ml; HR 3.44 for >1 vs ≤0.5 ng/ml)
Aichi Cancer Center Hospital [62]	51 (6 with HT)	BCR	3	Median PSA: 0.25 ng/ml GG ≥4: 37% pT3b/4: 10% NMs: 37%	60 (no WPRT)	8	Pre-SRT PSA was not predictive of BCR (when analyzed as <0.25 vs ≥0.25 ng/ml)
Karolinska [63]	184 (165 with HT)	BCR DM	4	Median PSA: 0.47 ng/ml GG ≥4: 16%	70 (no WPRT)	3	Pre-SRT PSA was a predictor of higher BCR (OR 5.48) but not DM

New York Harbor Veteran Affairs [64]	54	BCR DM	5.92	Median PSA: 0.45 ng/ml GG ≥4: 9% pT3b/4: 20% NMs: 35%	70.2 (WPRT 6%)	pre-SRT PSA >0.4 ng/ml was significantly associated with worse BCR (HR 6.4)
Memorial Sloan Kettering Cancer Center [65,66]	285 (87 with HT)	BCR	5	Median PSA: 0.4 ng/ml GG ≥4: 24% pT3b/4: 34% NMs: 54%	≥66 for95% (WPRT 7%)	Both pre-SRT PSA >0.4 ng/ml and HT omission were significantly associated with worse BCR (HR 1.64 and 1.46) Nearly all local failures were in patients with pre-SRT PSA >0.4 ng/ml
Virginia Commonwealth University/Duke/ Hunter Holmes McGuire Veteran Affairs [67]	197 (0 with HT)	BCR	4.33	Median PSA: 0.33 ng/ml GG ≥4: 25% pT3b/4*:10% NMs: 34%	66 (WPRT 52%)	Higher pre-SRT PSA was significantly associated with BCR (HR 1.87) With GG ≥4, 5-yr BCR was 23% vs 74% for SRT initiated at PSA ≤0.33 vs. >0.33 ng/ml There was no significant difference in BCR for GG 1–3 lesions

ACM = all-cause mortality; BCR = biochemical recurrence; DM = distant metastasis; FU = follow-up; GG = Gleason grade group; HR = hazard ratio; HT = hormonal therapy; HTD = HT duration; NMs = negative margins; NR = not reported; PCSM = prostate cancer–specific mortality; PSA = prostate-specific antigen; OR = odds ratio; RD = radiation dose; SRT = salvage radiotherapy; WPRT = whole-pelvis radiotherapy.

Table 2 – Concurrent androgen deprivation therapy: comparison of the RTOG 96-01 and GETUG-AFU 16 trials

Trial design	RTOG 96-01 [47]	GETUG-AFU-16 [48]
Patients eligible for analysis (*n*)	760	742
Follow-up (yr)	13	5.25
Years active	1998–2003	2006–2010
Inclusion criteria	pT2 with positive margins or pT3 pN0 PSA 0.2–4.0 ng/ml at least 8 wk after RP (originally, the lower limit was 0.5, then decreased over time to 0.2 ng/ml)	pT2, pT3, pT4a (bladder neck) pN0 or pNx PSA <0.1 ng/ml following surgery for 6 mo Consecutive PSA rises to 0.2–2 ng/ml
Treatment arms	RT + 24 mo of bicalutamide vs RT alone	RT + 6 mo of goserelin acetate vs RT alone
RT parameters		
Dose (Gy)	64.8	66
Fields/volumes	No nodal radiation	16% received pelvic RT to 46 Gy (for Partin table risk of pN+ >15%) for pT3b, received 50 Gy to SV remnant
Patient characteristics		
PSA	Median 0.6 ng/ml (46.7% ≥0.7) <0.7 ng/ml: 53.3% 0.7–1.5 ng/ml: 31.2% >1.5–4.0 ng/ml: 15.5%	Median 0.3 ng/ml (75% 0.2–0.5) 0.2–0.3 ng/ml: 50% 0.2–0.5 ng/ml: 75% >1.0 ng/ml: 10%
Pathologic stage	pT3: 67.4%	pT3a: 33.4% PT3b/4: 12.7%
Gleason grade group	GG 1–3: 82.7% GG 4–5: 17.3%	GG 1–3: 89.1% GG 4–5: 10.9%
Negative margins (%)	25.1	50
PSADT <6 mo (%)	Not reported	26.5
Results		
Primary endpoint	OS	PFS (clinical or biochemical progression included)
Conclusions	12-yr OS: 76.3% vs 71.3%	5-yr PFS: 80% vs 62%; overall HR 0.5
Subgroup analyses	12-yr PCSM: 5.8% vs. 13.4% (HR 0.49) 12-yr DM: 14.5% vs 23.0% (HR 0.63) 12-yr BCR: 44.0% vs. 67.9% (HR 0.48) HT improved 12-yr OS in: • GG 2–3 (HR 0.69) but not GG 1 or 4–5 • PSA >1.5 (HR 0.45) and 0.7–1.5 (HR 0.61) but not <0.7 ng/ml • Positive margins (HR 0.73) but not negative margins HT improved 12-yr DM in: • GG 4–5 (HR 0.35) but not GG 1–3 • PSA >1.5 (HR 0.36) but not ≤1.5 ng/ml • Positive margins (HR 0.56) but not negative margins	5-yr OS: 96% vs 95% PCSM: 1% vs 2% Metastatic or local progression with BCR: 4% vs 7% HT improved PFS in: • Low-risk [a] and high-risk group (HR 0.4 and 0.51) • PSA ≤0.5 and >0.5 ng/ml (HR 0.55 and 0.32) • PSA ≤1 (HR 0.5) but not >1 ng/ml • PSADT >6 mo and ≤6 mo (HR 0.42 and 0.53)

BCR = biochemical recurrence; DM = distant metastasis; GG = Gleason grade group; HR= hazard ratio; HT = hormonal therapy; OS = overall survival; PCSM = prostate cancer-specific mortality; PFS = progression-free survival; PSA = prostate-specific antigen; PSADT = PSA doubling time; RT = radiotherapy; SV = seminal vesicle; WPRT = whole-pelvis RT.
[a] Low risk: GG 1–3, positive margins, PSADT >6 mo, no SV invasion.

Table 3 – Concurrent hormonal therapy: a retrospective synthesis

Reference	Patients (*n*)	Primary outcome	Median FU (yr)	Patient risk profile	Median RT dose (Gy)	Median HTD (mo)	Conclusions
European multi-institutional study [52]	525 (178 HT)	DM	8.67	Median PSA: 0.42 ng/ml GG ≥4: 15% pT3b/4: 9% NMs: 58%	66 (WPRT in 21%)	15	HT was beneficial only in men with pT3b/4 and GG ≥4 or pT3b/4 and PSA ≥0.4 ng/ml
US multi-institutional study [35]	1861 (267 HT)	BCR DM	4.58	Median PSA: 0.5 ng/ml GG ≥4: 25% pT3b/4: 21% [a] NMs: 59%	66 (WPRT in 8.7–11.9%)	6	HT was beneficial on multivariate analysis, independent of WPRT (HR 1.70 for no HT vs HT; 5-yr BCR-free survival of 50% vs 55%). There was a trend towards a DM benefit (HR 1.36; p = 0.09) Increasing pre-SRT PSA associated with increasing HR for BCR: ≤0.2 ng/ml: 0.28 0.21–0.5 ng/ml: 0.43 0.51–1.0 ng/ml: 0.61 >1.0–2.0 ng/ml: 0.86 (with reference to >2.0 ng/ml) Increasing pre-SRT PSA associated with increasing HR for DM: ≤0.2 ng/ml: 0.20 0.21–0.5 ng/ml: 0.33 0.51–1.0 ng/ml: 0.50 >1.0–2.0 ng/ml: 0.69 (p = 0.07) (with reference to >2.0 ng/ml)
Dana-Farber Cancer Institute [68]	108 (43 HT)	BCR	5.275	Median PSA: 0.24 ng/ml GG ≥4: 26.9% pT3b/4: 23.1% NMs: 44.1%	66 (WPRT not reported)	6	HT was associated with better BCR (HR 0.44), but this was only significant for patients with NMs (HR 0.27) Increasing pre-SRT PSA was significantly associated with BCR (HR 20.99)
University of Michigan [53,69]	680 [a] (144 HT)	BCR DM	4.75	Median PSA: 0.5 ng/ml no HT, 0.9 ng/ml HT GG ≥4: 23.3% pT3b/4: 20.1% NMs: 56%	68.4 (WPRT in 15-27%)	11.9	On univariate analysis, HT was significantly associated with better BCR (HR 0.74), but not DM Among patients receiving HT, HTD <12 mo was associated with better BCR (HR 2.27) and DM (HR 2.48) vs HDT ≥12 mo Following propensity score matching, the HTD-dependent improvement in BCR (HR 0.39) and DM (HR 0.21) remained significant. When analyzed as a continuous variable, HTD (mo) was significantly associated with better DM (HR 0.88) and PCSM (HR 0.90) outcomes
Boramae Medical Center [70]	162 (69 with HT)	BCR DM	5	Median PSA: 0.67 ng/ml GG ≥4: 37.7% pT3b/4: 22.8% NMs: 39.9%	66 (WPRT not reported)	18	HT was significantly associated with better BCR (HR 0.264) DM-free survival was also significantly higher at 5 yr with HT (100% vs 87.3%) On subset analyses, the HT benefit for BCR and DM outcomes was restricted to patients with pT3b or PSA ≥0.6 ng/ml Pre-SRT PSA ≥0.6 ng/ml was associated with significantly better BCR (HR 3.551)
Aarhus University [71]	259 (115 with HT)	BCR	3.1	Median PSA: 47% ≥0.5 ng/ml GG ≥4: 23% pT3b/4: 4% NMs: 31%	68 (no WPRT)	15	HT was significantly associated with better BCR outcomes (HR 0.5) On subset analysis, HT was only correlated with BCR-free survival for pre-SRT PSA >0.2 ng/ml Pre-SRT PSA ≤0.5 ng/ml was associated with better BCR (HR 0.48)
Bundang Hospital [72]	212 (124 with HT)	BCR	5.29	Median PSA: 44.3% >0.5 ng/ml GG ≥4: 42% pT3b/4: 42.5% NMs: 31.6%	66 (WRPT in 25%)	15	Omitting HT was associated with significantly higher BCR risk (HR 2.00) both overall and among patients with pre-SRT PSA ≤0.5 ng/ml (HR 2.611) Pre-SRT PSA >0.5 ng/ml was significantly associated with higher risk of BCR (HR 3.012)
University of Pennsylvania [73]	191 (62 with HT)	BCR	5.4	Median PSA: 0.6 ng/ml no HT, 0.5 ng/ml HT GG ≥4: 21.5% pT3b/4: 23.0% NMs: 50.2%	66 (WPRT in 16.2%)	11	HT was associated with significantly higher 10-yr BCR-free survival (54.2% vs 28.5%) On multivariate analysis, this association was only a trend (p = 0.052).

City of Hope [74]	313 [a] (122 with HT)	BCR DM	4.58	Median PSA: 0.3 ng/ml GG ≥4: 22.0% pT3b/4: 24.0% NMs: 47.0%	67 (WPRT in 87%)	9	HT for >6 mo was associated with better BCR vs no HT (HR 0.39 for 6-12 mo vs none, and 0.49 for >12 mo vs none) Pre-SRT PSA 0.2–1. ng/ml0 and PSA >1.0 ng/ml associated with higher BCR risk (HR 2.2 and 9.2) Neither HT nor pre-SRT PSA was associated with DM outcomes
Ghent [75]	136 (97 with HT)	BCR Clinical recurrence	5	Median PSA: 38% <0.5 37% >1 ng/ml GG ≥4: 17% pT3b/4: 22.0% NMs: 48%	76 (no WPRT)	6	HT significantly decreased the risk of BCR (HR 0.33) Clinical recurrence-free survival was not affected by HT
Johns Hopkins University [6]	238 (78 with HT)	PCSM DM	6	Median PSA: 0.7 ng/ml without HT, 0.9 ng/ml with HT GG ≥4: 20.1% pT3b/4: 13.9% NMs: 58.8%	66.5–67.2 (100% WPRT)		HT did not significantly alter the impact of SRT on PCSM (analyzing the latter relationship was the primary objective of the study) Crude DM incidence rate numerically lower for HT (27.2% vs. 19.5%) but not explicitly compared
MD Anderson Cancer Center [76]	101 (59 with HT)	BCR	4.175	Median PSA: 0.4 ng/ml without HT, 1.1 ng/ml with HT GG ≥4: 26.7% pT3b/4: 24.8% NMs: 38.6%	70 (small WPRT fields used)	19.8	HT significantly improved BCR in all patients except those considered low risk (PSA <0.5 ng/ml and positive margins) Lower pre-SRT PSA significantly associated with BCR (HR 1.19)
Stanford [77,78]	122 (53 with HT)	BCR	5.9	Median PSA: 1.55 ng/ml without HT, 0.3 ng/ml with HT GG ≥4: 27.8% pT3b/4: 4% NMs: 34.4%	64.2–67 (42% WPRT)	4	Omission of HT associated with significantly greater BCR (HR 2.81)

BCR = biochemical recurrence; DM = distant metastasis; FU = follow-up; GG = Gleason grade group; HR = hazard ratio; HT = hormonal therapy; HTD = HT duration; NMs = negative margins; PCSM = prostate cancer–specific mortality; PSA = prostate-specific antigen; SRT = salvage radiotherapy; WPRT = whole-pelvis radiotherapy.

[a] Included additional patients receiving adjuvant radiotherapy.

Table 4 – Ongoing randomized trials: concurrent androgen deprivation therapy with salvage radiotherapy

Trial	NCT link	Inclusion criteria and arms	Primary endpoint	RT notes
RTOG 0534	https://clinicaltrials.gov/ct2/show/NCT00567580	pT2–3N0 GG ≤9 Postoperative PSA ≥0.1 and <2.0 ng/ml Randomization: no HT, prostate bed alone vs prostate bed + HT vs prostate bed + WPRT + HT	Freedom from progression (biochemical, local, regional, distant)	64.8–70.2 Gy in 36–39 fractions WPRT dose 45 Gy HT 4–6 mo
MRC RADICALS-HD	https://clinicaltrials.gov/ct2/show/NCT00541047	Subrandomization of MRC RADICALS-RT Randomization: no HT, 6 mo of HT, or 24 mo of HT	Freedom from metastasis	66 Gy in 33 fractions 52.5 Gy in 20 fractions WPRT at discretion of physician
EORTC 22043-30031 [a]	https://clinicaltrials.gov/ct2/show/NCT00949962	pT2 with positive margins, or pT3 with or without positive margins Undetectable postoperative PSA Allows either adjuvant or early SRT (criteria not specified) [a] Randomization: no HT or 6 mo of HT	BCR-free survival	64 Gy in 32 fractions WPRT not permitted
SALV-ENZA	https://clinicaltrials.gov/ct2/show/NCT02203695	Randomization: no HT or 6 mo of HT (enzalutamide)	PSA PFS	66.6–70.2 Gy in 37–39 fractions
FORMULA-509	https://clinicaltrials.gov/ct2/show/NCT03141671	PSA ≥0.1 ng/ml after RP (within 3 mo of registration) AND at least 1 unfavorable risk factor listed below. • GG ≥4 • PSA >0.5 ng/ml • Pathologically positive lymph nodes • pT3 • PSA doubling time <10 mo • Negative margins • Post-RP PSA nadir ≥0.1 ng/ml • Local/regional recurrence on imaging • Decipher "high risk" Randomization: 6 mo HT (GnRH agonist + bicalutamide) vs 6 mo GnRH agonist + apalutamide + abiraterone)	PSA PFS	66.6–70.2Gy in 37–39 fractions WPRT at discretion of physician
NRG GU-002	https://clinicaltrials.gov/ct2/show/NCT03070886	GG ≥2 AND post-RP PSA nadir ≥0.2 ng/ml Randomization: SRT + HT vs SRT + HT + docetaxel	Phase 2: freedom from progression (biochemical, local, regional, distant) Phase 3: metastasis-free survival	

BCR = biochemical recurrence; DM = distant metastasis; GG = Gleason grade group; GnRH = gonadotropin-releasing hormone; HT = hormonal therapy; PFS = progression-free survival; PSA = prostate-specific antigen; RP = radical prostatectomy; WPRT = whole-pelvis radiotherapy.
[a] Terminated because of poor accrual.

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Acquisition of data: Kishan, Carrie.
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Satisfaction with Care Among Men with Localised Prostate Cancer: A Nationwide Population-based Study

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Abstract

Background: Information about how men with prostate cancer (PC) experience their medical care and factors associated with their overall satisfaction with care (OSC) is limited.

Objective: To investigate OSC and factors associated with OSC among men with low-risk PC.

Design, setting, and participants: Men registered in the National Prostate Cancer Register of Sweden as diagnosed in 2008 with low-risk PC at the age of ≤70 yr who had undergone radical prostatectomy (RP), radiotherapy (RT), or started on active surveillance (AS) were invited in 2015 to participate in this nationwide population-based survey (n = 1720).

Outcome measurements and statistical analysis: OSC data were analysed using ordinal logistic regression. Odds ratios (ORs) were calculated for comparisons between the highest and lowest possible response categories.

Results and limitations: A total of 1288 men (74.9%) responded. High OSC was reported by 958 (74.4%). Factors associated with high OSC were high participation in decision-making (OR 4.18, 95% confidence interval [CI] 2.61–6.69), receiving more information (OR 11.1, 95% CI 7.97–15.6), high-quality information (OR 7.85, 95% CI 5.46–11.3), access to a nurse navigator (OR 1.80, 95% CI 1.44–2.26), and better functional outcomes (defined as 25 points higher on the EPIC-26 questionnaire; OR 1.34, 95% CI 1.21–1.48). OSC was not affected by whether a doctor or specialist nurse conducted follow-up (OR 0.84, 95% CI 0.66–1.07). These findings were similar across treatment groups. Men who had undergone RP or RT reported high OSC more often than men on AS (78.2% vs 84.0% vs 72.6%), high participation in decision-making (70.5% vs 64.5% vs 49.2%), and having received more information (40.5% vs 45.8% vs 28.6%), and were less likely to believe they would die from PC (3.8% vs 3.9% vs 8.0%). Limitations include the nonrandomised retrospective design and potential recall bias.

Conclusions: Information and participation in decision-making, as well as access to a nurse navigator, are key factors for OSC, regardless of treatment. Men on AS need more information about their treatment and need to participate more in decision-making. OSC was as high among men who had nurse-led follow-up as among men who had doctor-led follow-up.

Patient summary: Information about how men with low-risk prostate cancer experience their medical care is limited. In this nationwide population-based study we found that information and participation in decision-making as well as access to a nurse navigator are key factors for satisfaction regardless of treatment. Men who are being closely watched for prostate cancer without immediate curative treatment need more information than they now receive and need to participate more in decision-making than they currently do.

1. Introduction

Earlier detection and advances in cancer treatment have dramatically prolonged the lifespan of cancer patients, resulting in longer relations with caregivers. Overall satisfaction with health care (OSC) is considered an important indicator of the quality of care [1,2], and information and support given by health care professionals during the course of an illness are believed to play a key role in patient well-being [3,4]. As a consequence, evaluation of patients' health care experiences is gaining interest from researchers and health care providers. Patient-reported experience measures are used to improve the quality of care, while patient-reported outcome measures investigate the functional outcomes of treatments and quality of life [5].

Men with localised prostate cancer (PC) usually have several treatment options, including radical prostatectomy (RP), radiotherapy (RT), and active surveillance (AS). AS is the recommended management for men with low-risk PC in Sweden [6] and is gaining acceptance in other countries [7,8]. Little is known about how OSC differs between men who have had different treatments and whether there are any specific areas that need attention to improve OSC. We could not find any previous studies assessing OSC in men on AS for localised PC.

We used the National Prostate Cancer Register of Sweden (NPCR) to investigate OSC among men with low-risk PC who have undergone RP or RT or started on AS, and explored potential explanatory factors for their satisfaction.

2. Patients and methods

2.1. Study design and participants

In February 2015, we identified all men registered in the NPCR diagnosed in 2008 with low-risk PC at the age of ≤70 yr who had undergone RP or RT or started on AS and were still alive in 2015. The NPCR has a capture rate of >96% [9]. Low-risk disease was defined as Gleason score ≤6, prostate-specific antigen (PSA) <10 ng/ml, and clinical stage T1 or T2. In all, 1720 men were invited to participate in the study via a letter, in which we presented the study and its purpose. The letter included a questionnaire that combined study-specific questions, the Expanded Prostate Cancer Index Composite 26-item short-form version (EPIC-26), and an addressed and stamped envelope. The participants could also fill out the questionnaire online by using an individual code. Men who failed to return the questionnaire were contacted by a research assistant via telephone and were sent a second questionnaire.

The Regional Ethical Review Board at Uppsala University approved the study.

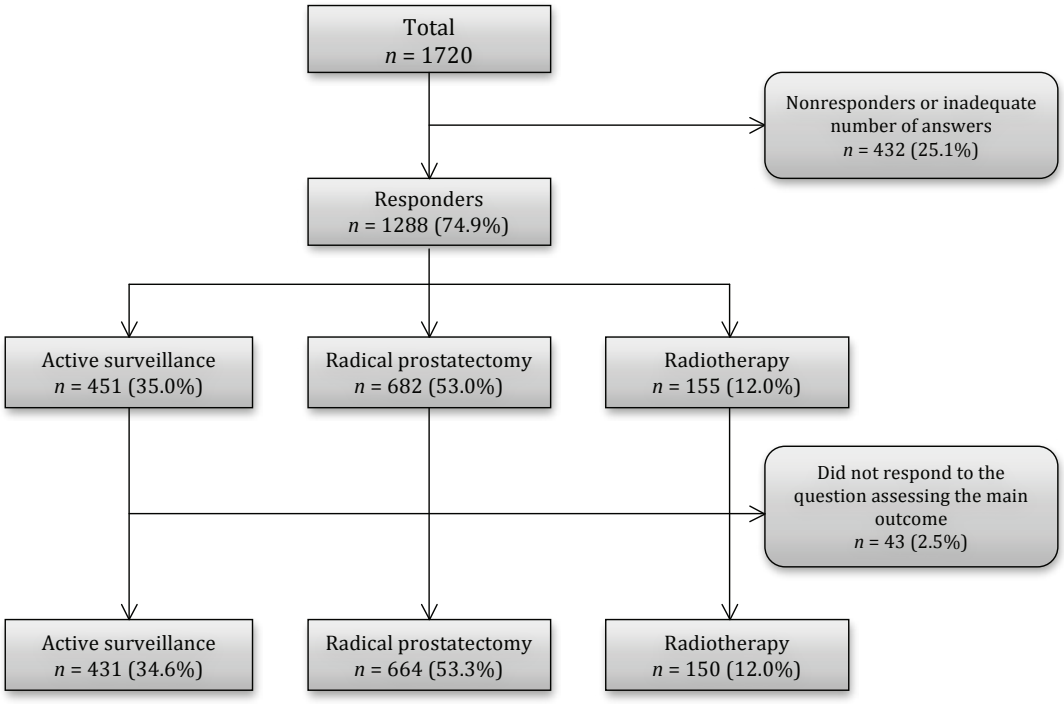
2.2. Questionnaire design

The questionnaire consisted of EPIC-26 and 49 study-specific questions. EPIC-26 is an instrument designed to assess pelvic organ function and bother after PC treatment. Results are presented for each domain as a median score on a scale from 0 to 100, where 100 is the most favourable outcome [10]. The study-specific questions were developed after interviews with men living with PC, and were tested for face validity with one investigator accompanying the men while they completed the questionnaire. Questions not fully understood as intended were changed to achieve clarity. The questionnaire was further validated in an unpublished pilot study. Our technique for developing a study-specific questionnaire is based on a one-concept–one-question method producing self-reported outcomes and has been previously described [11–13]. The questionnaire explored mental symptoms (anxiety, depressed mood, sense of well-being), quality of life, and OSC on a seven-point visual digital scale, with seven representing the best possible quality of life, the best possible health care, and being depressed all the time, respectively (Supplementary material). OSC was assessed using the following question: "How satisfied are you as a prostate cancer patient with your health care". The study-specific questionnaire also assessed experiences at the time of diagnosis and at follow-up, sociodemographics, smoking, alcohol consumption, physical activity, treatments, concurrent diseases (which were converted into a Charlson comorbidity index score [14]), and psychiatric comorbidity, which was obtained by asking the men if they suffered from depression and/or any other mental illness.

2.3. Data collection, analysis, and statistics

To assess long-term outcomes, data were collected 7 yr after PC diagnosis, between February and October 2015. The response rate is shown in Figure 1. The answers to the questionnaires and cancer characteristics data from the NPCR were assembled in a database. Potential differences between responders and nonresponders were analysed. The responders were grouped by their initial treatment: RP, RT, or AS. Variables affecting OSC were divided into perceived quantitative variables (no, little, moderate, or much information) and more qualitative variables that were influenced by the participants' personal preference (experience of insufficient or sufficient time). Statements such as "substantial information" or "high quality information" were defined as the highest possible response to that specific question. Missing data were handled using multiple imputations based on the method of chained equations

Figure 1 Flow chart showing patient participation and treatment.



[15]. Five imputation data sets were created. The analysis of factors potentially associated with OSC was carried out using ordinal logistic regression adjusted for age, marital status, fatherhood, profession, education, Charlson comorbidity index, and psychiatric comorbidity. Odds ratios (ORs) with 95% confidence interval (CI) show the probability of advancing one step on the seven-point visual digital scale for OSC when comparing the highest versus the lowest possible response.

3. Results

3.1. Patient characteristics

In all, 1288 of the 1720 men invited (74.9%) responded. Of these, 682 (53.0%) had undergone RP, 155 (12.0%) had received RT, and 451 (35.0%) had started on AS (Table 1). The mean age at diagnosis was 63 yr (range 40–70), with small differences between the groups. The proportion of men who were retired was 72.9% in the RP group, 83.2% in the RT group, and 83.6% in the AS group. The corresponding proportion of men who had university-level education was 33.6%, 23.2%, and 28.4% in these groups. A Charlson comorbidity index of ≥2 was reported for 12.4% in the RP group, 20.1% in the RT group, and 21.1% in the AS group.

A dropout analysis showed some differences between responders and nonresponders. Compared to responders, the nonresponders were on average 1 yr younger, had lower T stage and lower PSA, were more likely to be diagnosed after PSA testing, and were more likely to be initially managed with AS (Supplementary Table 1).

3.2. Overall satisfaction with care

High OSC was reported by 958 men (74.4%) and low OSC by 28 (2.2%). An additional 43 men (2.5%) of those who returned the questionnaire did not respond to the question assessing OSC. An analysis including all responding men using imputed main outcome data for the 43 men who did not answer this question gave similar results to an analysis excluding these 43 men (data not shown). The analysis based on the men who did answer the main outcome question is presented below.

3.3. Patient characteristics associated with OSC

We found no association between age and OSC (OR 0.97, 95% CI 0.71-1.33 for men aged <60 yr vs men aged 66–70 yr; Fig. 2). Low OSC was associated with long education (OR 0.70, 95% CI 0.52–0.94, compared to short education), Charlson comorbidity index ≥2 (OR 0.61, 95% CI 0.44–0.84, compared to Charlson comorbidity index 0), and psychiatric comorbidity (OR 0.55, 95% CI 0.37–0.80). Neither being married/cohabitating (OR 0.84, 95% CI 0.62–1.13) nor having children (OR 0.77, 95% CI 0.52–1.13) significantly affected OSC.

3.4. Health care aspects associated with OSC

Of the responders, 37% had received substantial information on PC, 68.6% had received high-quality information (6 or 7 on the 7-point scale), 62.3% had participated substantially in decision-making, 45.3% of all men had a designated nurse navigator (39.0% of men who initially had AS, 50.7% of those who underwent RP, and 39.4% of men who received RT), and 27.6% had nurse led follow-up.

Having had a friend or a relative present when being notified of the cancer diagnosis (reported by 28.2%) was not significantly associated with OSC (OR 0.98, 95% CI 0.77–1.25). Receiving more information from a doctor (OR 11.1, 95% CI 7.97–15.6), higher quality of information at the time of cancer diagnosis (OR 7.85, 95% CI 5.46–11.3), and higher participation in decision-making (OR 4.18, 95% CI 2.61–6.69) were associated with higher OSC (OR represent comparisons between the highest and lowest possible responses). In addition, having a nurse navigator (OR 1.80, 95% CI 1.44–2.26) was associated with higher OSC. There was no difference in OSC depending on whether the men saw a doctor (OR 0.84, 95% CI 0.66–1.07) or a nurse (OR 1.19, 95% CI 0.96–1.48) during follow-up.

The time from diagnosis to treatment decision was reported as sufficient by 85.6%. The time from the decision to treatment initiation was reported as adequate by 79.3%. Sufficient time from diagnosis to treatment decision (OR 4.40, 95% CI 3.03–6.37) and adequate time from the treatment decision to treatment initiation (OR 2.35, 95% CI 1.87–2.94) were associated with higher OSC.

3.5. Associations between functional outcomes and OSC

The median EPIC-26 scores were 94 (range 65–100) for urinary incontinence, 88 (range 75–100) for voiding symptoms, 100 (range 88–100) for bowel function, and 32 (8-62) for sexual function (Table 1).

Higher functional outcome scores, defined as a 25-point higher EPIC-26 score, were associated with OSC: urinary continence, OR 1.31 (95% CI 1.17–1.47); urinary function, OR 1.79 (95% CI 1.51–2.13); bowel function, OR 1.79 (95% CI 1.49–2.16); and sexual function, OR 1.34 (95% CI 1.21–1.48).

3.6. Differences between treatment groups

High OSC was reported by a greater proportion of the men who had undergone RP (78.2%) or RT (84.0%) than by men who were on AS (72.6%; Fig. 3). Similarly, more men who had undergone RP (40.5%) or RT (45.8%) reported having received substantial information than did men who had started on AS (28.6%). The treated men were also more likely to report substantial participation in decision-making (RP 70.5%, RT 64.5%, AS 49.2%), but they were less likely to answer "Yes" to the question "Do you think you will die from prostate cancer?" (RP 3.8%, RT 3.9%, AS 8.0%). The variables affecting OSC were similarly distributed in the three treatment groups.

A subgroup analysis was performed for men who initially started on AS but later underwent curative treatment (55.4%) and men still on AS when completing the questionnaire (44.6%). Patients on AS who later underwent curative treatment more often reported high OSC (77.3% vs 67.3%) and having received substantial information (35.4% vs 21.3%) and were also more likely to report substantial participation in decision-making (66.1% vs 36.1%). Patients on AS who later underwent curative treatment were less likely to answer "Yes" to the question "Do you think you will die from prostate cancer?" (7.0% vs 9.4%).

4. Discussion

In this nationwide population-based study, a large majority of men with localised PC reported high OSC, with only a low percentage reporting low OSC. Information and participation in decision-

making affected OSC the most, whereas the functional outcomes of treatment influenced OSC to a lesser degree. Having access to a nurse navigator was also associated with higher OSC. Higher education, concurrent diseases, and psychiatric comorbidity were associated with lower OSC. Men who initially had AS reported lower OSC, lower participation in decision-making, and having received less information about their treatment than men who had undergone immediate curative treatment.

We believe that this is the first article assessing overall satisfaction among men under AS and the first to suggest that nurse navigators may improve satisfaction among men with PC.

Our findings are in line with previous studies on satisfaction with care. Heerdegen and co-workers [16] reported in 2017 that 62% of 2315 cancer patients in a Danish study rated their care during treatment as excellent. A study from the USA of 3056 men with clinically localised or locoregional PC treated with RP, RT, or primary androgen deprivation therapy found a median satisfaction score of 78 on a scale from 0 to 100 [17].

Higher education was associated with lower OSC, which might reflect higher expectations for health care by these men. Participants with more concurrent diseases and psychiatric comorbidity also reported lower OSC, which is in accordance with the Danish study in which patients with comorbidity had lower odds of rating their care as excellent [16]. Men with psychiatric comorbidity are a particularly vulnerable group and may actually receive poorer cancer care, which calls for extra attention in future studies.

The quality of the information received as well as participation in decision-making strongly affected OSC. These results correspond well with those from a previous US study showing that shared decision-making and patient-perceived control were related to patient satisfaction [18]. In the Danish study by Heerdegen and co-workers [16], determinants of patient satisfaction with cancer care were investigated; patients with negative experiences for the information they had received reported lower satisfaction. Similarly, in a recently published study by Hoffman and co-workers [19], men who reported having made an informed treatment decision were less likely to report regret. In agreement with earlier studies, we found that a decline in sexual, urinary, or bowel function was associated with lower OSC [20,21], although treatment side effects affected OSC less than information and participating in decision-making did, probably reflecting the strong effect that a cancer diagnosis has on a man's life, as well as the dependent relationship that cancer survivors have with their care-givers.

The men who had access to a nurse navigator reported higher OSC than men who had not. Nurse navigators facilitate contacts between patients and health care providers. They may confer feelings of safety and stability, and help with both disease-specific and psychological problems. In a recently published Danish randomised pilot study, breast cancer patients with nurse navigation reported less distress, anxiety, and depression at 12 mo of follow-up [22]. To the best of our knowledge, our study is the first to suggest that nurse navigators may improve patient OSC. This supports the goal of Swedish health care authorities to provide all patients diagnosed with cancer with access to a specified nurse navigator. Our finding that OSC did not differ between men followed by a doctor and men followed by a nurse is in line with a UK study showing that nurse-led AS was usually highly rated [23]. In this study, continuity of care and resource savings were identified as key attributes.

Men who had started on AS reported lower OSC than men who had undergone immediate curative treatment. Among the men who started on AS, men who were still on AS when completing the questionnaire reported lower OSC than men who started on AS but later received curative treatment. The aim of the comparison between groups was to assess explanatory factors for differences in OSC only, and because of this we refrained from testing for statistical significance of the differences. Hoffman and co-workers [19] examined treatment decision regret in long-term survivors of localised PC in the USA. They found that men managed conservatively were less likely to report decision regret than men who had undergone surgery. Although not directly comparable, these results somewhat contradict ours. In our study, men on AS experienced lower participation in decision-making, were more likely to report receiving less information about their treatment, and were twice as likely to believe that they would die from PC. The responses to the question about the amount of information they had received might be viewed as a subjective estimate of the relation between the amount of information they received and the amount they would want to receive, rather than a measure of the actual volume of information. We found that information and participation in decision-making were strongly associated with OSC in the entire group of men, so the perceived lack of information and participation in decision-making among men on AS are likely causes of their lower OSC. As many as 8% believed they would die from their PC, which is twice as many as in the groups receiving curative treatment. This overestimation [24,25] probably reflects an objective lack of effective information.

The strengths of our study include its population-based design, the high response rate, and the face-validated study-specific questionnaire that was combined with EPIC-26. The stratified analyses enabled us to investigate potential predictive factors for OSC separately for the three treatment groups, although none were found. We acknowledge that various selection mechanisms affected the men's choice of treatment and that despite adjusting for potential confounders such as age, education, and concurrent diseases, residual confounders were not accounted for (eg, extent of disease, personality, and hospital characteristics). Furthermore, recall bias is a limitation in this retrospective study, as the patients' experiences during the 7-yr follow-up might have influenced their recollection of their experiences at the time of diagnosis. Nonresponders were more likely to be initially managed with AS; therefore, satisfied AS patients may be under-represented. The study included Swedish men only and the findings might therefore not be generalisable to other cultural and health care settings.

5. Conclusions

Our study suggests that among men with localised PC, information and participation in decision-making, as well as access to a nurse navigator, are key factors for OSC, regardless of treatment. Men on AS may need more information about their treatment than they now receive and may need to participate more in decision-making than they currently do. Patient satisfaction was as high among men who had nurse-led follow-up as among men who had doctor-led follow-up.

Author contributions: Oskar Bergengren had full access to all the

data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Obtaining funding: Bill-Axelson.
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Figure 2

Forest plot showing the odds ratio (95% confidence interval) for all participants who answered the main outcome question. The odds ratio indicates the probability of advancing one step on the seven-point visual digital scale for overall satisfaction with care when comparing the highest versus the lowest possible response. Adjusted for age, marital status, fatherhood, profession, education, Charlson comorbidity index (CCI), and psychiatric comorbidity. Ref. = reference.

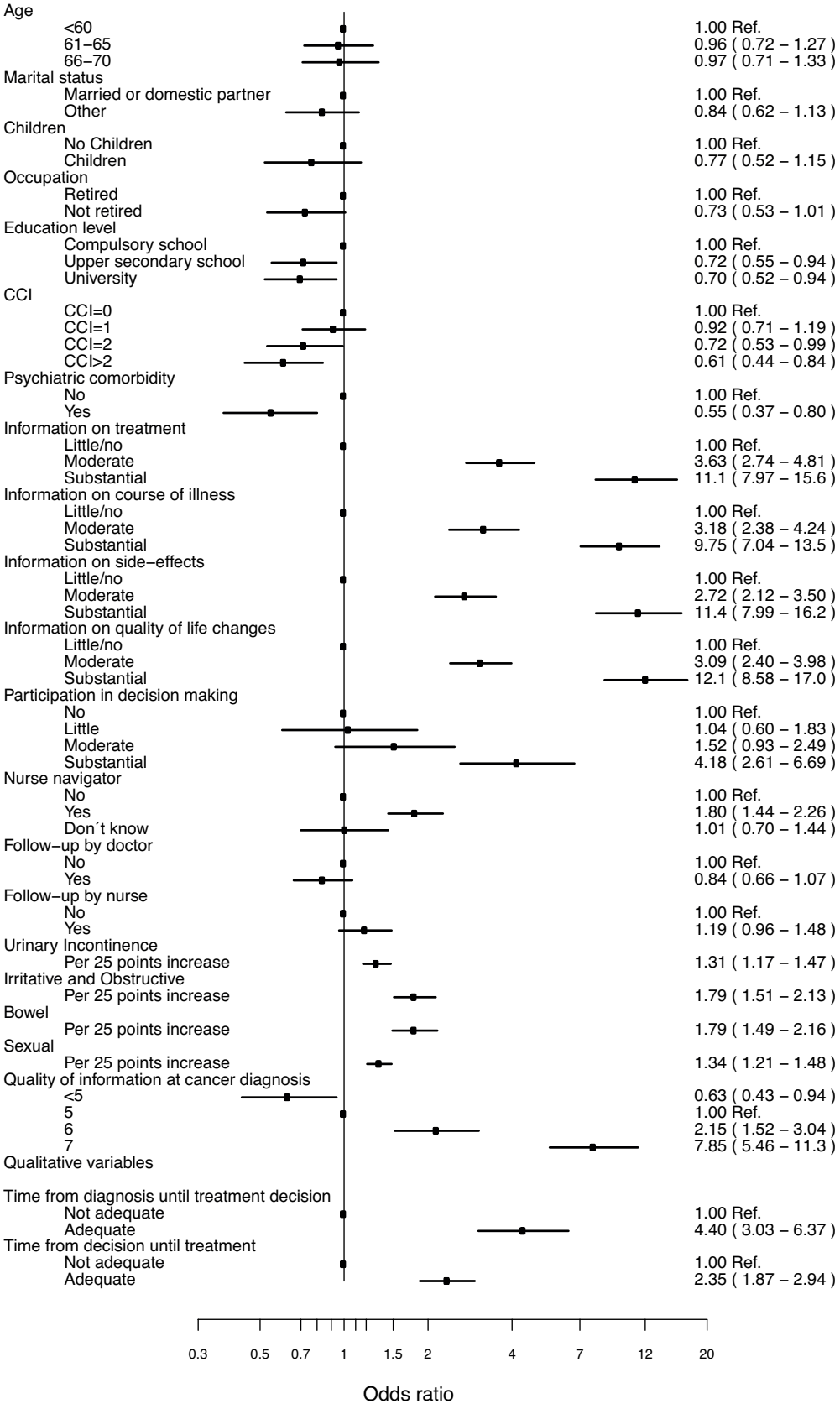

Figure 3
Bar charts showing percentage differences between treatment groups. AS = active surveillance; RP = radical prostatectomy; RT = radiotherapy.

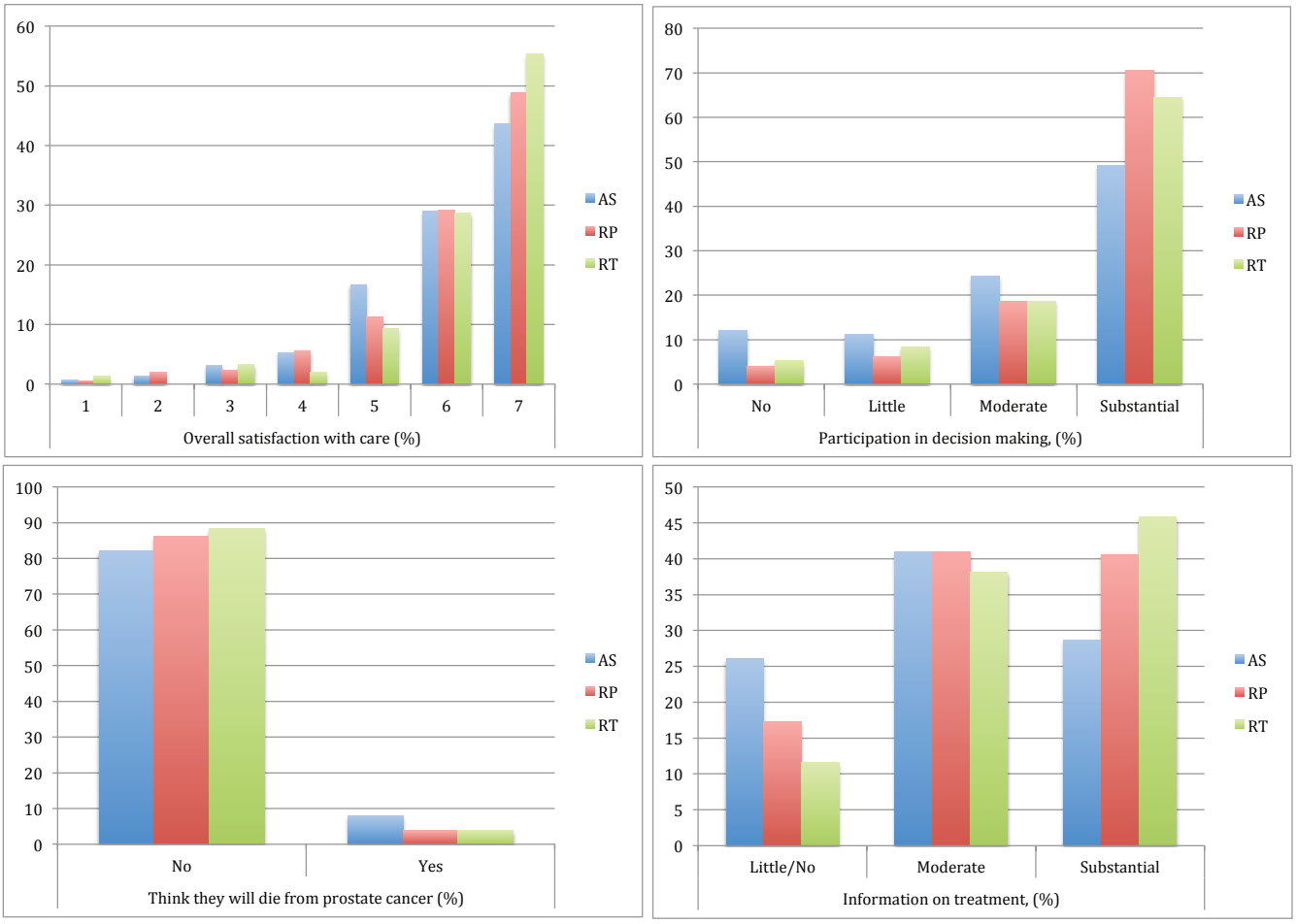

Table 1 – Demographics, clinical characteristics and potential factors associated with overall satisfaction with care by treatment group

	AS (*n* = 451)	RP (*n* = 682)	RT (*n* = 155)	All (*n* = 1288)
Age, yr (range)	64 (42–70)	62 (40–70)	63 (49–70)	63 (40–70)
Marital status, *n* (%)				
Married or domestic partner	367 (81.4)	578 (84.8)	123 (79.4)	1068 (82.9)
Other	73 (16.2)	97 (14.2)	29 (18.7)	199 (15.5)
Missing	11 (2.4)	7 (1.0)	3 (1.9)	21 (1.6)
Children, *n* (%)				
No children	36 (8.0)	52 (7.6)	18 (11.6)	106 (8.2)
Children	401 (88.9)	615 (90.2)	132 (85.2)	1148 (89.1)
Missing	14 (3.1)	15 (2.2)	5 (3.2)	34 (2.6)
Occupation, *n* (%)				
Not retired	53 (11.8)	169 (24.8)	23 (14.8)	245 (19.0)
Retired	377 (83.6)	497 (72.9)	129 (83.2)	1003 (77.9)
Missing	21 (4.7)	16 (2.3)	3 (1.9)	40 (3.1)
Education level, *n* (%)				
Compulsory school	143 (31.7)	163 (23.9)	45 (29.0)	351 (27.3)
Upper secondary school	166 (36.8)	275 (40.3)	72 (46.5)	513 (39.8)
University	128 (28.4)	229 (33.6)	36 (23.2)	393 (30.5)
Missing	14 (3.1)	15 (2.2)	2 (1.3)	31 (2.4)
Charlson comorbidity index, *n* (%)				
0	129 (28.6)	239 (35.0)	43 (27.7)	411 (31.9)
1	142 (31.5)	240 (35.2)	56 (36.1)	438 (34.0)
2	85 (18.8)	119 (17.4)	25 (16.1)	229 (17.8)
>2	95 (21.1)	84 (12.3)	31 (20.0)	210 (16.3)
Psychiatric comorbidity, *n* (%)				
No	411 (91.1)	626 (91.8)	144 (92.9)	1181 (91.7)
Yes (depression/other)	40 (8.9)	56 (8.2)	11 (7.1)	107 (8.3)
Information on treatment, *n* (%)				
Little/no	118 (26.1)	118 (17.3)	18 (11.6)	254 (19.7)
Moderate	185 (41.0)	279 (40.9)	59 (38.1)	523 (40.6)
Substantial	129 (28.6)	276 (40.5)	71 (45.8)	476 (37.0)
Missing	19 (4.2)	9 (1.3)	7 (4.5)	35 (2.7)
Participation in decision-making, *n* (%)				
No	54 (12.0)	27 (4.0)	8 (5.2)	89 (6.9)
Little	50 (11.1)	42 (6.2)	13 (8.4)	105 (8.2)
Moderate	109 (24.2)	126 (18.5)	29 (18.7)	264 (20.5)
Substantial	222 (49.2)	481 (70.5)	100 (64.5)	803 (62.3)
Missing	16 (3.5)	6 (0.9)	5 (3.2)	27 (2.1)
Nurse navigator, *n* (%)				
No	208 (46.1)	254 (37.2)	68 (43.9)	530 (41.1)
Yes	176 (39.0)	346 (50.7)	61 (39.4)	583 (45.3)
Don’t know	50 (11.1)	69 (10.1)	20 (12.9)	139 (10.8)
Missing	17 (3.8)	13 (1.9)	6 (3.9)	36 (2.8)
Follow-up, *n* (%)				
Doctor and nurse	63 (14.0)	107 (15.7)	24 (15.5)	194 (15.1)
Nurse	87 (19.3)	218 (32.0)	51 (32.9)	356 (27.6)
Doctor	264 (58.5)	283 (41.5)	70 (45.2)	17 (47.9)
Missing data	37 (8.2)	74 (10.9)	10 (6.5)	121 (9.4)
Quality of information at cancer diagnosis, *n* (%)				
<5	82 (18.2)	111 (16.2)	20 (12.8)	213 (16.5)
5	45 (10.0)	85 (12.5)	22 (14.2)	152 (11.8)
6	136 (30.2)	200 (29.3)	44 (28.4)	380 (29.5)
7	173 (38.4)	270 (39.6)	61 (39.4)	504 (39.1)
Missing	15 (3.3)	16 (2.3)	8 (5.2)	39 (3.0)
Thinks he will die from prostate cancer, *n* (%)				
No	370 (82.0)	587 (86.1)	137 (88.4)	1094 (85.0)
Yes	36 (8.0)	26 (3.8)	6 (3.9)	68 (5.3)
Missing	45 (10.0)	69 (10.1)	12 (7.7)	126 (9.8)

Time from diagnosis until treatment decision, *n* (%)				
Not adequate	38 (8.4)	67 (9.8)	16 (10.3)	121 (9.4)
Adequate	363 (80.5)	605 (88.7)	134 (86.5)	1102 (85.6)
Missing	50 (11.1)	10 (1.5)	5 (3.2)	65 (5.0)
Time from decision until treatment, *n* (%)				
Not adequate	NA	127 (18.6)	32 (20.6)	159 (19.0)
Adequate	NA	546 (80.1)	118 (76.1)	664 (79.3)
Missing	NA	9 (1.3)	5 (3.2)	14 (1.7)
Urinary incontinence, EPIC-26 score				
Median (IQR)	100 (73–100)	86 (58–100)	100 (86–100)	94 (65–100)
Missing data, *n* (%)	78 (17.3)	90 (13.2)	26 (16.8)	194 (15.1)
Urinary irritative/obstructive, EPIC-26 score				
Median (IQR)	81 (69–94)	94 (81–100)	81 (69–97)	88 (75–100)
Missing data, *n* (%)	108 (23.9)	125 (18.3)	32 (20.6)	265 (20.6)
Bowel, EPIC-26 score				
Median (IQR)	100 (83–100)	100 (88–100)	92 (71–100)	100 (88–100)
Missing data, *n* (%)	124 (27.5)	152 (22.3)	43 (27.7)	319 (24.8)
Sexual, EPIC-26 score				
Median (IQR)	36 (10–67)	28 (8–61)	32 (13–53)	32 (8–62)
Missing data, *n* (%)	117 (25.9)	147 (21.6)	36 (23.2)	300 (23.3)

AS = active surveillance; RP = radical prostatectomy; RT = radiotherapy; IQR = interquartile range; EPIC-26 = Expanded Prostate Cancer Index Composite 26-item short-form version.

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Docetaxel Treatment in PTEN- and ERG-aberrant Metastatic Prostate Cancers

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Abstract

Background: Loss of PTEN is a common genomic aberration in castration-resistant prostate cancer (CRPC) and is frequently concurrent with ERG rearrangements, causing resistance to next-generation hormonal treatment (NGHT) including abiraterone. The relationship between PTEN loss and docetaxel sensitivity remains uncertain.

Objective: To study the antitumor activity of docetaxel in metastatic CRPC in relation to PTEN and ERG aberrations.

Design, setting, and participants: Single-centre, retrospective analysis of PTEN loss and ERG expression using a previously described immunohistochemistry (IHC) binary classification system. Patients received docetaxel between January 1, 2006 and July 31, 2016.

Outcome measurements and statistical analysis: Response correlations were analyzed using Pearson's χ^2 tests and independent-sample t tests. Overall (OS) and progression-free survival (PFS) were analyzed using univariable and multivariable (MVA) Cox regression and Kaplan-Meier methods.

Results and limitations: Overall, 215 patients were eligible. Established metastatic CRPC prognostic factors were well balanced between PTEN loss (39%) and normal patients (61%). PTEN loss was associated with shorter median OS (25.4 vs 34.7 mo; hazard ratio [HR] 1.66, 95% confidence interval [CI] 1.23-2.34; p = 0.001). There were no differences in median PFS (8.0 vs 9.1 mo; univariable HR 1.20, 95% CI 0.86–1.68; p = 0.28) and PSA response (53.5% vs 50.6%; p = 0.74). PTEN loss was an independent prognostics factor in MVA. ERG status was available for 100 patients. ERG positivity was not associated with OS or PFS. Limitations include the retrospective nature and the single-centre analysis.

Conclusions: Our findings suggest that metastatic CRPC with PTEN loss might benefit more from docetaxel than from NGHT.

Patient summary: In this study, we found that metastatic prostate cancer with loss of the PTEN switch may benefit more from docetaxel than from abiraterone.

Keywords: Prostate cancer; PTEN; ERG; Docetaxel

1. Introduction

Prostate cancer (PC) is the most common malignancy in men and a common cause of cancer-related death in Western countries [1]. Molecular characterization of metastatic castration-resistant PC (mCRPC) through whole-exome and transcriptome sequencing has offered an insightful understanding of its biology, identifying aberrations of the androgen receptor (AR); gene fusions including those involving TMPRSS2 and ERG; and PTEN loss, commonly via deletion [2].

PTEN acts as a phosphatase regulator of the PI3K/AKT pathway, which is also involved in regulating AR signaling and in hormonal resistance in preclinical models [3]. PTEN loss is an early and stable event in the carcinogenesis process and is associated with poor prognosis [4–7] and short response to next-generation hormonal treatment (NGHT) such as abiraterone acetate (AA) [8]. This has prompted investigators to design studies evaluating the efficacy of the combination of NGHT and PI3K/AKT inhibitors [9,10].

The impact of PTEN loss, which commonly co-occurs with ERG genomic rearrangements, on the taxane sensitivity of mCRPC has not yet been clearly elucidated. Therefore, in this retrospective study we investigated PTEN protein expression in both hormone-naïve PC and mCRPC samples from patients with advanced disease and evaluated clinical outcomes and the association of docetaxel response with PTEN status. We then analyzed the association of PTEN loss and ERG expression and retrospectively evaluated the impact of ERG status on outcome from docetaxel in this cohort of patients.

2. Patients and methods

2.1. Patient cohort

Potentially eligible cases were identified from a population of men with mCRPC treated at the Royal Marsden NHS Foundation Trust between January 2006 and July 2016. Patients were included in the study if they had received docetaxel treatment for mCRPC (either as first-line treatment or after NGHT) and had paraffin tissue blocks from metastatic sites or diagnostic samples for PTEN immunohistochemistry (IHC) available. Exclusion criteria were

previous treatment with a PI3K/AKT inhibitor and histologic features of neuroendocrine or small cell cancer. All patients gave their written informed consent and were enrolled in institutional protocols approved by the Royal Marsden NHS Foundation Trust Hospital ethics review committee (reference no. 04/Q0801/60). Demographic and clinical data were retrospectively collected using the hospital electronic patient record system.

2.2. Tissue samples

PC tissue was obtained from prostate needle biopsies, transurethral resections of the prostate, prostatectomies, or PC metastases at the time of castration resistance within bone (bone marrow trephine), lymph nodes, or viscera (needle biopsies). All tissue blocks were sectioned and reviewed by a pathologist (D.N.R.) for confirmation of the adequacy of the material (>50 viable cells).

2.3. PTEN IHC

PTEN protein expression was determined via IHC on 4-mm-thick formalin-fixed, paraffin-embedded sections as previously described [11,12]. In brief, PTEN immunoreactivity was investigated using rabbit monoclonal anti-PTEN antibody 138G6 (Cell Signaling Technology, Danvers, MA, USA) [13] and detected using a Vectastain Elite ABC kit (Vector Laboratories, Burlingame, CA, USA). The intensity of nuclear and cytoplasmic staining was semiquantitatively assessed using the H-score formula as previously defined [8]. PTEN-positive controls included normal prostate tissue and 22RV1 xenograft tissue, and PTEN-loss controls included PC3 (PTEN-null PC cell line) xenografts. Endothelial cells and stroma were used as internal positive controls for PTEN. A binary classification was used for IHC PTEN positivity or loss according to validation studies previously published by our group [8]. Cases were considered PTEN-negative if they either showed a complete absence of PTEN staining or weak-intensity staining compared to the internal control in no more than 10% of cancer cells (H-score >10). All IHC sections were evaluated by a pathologist (D.N.R.) blinded to the patients' clinical characteristics and outcome data.

A small fraction of tumors showed prominent intratumor heterogeneity for PTEN expression with clearly distinct PTEN-positive and PTEN-negative areas, suggesting two clear populations of tumor cells in which one population had PTEN loss and the other did not. For the purpose of this data analysis, a case was considered PTEN-negative if any tumor area showed a complete absence of PTEN staining. For the survival analyses, when a change in PTEN status was observed between patient-matched hormone-naïve PC and CRPC samples, cases were classified according to the PTEN status in the CRPC sample.

2.4. ERG IHC

Antigen retrieval was conducted by heating slides in Tris-EDTA buffer (pH 8.1) using a microwave. Protein blocking was performed to eliminate nonspecific background staining using serum-free protein block #X0909 (Dako, Glostrup, Denmark). The primary antibody was #ab92513 from Abcam (Cambridge, UK) diluted 1:200 in Dako antibody diluent. The detection kit was a REAL EnVision detection system and DAB reagent (Dako). A negative control serum (rabbit IgG control antibody I-1000; Vector Laboratories) was used instead of the primary antibody for the negative controls. Control sections included a VCaP xenograft, a PC3 xenograft, and normal prostate tissue. Cases were scored by a pathologist (D.N.R) blinded to clinical data using a modified H-score (HS) method, which is a semiquantitative assessment of staining intensity that reflects antigen concentration. HS was determined according to the formula [(% of weak staining) × 1] + [(% of moderate staining) × 2] + [(% of strong staining) × 3], yielding a range from 0 to 300.

2.5. Statistical analysis

Biochemical response to docetaxel was defined according to Prostate Cancer Working Group Criteria 3 as a 30% decline in prostate-specific antigen (PSA) from baseline, confirmed at least 3 wk later [14]. Survival was measured from the first date of docetaxel treatment to the date of last contact or the date of death from any cause. Progression-free survival (PFS) was defined as the time from docetaxel initiation to the time of progression during or beyond the discontinuation of docetaxel because of radiological and/or biochemical progression or death. In patients with measurable disease on computed tomography imaging, the radiographic response was also assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1 [15]. The Kaplan-Meier product limit method was used to estimate the duration of docetaxel treatment, PFS, and overall survival (OS) by PTEN status. Independent-sample t tests and Pearson's χ^2 tests were used to investigate the association of PTEN loss with continuous and categorical variables, respectively. All tests were two-sided, and $p \leq 0.05$ was considered statistically significant.

Approximately 50% of patients were missing one or more independent factors at baseline, 30% of patients were missing values for all laboratory measurements. These values were considered to be missing at random from clinical notes and it was thought to be unlikely that there were systematic differences between the missing and observed values. To avoid a loss in precision, multiple imputation by chained equations was conducted using baseline patient and tumor characteristics. PTEN status and visceral disease were completely observed and were included in the imputation model with the Nelson-Aalen estimate and censoring indicators for mortality or progression depending upon the analysis. ECOG performance status≥1, Gleason score≥8 and previous experience of AA were imputed using logistic regression models; albumin, log10 alkaline phosphatase, hemoglobin, log10 neutrophil to lymphocyte ratio and log10 lactate dehydrogenase were imputed using linear regression models which assumed normality. In total, after a 100 imputation burn-in, 50 imputations were used and results were combined using Rubin's rules. Univariable and multivariable analyses of PTEN status, ERG status and other potential independent factors for OS, duration of docetaxel treatment and PFS were performed using the Cox regression model with a 95% confidence interval (CI). Descriptive statistics and survival analyses were performed using Stata v13.1 (Stata Corp., College Station, TX, USA).

3. Results

3.1. Tissue samples and patient characteristics

We identified 215 patients who received treatment with docetaxel and had tissue available for PTEN analysis. A single tissue sample was available for 160 patients, while 55 patients had matched samples collected at the time of diagnosis and in the castration-

resistant phase. A total of 270 samples were scored for PTEN by IHC. Intrapatient concordance was present in 87% of the matched samples (48 of 55) with a change in PTEN status observed in only seven of 55 patients (13%). Overall, PTEN loss was demonstrated in 83 of the 215 patients (39%).

Key baseline patient characteristics are listed in Table 1. Patients received a median of eight cycles of docetaxel, with median treatment duration of 5.1 mo. There were no significant differences in hemoglobin, albumin, lactate dehydrogenase, neutrophil/lymphocyte ratio, or performance status between PTEN-loss and PTEN-positive patients before docetaxel initiation; only alkaline phosphatase levels were higher in PTEN-loss patients (p = 0.02). Globally, 33 patients (15.4%) had visceral metastases at docetaxel initiation, with no significant difference between the groups (14.5% vs 15.9%; p = 0.77).

3.2. Outcomes

Median OS from the start of docetaxel treatment for the whole cohort was 29.3 mo (95% confidence interval [CI] 26.6–35.1); 180 patients (83.7%) had died by the time of data cutoff. Median PFS was 8.9 mo (95% CI 8.1–10.3). Patients with PTEN loss had worse OS than patients with normal PTEN expression (25.4 vs 34.7 mo; univariable hazard ratio [HR] 1.66, 95% CI 1.23–2.24; p = 0.001; Fig. 1) in both univariable and multivariable (MVA) Cox regression analyses (Table 2). PTEN loss, higher lactate dehydrogenase levels, and lower albumin remained strongly associated with worse OS in MVA (p < 0.05).

There was no difference in PFS observed between patients whose tumors had PTEN loss and those with PTEN-positive disease (median 8.0 vs 9.1 mo; HR 1.20, 95% CI 0.86–1.68; p = 0.28; Fig. 1B, Supplementary Table 1), with a similar median number of docetaxel cycles (7.5 vs 8.0; p = 0.29) and median time on docetaxel (5.0 mo [95% CI 4.2–5.5] vs 5.2 mo [95% CI 4.7–6.0]; p = 0.23). Overall, 86 patients (40.1%) received further treatment with cabazitaxel; of these, 56 (65.1%) had tumors with PTEN loss.

Data on PSA response were available for 143 patients. The overall median PSA decline was 53.3% (95% CI 61.7% to –42.9%); 74 of the 143 patients (51.8%) experienced a PSA response. Patients receiving docetaxel as first-line therapy for mCRPC were more likely to experience a PSA response than those receiving second-line docetaxel (58.4% vs 38.5%; p = 0.03). There was no difference in PSA response rate between patients with and without PTEN loss (53.5% vs 50.6%; p = 0.74; Fig. 2). Furthermore, 128 patients (59.5%) had scans available for assessment of radiological response. Of these 128, 55 patients (43.0%) had bone-only disease and 73 (57.0%) had measurable disease by RECIST. Among the latter 73 evaluable patients, 23 (31.5%) had a partial response during docetaxel treatment or at treatment completion. Response rates were not different between PTEN-loss and PTEN-positive mCRPC (28.6% vs 33.3%; p = 0.67; Table 3).

3.3. ERG status and correlation with outcome

To further characterize this mCRPC population, we evaluated ERG status in 100 tumors. IHC revealed 58 tumors (58%) with ERG-negative status and 42 (42%) with ERG positivity. ERG status was consistent between matched hormone-naïve and CRPC samples from the same patient, with only one patient having discordant hormone-naïve and CRPC ERG staining. There was a significant association between ERG-positive staining and PTEN loss (Fisher's exact test, p = 0.02; Supplementary Table 2). Despite this, no difference was observed in terms of OS (univariable HR 0.94, 95% CI 0.60–1.47; p = 0.79), PFS (HR 1.08, 95% CI 0.65–1.77; p = 0.77), and time on docetaxel (HR 1.06, 95% CI 0.70–1.58; p = 0.79) when patients were dichotomized according to ERG tumor status (Supplementary Figs. 1–3). In the subgroup with known ERG status, PTEN loss remained associated with worse survival (univariable HR 1.62, 95% CI 1.20–2.18; p = 0.002).

4. Discussion

Hyperactivation of the PI3K/AKT/mTOR pathway, generally through loss of PTEN function, is one of the most common aberrations driving progression in mCRPC [2]. PTEN loss of function can be due to different genomic (deletion, microdeletions, and rearrangements, including intronic rearrangements) and nongenomic mechanisms (methylation, miRNA, pseudo-gene expression) [2]. At the post-translational level, PTEN function is regulated by various modifications, including phosphorylation, oxidation, and ubiquitination, with intrapatient heterogeneity in approximately 10% of cases [16,17].

PTEN loss results in hyperactivation of the PI3K/AKT/mTOR pathway, which in turn is highly related to the activity of the AR pathway [3]. While PI3K/AKT/mTOR activation can suppress AR transcriptional output and stability [18], PI3K/AKT/mTOR signaling is activated following androgen deprivation, especially in patients with PTEN loss [19].

In the present analysis for patients treated with docetaxel, we confirmed the prognostic importance of PTEN loss in mCRPC. However, we found no evidence that docetaxel antitumor activity is impaired in PTEN-loss mCRPC, with no difference in the number of cycles administered, the duration of docetaxel treatment, or the PSA or RECIST response between PTEN-loss and PTEN-positive tumors. Nevertheless, this may not be the case in earlier stages of the disease, as PTEN loss was associated with shorter PFS among 57 patients treated on a trial of adjuvant docetaxel after radical prostatectomy [20].

In this study, in the PTEN-positive group, 31 patients (23.5%) received AA before chemotherapy and 97 patients (73.5%) received AA after chemotherapy. In the PTEN-loss group, 20 patients (24.1%) received AA before docetaxel and 62 patients (74.7%) received AA after docetaxel (Table 1). Therefore, the two groups were well balanced in term of anticancer treatments. We previously showed that AA has lower antitumor activity against PTEN-loss tumors [8], which might explain why patients with PTEN-loss tumors experience shorter OS despite no difference in term of PFS on docetaxel.

These data were recently confirmed by a phase 2 trial of AA + ipatasertib/placebo in which patients with PTEN-loss tumors in the AA + placebo arm had significantly shorter radiographic PFS when compared to the PTEN-positive group. Conversely, co-targeting of AR and AKT using AA + ipatasertib in combination improved outcomes compared to AA alone in PTEN-loss cancers [9]. Taken together, these data suggest that docetaxel might be a preferable option for this patient population.

As mCRPCs with PTEN deletion are enriched in ERG genomic

rearrangements [21], with PTEN loss postulated as being a later event to ERG rearrangements [22], we analyzed ERG status in the tumors from 100 patients in this cohort. Gene fusions involving TMPRSS2 and ERG can be detected by IHC and/or fluorescent in situ hybridization (FISH), and are common in PC (30–50%) [23], being highly associated with ERG protein overexpression [24]. The role of these ERG rearrangements in prognosis and survival remains controversial, although a recent meta-analysis of 5074 men treated with radical prostatectomy revealed no association between ERG rearrangements and clinical outcome [25–28]. A recent study evaluating ERG rearrangements in peripheral blood mononuclear cells using quantitative reverse transcription polymerase chain reaction demonstrated that TMPRSS2-ERG was associated with taxane resistance in mCRPC. However the incidence of ERG rearrangements detected with this method appeared to be particularly low (16%) compared to IHC and FISH tumor tissue–based testing [29]. Our analyses confirm that ERG positivity is a common event in PC and correlates with PTEN loss; however, we found no association between ERG status and clinical outcome from or response to docetaxel in mCRPC.

4.1. Limitations

Patients in this study came from a single centre, so these findings may not be generalizable to patients treated at other institutions and require prospective confirmation through a multicenter study. Furthermore, the patient cohort was retrospectively collected and so could suffer from selection bias.

5. Conclusions

We have shown for the first time and in the largest series on PTEN loss reported to date that despite being a prognostic factor, independent of ERG status, PTEN loss does not alter response to taxane-based chemotherapy. We envision that these findings may be relevant to treatment selection. Prospective trials are warranted to determine whether mCRPC patients with PTEN loss might be better served by docetaxel treatment rather than NGHT.

Author contributions: Johann S. de Bono had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Figure 1
Kaplan-Meier curves for (A) median overall survival (OS) and (B) median progression-free survival (PFS) from the start of docetaxel chemotherapy for patients with PTEN loss and those with PTEN-positive tumors. CI = confidence interval; DTX = docetaxel.

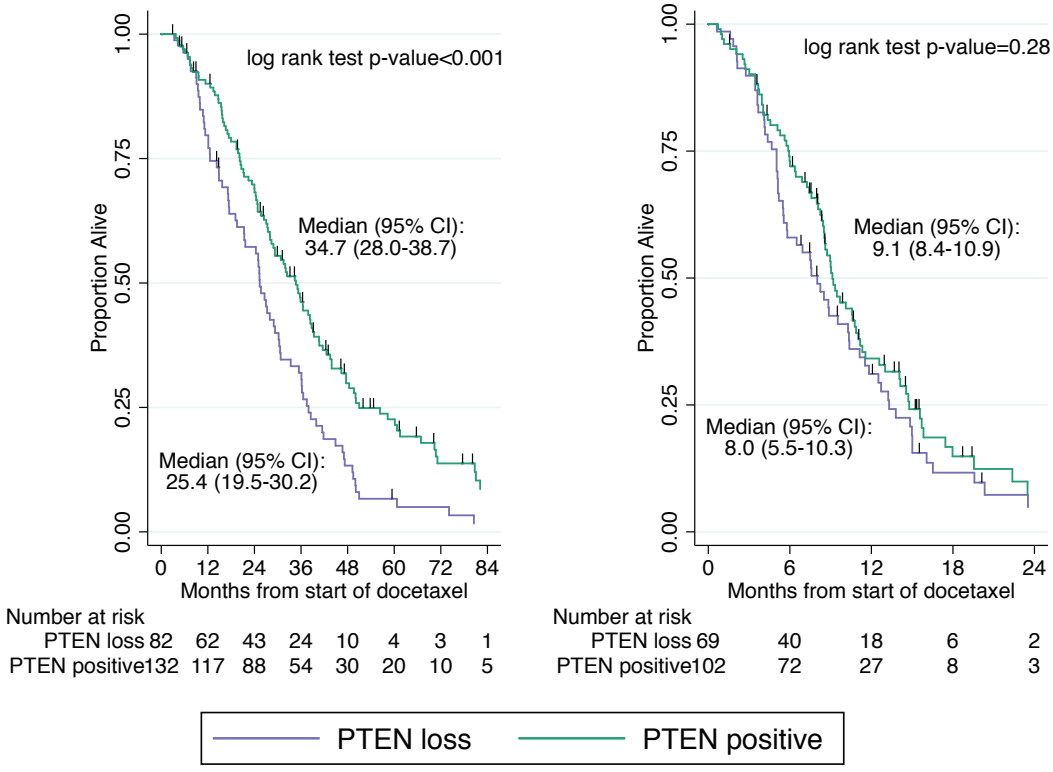

Figure 2
Waterfall plot of prostate-specific antigen (PSA) change for patients with PTEN loss and those still PTEN-positive. The bar indicates a 30% decline in PSA from baseline.

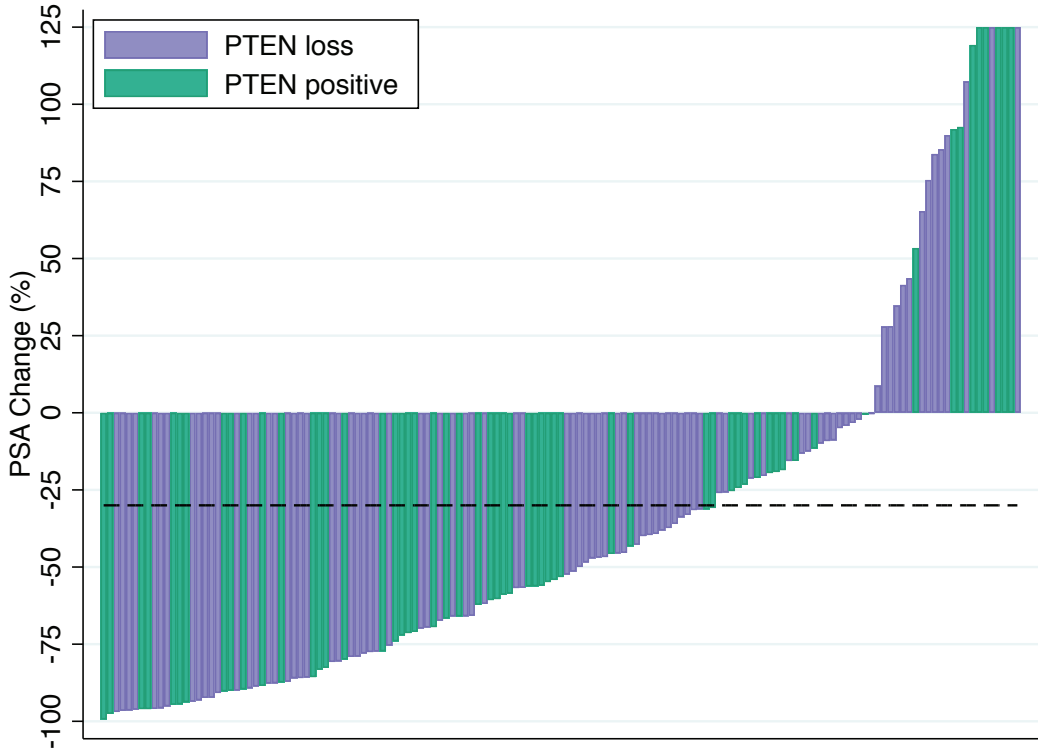

Table 1 – Patient characteristics at baseline

	Overall	PTEN-positive	PTEN loss	*p* value
Patients (*n*)	215	132	83	
Median age, yr (IQR)	70 (66–75)	68 (63–73)	66 (61–72)	0.23
Gleason score at diagnosis, *n* (%)				0.66
≤6	17 (7.9)	10 (7.6)	7 (8.4)	
7	51 (23.7)	28 (21.2)	23 (27.7)	
8–10	113 (52.6)	71 (53.8)	42 (50.6)	
Missing	34 (15.8)	23 (17.4)	11 (13.3)	
Sites of metastases at start of DTX, *n* (%)				0.78
Bone only	84 (39.1)	48 (36.4)	36 (43.4)	
Nodal	63 (29.3)	40 (30.3)	23 (27.7)	
Visceral	33 (15.4)	21 (15.9)	12 (14.5)	
Missing	35 (16.3)	23 (17.4)	12 (14.5)	
ECOG performance status, *n* (%)				0.46
0	78 (36.3)	30 (36.1)	48 (36.4)	
1	78 (36.3)	33 (39.8)	45 (34.1)	
2	5 (2.3)	3 (3.6)	2 (1.5)	
Missing	54 (25.1)	17 (20.5)	37 (28.0)	
Prostate-specific antigen				0.15
Median, ng/ml (IQR)	116 (47–404)	139 (58–569)	109 (32–369)	
Missing, *n* (%)	59 (27.4)	39 (29.6)	20 (24.1)	
Hemoglobin				0.81
Median, g/dl (IQR)	12 (11–13)	12 (11–13)	12 (11–13)	
Missing, *n* (%)	80 (37.2)	53 (40.2)	27 (32.5)	
Alkaline phosphatase				0.02
Median, IU/l (IQR)	127 (76–259)	116 (72–203)	211 (81–435)	
Missing, *n* (%)	79 (36.7)	52 (39.4)	27 (32.5)	
Lactate dehydrogenase				0.35
Median, IU/l (IQR)	192 (149–239)	188 (146–239)	197 (156–245)	
Missing, n (%)	84 (39.1)	56 (42.4)	28 (33.7)	
Albumin				0.19
Median, g/l (IQR)	36 (32–38)	36 (33–39)	35 (32–38)	
Missing, *n* (%)	80 (37.2)	53 (40.2)	27 (32.5)	
Neutrophils				0.99
Median (IQR)	4.6 (3.5–6.8)	4.6 (3.6–6.9)	4.5 (3.3–6.9)	
Missing, *n* (%)	81 (37.7)	54 (40.9)	27 (32.5)	
Lymphocytes				0.72
Median (IQR)	1.2 (0.8–1.6)	1.2 (0.8–1.6)	1.1 (0.8–1.7)	
Missing, *n* (%)	81 (37.7)	54 (40.9)	27 (32.5)	
Neutrophil/lymphocyte ratio				0.65
Median (IQR)	4.0 (2.5–8.8)	4.0 (2.4–9.0)	4.0 (2.4–8.6)	
Missing, *n* (%)	81 (37.7)	54 (40.9)	27 (32.5)	
Previous abiraterone, *n* (%)				0.69
Yes	51 (23.7)	31 (23.5)	20 (24.1)	
No	159 (74.0)	97 (73.5)	62 (74.7)	
Missing	5 (2.3)	4 (3.0)	1 (1.2)	

IQR = interquartile range; DTX = docetaxel; ECOG = Eastern Cooperative Oncology Group.

Table 2 – Univariable and multivariable Cox regression analyses for overall survival

	Univariable		Multivariable	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
PTEN status (loss)	1.66 (1.23–2.34)	0.001	1.73 (1.21–2.46)	0.003
Previous abiraterone	1.52 (1.06–2.17)	0.02	1.40 (0.90–2.18)	0.13
Hemoglobin (g/dl)	1.00 (0.97–1.03)	0.94	–	–
Albumin (g/l)	0.92 (0.87–0.97)	0.002	0.94 (0.88–1.00)	0.05
ALP (log_{10} IU/l)	2.02 (1.14–3.58)	0.02	1.11 (0.59–2.11)	0.73
LDH (log_{10} IU/l)	5.33 (1.39–20.49)	0.02	4.78 (1.33–17.22)	0.02
NLR (log_{10})	1.09 (0.78–1.52)	0.62	–	–
ECOG PS ≥1	1.74 (1.23–2.46)	0.001	1.45 (0.94–2.24)	0.09
Gleason score ≥8	1.43 (1.02–2.00)	0.04	1.37 (0.93–2.02)	0.11
Visceral disease	1.65 (1.10–2.46)	0.01	1.57 (0.97–2.53)	0.07

HR = hazard ratio; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; PSA = prostate-specific antigen; ALP = alkaline phosphatase; LDH = lactate dehydrogenase; NLR = neutrophil/lymphocyte ratio.

Table 3 – PSA and RECIST responses to treatment

	Patients, *n* (%)			*p* value
	Total	PTEN-positive	PTEN loss	
PSA response [a]	74 (51.8)	43 (50.6)	31 (53.5)	0.74
No PSA response	69 (48.3)	42 (49.4)	27 (46.6)	
RECIST response (PR)	23 (31.5)	15 (33.3)	8 (28.6)	0.67
No RECIST response (SD or PD)	50 (68.5)	30 (66.7)	20 (71.4)	

PSA = prostate-specific antigen; RECIST = Response Evaluation Criteria in Solid Tumors; PR = partial response; SD = stable disease; PD = progressive disease.
[a] A PSA response was defined as a 30% PSA decline from baseline.

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Is Robot-assisted Surgery Contraindicated in the Case of Partial Nephrectomy for Complex Tumours or Relevant Comorbidities? A Comparative Analysis of Morbidity, Renal Function, and Oncologic Outcomes

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Keywords: Partial nephrectomy; Robot-assisted surgery; Open surgery; Complications; Renal function; Oncologic outcomes

Abstract

Background: Available comparisons between open partial nephrectomy (OPN) and robot-assisted partial nephrectomy (RAPN) are scarce, incomplete, and affected by non-negligible risk of bias.

Objective: To compare RAPN and OPN.

Design, setting, and participants: This was an observational study of 472 patients diagnosed with a cT1–2cN0cM0 renal mass and treated with RAPN or OPN assessed in two prospective institutional databases.

Outcome measurements and statistical analysis: The study outcomes were morbidity, complications, warm ischaemia time, renal function, positive surgical margins, and oncologic outcomes. To account for baseline confounders, propensity score matching was used to account for age at diagnosis, gender, Charlson comorbidity index, preoperative estimated glomerular filtration rate (eGFR), single kidney status, tumour size and side, total PADUA score, any individual PADUA score item, and year of surgery. The effect of surgical approach was estimated using linear and logistic regressions for continuous and categorical outcomes. An interaction test was used for subgroup analyses.

Results and limitations: Relative to OPN, RAPN was associated with lower rates for overall (21% vs 36%; $p < 0.0001$) and major (3% vs 9%; $p = 0.03$) complications. This benefit was consistent in patients with high PADUA scores, high CCI, large tumours, and low preoperative eGFR (all $p > 0.05$, interaction test). No difference between the groups was observed for warm ischaemia time, postoperative and 1-yr eGFR, and positive surgical margins (all $p > 0.05$). After median follow-up of 41 mo, there was no difference between the groups for the 5-yr rates of local recurrence-free, systemic progression-free, and disease-free survival (all $p > 0.05$).

Conclusions: RAPN is associated with overall better perioperative morbidity and lower rates of complications, regardless of characteristics such as tumour complexity and patient comorbidity status. Functional and oncologic outcomes are equal after RARP and OPN.

1. Introduction

Nephron-sparing surgery represents the standard of care for active treatment of patients diagnosed with a cT1 renal mass [1–3]. Since its first description [4], the adoption of robot-assisted partial nephrectomy (RAPN) has gained remarkable momentum, with a 45% relative annual increase from 2008 to 2010 in the USA [5].

To date, comparisons between open partial nephrectomy (OPN) and RAPN are scarce, affected by a non-negligible risk of bias owing to a lack of detailed information about tumour anatomic complexity and incomplete data for postoperative renal function and oncologic outcomes assessment. Therefore, evidence generating definitive recommendations regarding the surgical approach for PN is not available [6,7] and current guidelines do not favour a specific surgical approach in the decision between OPN and RAPN.

For this reason, the current study relied on two prospectively collected institutional databases to perform a comprehensive comparison of perioperative morbidity, renal function, and oncologic outcomes following RAPN or OPN after the most precise adjustment for patient and tumour preoperative characteristics. We hypothesised that RAPN is associated with lower perioperative morbidity and similar functional and oncologic outcomes relative to OPN.

2. Patients and methods

2.1. Study population

Clinical data were prospectively collected for 472 patients diagnosed with a cT1–2 cN0 cM0 renal mass at computed tomography or magnetic resonance imaging and treated at IRCCS Ospedale San Raffaele (170 OPN, 84 RAPN) and Onze Lieve Vrouw Ziekenhuis (218 RAPN) from 2005 to 2016 by surgeons with extensive PN experience. The approach was selected according to the surgeon's choice. To precisely measure tumour anatomic complexity using an

established classification system [8], cases with multiple tumours were excluded. Non-naïve patients with a previous history of kidney cancer were also excluded. For the same reason, cases without availability of preoperative imaging were also excluded.

2.2. Outcomes

The study outcomes were as follows:

1. Morbidity and complications: overall and grade-specific complications according to the Clavien-Dindo (CD) classification [9].
2. Functional outcomes: warm ischaemia time, postoperative estimated glomerular filtration rate (eGFR) defined according to the Chronic Kidney Disease Epidemiology Collaboration equation for patients aged <70 yr and the Berlin Initiative Study formula for patients aged ≥70 yr [10] and measured at the last determination before discharge and 1 yr after surgery.
3. Pathologic and oncologic outcomes: positive surgical margins, local recurrence-free survival (RFS; defined as evidence of disease in the resection bed), systemic progression-free survival (PFS; defined as evidence of disease elsewhere than the treated kidney), and disease-free survival (DFS; defined as combination of RFS and systemic PFS.

2.3. Covariates

Covariates consisted of age at diagnosis, gender (male vs female), Charlson comorbidity index (CCI) [11], preoperative eGFR, single kidney status, clinical tumour size (defined as the greatest tumour diameter in millimetres at preoperative imaging), clinical tumour stage (cT1a vs cT1b vs cT2 defined according to the American Joint Committee on Cancer manual [12]), tumour side (left vs right), and year of surgery. Tumour complexity was determined by the urologist and was defined using total PADUA score [8] and any individual PADUA score item, namely longitudinal location, rim location, renal sinus involvement, relationship with urinary collecting system, and exophytic rate. Cases treated after 2009 were assessed before surgery and prospectively collected; cases treated earlier were retrospectively evaluated.

2.4. Statistical analyses

Statistical analyses and reporting and interpretation of the results were conducted according to established guidelines [13] and consisted of four steps. First, the median and interquartile range and the frequency and proportion were reported for continuous and categorical variables, respectively. Mann-Whitney and $\chi 2$ tests were used to compare the statistical significance of differences in the distribution of continuous and categorical variables, respectively, between the OPN and RAPN groups.

Second, to account for any potential baseline differences between OPN and RAPN patients, adjustment was performed using 1:1 nearest-neighbour propensity score matching [14]. Propensity scores were computed using a logistic regression model with the odds of receiving OPN as the dependent variable and age at diagnosis, gender, CCI, preoperative eGFR, single kidney status, clinical tumour size, tumour side, total PADUA score, any individual PADUA score item, and year of surgery as the independent variables.

Third, after estimation of covariates balanced between the matched groups [15], the effect of surgical approach (RAPN vs OPN) on study outcomes was estimated using linear and logistic regression for continuous and categorical outcome variables, respectively.

Fourth, the hypothesis that the effect of surgical approach on complications differed by selected subgroups, namely cases with high PADUA score, high CCI, large tumours, and low preoperative eGFR, was tested using an interaction term between treatment type (RAPN vs OPN) and PADUA score, CCI, clinical tumour size, and preoperative eGFR on an individual basis. Regression-derived coefficients were used to estimate the overall complication risk following RAPN or OPN. A locally weighted scatter plot smoothing method [16] was used to graphically explore the risk of overall complications according to PADUA score, CCI, clinical tumour size, and preoperative eGFR.

All statistical tests were performed using the RStudio graphical interface v.0.98 for R software environment v.3.0.2 [17] with the following libraries, packages and scripts: Hmisc, plyr, stats, MatchIt, rms, and graphics. All tests were two-sided with the significance level set at $p < 0.05$.

3. Results

3.1. Patient characteristics

Overall, 472 patients were included in the study (Table 1). In the cohort before propensity score matching, patients treated with RAPN were diagnosed with a smaller tumour (3.5 vs 3 cm; $p = 0.01$) relative to patients treated with OPN. In the cohort after propensity score matching, there was no difference between the RAPN and OPN groups with respect to all the covariates evaluated (all $p > 0.05$).

3.2. Morbidity and complications

In the cohort after propensity score matching (Table 2), relative to the OPN group, patients treated with RAPN had a lower risk of overall complications (21% vs 36%; odds ratio [OR] 0.46, 95% confidence interval [CI] 0.28–0.75; $p = 0.002$), CD ≥2 complications (8% vs 25%; OR 0.27, 95% CI 0.14–0.52; $p < 0.0001$), and CD ≥3 complications (3% vs 9%; OR 0.31, 95% CI 0.11–0.88; $p < 0.03$). Similarly, relative to the OPN group, patients treated with RAPN experienced a lower estimated blood loss (median 100 vs 400 ml; estimate −381, 95% CI −469 to −293; $p < 0.0001$) and a shorter length of stay (median 5 vs 6 d; estimate −2, 95% CI −3 to −1; $p < 0.0001$). Supplementary Table 1 describes specific complication categories.

3.3. Complications profile

The lower risk of complications observed after RAPN relative to OPN was not affected by PADUA score (Fig. 1A), CCI (Fig. 1B), clinical tumour size (Fig. 1C), or preoperative eGFR (Fig. 1D; all $p > 0.05$ at interaction test) and was consistent in patients with high PADUA score, high CCI, large tumours, and low preoperative eGFR.

3.4. Functional outcomes

In the cohort after propensity score matching (Table 2), there was no difference between the OPN and RPN groups with respect to warm ischaemia time (estimate 1, 95% CI −1 to 3; $p = 0.2$) postoperative eGFR (estimate 3, 95% CI −3 to 8; $p = 0.4$), and 1-yr eGFR (estimate −5, 95% CI −11 to 1; $p = 0.1$)

3.5. Pathologic and oncologic outcomes

In the cohort after propensity score matching (Table 2), there was no difference between the OPN and RAPN groups with respect to positive surgical margins (OR 1, 95% CI 0.42–2.37; p = 1). After median follow-up of 41 mo, there was no difference between OPN and RAPN in 5-yr rates of local RFS (hazard ratio [HR] 1.76, 95% CI 0.56–5.49; p = 0.3), systemic PFS (HR 2.08, 95% CI 0.46–9.32; p = 0.3), and DFS (HR 1.7, 95% CI 0.67–4.03; p = 0.3).

4. Discussion

We hypothesised that RAPN is associated with lower perioperative morbidity and similar functional and oncologic outcomes relative to OPN. Our results confirm this hypothesis, and several findings from the current study deserve further discussion.

First, RAPN was associated with a relevant benefit in terms of perioperative complications relative to OPN. Remarkably, this benefit was consistent when major complications were taken into consideration (Table 2). Consistently, others indicator of perioperative morbidity such as estimated blood loss and length of stay also favoured RAPN. When the complication profile was assessed according to different preoperative characteristics (Fig. 1), the benefit observed after RAPN relative to OPN was consistent in patients with high PADUA score, high CCI, large tumours, and low preoperative eGFR.

Second, functional outcomes recorded after RAPN and OPN in terms of warm ischaemia time and postoperative and 1-yr eGFR (Table 2) were virtually identical.

Third, pathologic and oncologic outcomes after RAPN and OPN with respect to positive surgical margins, 5-yr local RFS, 5-yr systemic PFS, and 5-yr DFS (Table 2) were virtually identical.

These key findings can be summarised as equivalent cancer control and renal function preservation but better perioperative morbidity after RAPN relative to OPN, and are of utmost importance for patient and clinicians, since PN is associated with non-negligible perioperative morbidity [8,18–20] and the available evidence does not allow for definitive recommendations in favour of a specific surgical approach over the alternatives [1–3]. Therefore, current guidelines state that PN can be performed either with an open, pure laparoscopic or robot-assisted approach according to the surgeon's expertise and skills [1].

Previous original studies [5,21–24] and meta-analyses [25] revealed lower complication rates after RAPN relative to OPN. However, the risk of unmeasured baseline differences between RAPN and OPN candidates represents a major limitation of these reports. For example, critical determinants of perioperative morbidity such as tumour anatomical complexity [8,26] and patient comorbidities [19] were completely omitted [5] or only incompletely accounted for [21–23] when the effect of the approach was estimated, resulting in a non-negligible risk of biased observations.

The findings of the current study confirm the superiority of RAPN when complications are evaluated, and provide evidence that this benefit is clinically and statistically relevant after the most precise adjustment for each individual patient and tumour characteristic that can affect the risk of complications. Specifically, individual tumour anatomic details were measured and balanced between RAPN and OPN cases for the first time to provide the most unbiased comparison.

In addition, no study has ever investigated the relationship between complication profiles and specific preoperative conditions. Notably, the current study demonstrated that the lower perioperative morbidity observed following RAPN is consistent in patients with a high PADUA score, high CCI, large tumours, and low preoperative eGFR. These findings corroborate the superior perioperative outcomes recorded for other special RAPN categories, namely entirely endophytic tumours [27] and obese patients [28], and suggest that complex and large tumours, relevant comorbidities, and renal function detriments do not represent contraindications for robot-assisted surgery, implying a paradigm shift with respect to the role of RAPN in challenging clinical scenarios.

For instance, if RAPN is preferred over OPN for a low-complexity tumour (PADUA score 7), the complication risk would be reduced by 12% (Fig. 1A). Similarly, if RAPN is preferred over OPN for a high-complexity tumour (PADUA score 11), the overall complication risk would be reduced by 26%. If RAPN is preferred over OPN in a patient without comorbidities (CCI 0), the complication risk would be reduced by 11% (Fig. 1B). Similarly, if RAPN is preferred over OPN in a patient with relevant comorbidities (CCI 4), the overall complication risk would be reduced by 28%. These findings are even more important since concern for perioperative morbidity means that radical nephrectomy and active surveillance might be attractive alternatives to PN for patients with a complex tumour and relevant comorbidities, respectively, and confirm that adoption of robot-assisted surgery leads to higher PN utilisation rates [29].

Several unique features of robot-assisted surgery (eg, minimally invasive surgical access, enhanced vision, instrument precision, intraoperative ultrasonography, and availability of tracers for parenchymal ischaemia evaluation) might facilitate both the resection and reconstructive phases of PN and can contribute to the lower perioperative morbidity observed following RAPN. Furthermore, besides morbidity and complications, other observations of the current study deserve special attention, since most available comparisons of OPN and RAPN investigated perioperative outcomes only [5,21–23,30] and longitudinal studies assessing postoperative renal function and oncologic outcomes are extremely scarce.

The similar warm ischaemia time and postoperative and 1-yr eGFR recorded in the current study are in accordance with the results of a meta-analysis of the available comparative studies [25] and with the comparable renal function detriment following either RAPN or OPN observed in patients with a solitary kidney [31] and patients with baseline chronic kidney disease [32]. Taken together, these observations and the findings of the current study support equivalent functional outcomes after RAPN and OPN in both elective and imperative nephron-sparing surgery settings.

Finally, the similar positive surgical margins and local RFS, systemic PFS, and DFS rates observed are in accordance with the only other comparison of RAPN and OPN reporting oncologic outcomes [24]. However, the extremely short follow-up for RAPN candidates (median 13 mo) and the unadjusted comparison represent two sources of non-negligible bias. Remarkably, the current study extends these previous observations to a cohort of patients cautiously matched for preoperative characteristics and allows for intermediate-term evaluation due to the longer follow-up. In addition, it provides precise information regarding individual

oncologic outcomes rather than relying on the combined definition of DFS only. Of note, oncologic outcomes recorded in the current study are worse than those reported in another assessment of intermediate-term oncologic outcomes following RAPN [33]. However, critical differences in patient population (eg, younger age at diagnosis and smaller tumour) and study design (noncomparative analysis) prevent a valid comparison.

The current study is not devoid of limitations. First, despite the comprehensiveness of our data source allowed for the most precise estimation of any potential baseline differences between RAPN and OPN candidates, the observational design cannot exclude the presence of residual unmeasured source of bias. For instance, the surgeon specific background (robotic or open) might affect judgments on the feasibility of nephron-sparing surgery and might influence the choice for radical nephrectomy in challenging cases. Nephrometry scores are the most accurate and objective classification of the anatomic complexity of renal masses; nonetheless. it is possible that unmeasured factors might remain unaccounted for. In this regard, the lack of a centralised review of anatomic complexity and the lack of centralised pathology review represent additional limitations. However, the identical tumour size and the identical rate of benign histology diagnosed at final pathology represent an indirect proof of the adequacy of the propensity-score matching based case selection and are a strong argument in favour of the validity of our comparison. Moreover, the length of follow-up does not allow for a meaningful analysis of cancer-specific mortality in the context of patients diagnosed with a cT1–2 renal mass. Nonetheless, our study represents the RAPN and OPN comparison with the longest follow-up and is the first that allows assessment of intermediate-term oncologic outcomes. Finally, the study used data collected at a tertiary care institution with a high robotic surgery volume and high kidney cancer volume and cannot be generalised to providers with different characteristics.

5. Conclusions

The comparison of a cohort of patients treated with RAPN or OPN precisely balanced with respect to a comprehensive panel of preoperative patient and tumour characteristics revealed similar functional and oncologic outcomes after either treatment modality. RAPN is associated with a lower rate of overall and major complication and this benefit is consistent regardless of preoperative characteristic such as tumour complexity and patient comorbidity status.

Author contributions: Alessandro Larcher had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Larcher, Mottrie.
Acquisition of data: Larcher, Capitanio, De Naeyer, Fossati, D'Hondt, Muttin, De Groote, Guazzoni, Salonia, Briganti, Montorsi, Mottrie.
Analysis and interpretation of data: Larcher, Fossati, Capitanio.
Drafting of the manuscript: Larcher, Capitanio.
Critical revision of the manuscript for important intellectual content: De Naeyer, Fossati, D'Hondt, Muttin, De Groote, Guazzoni, Salonia, Briganti, Montorsi.
Statistical analysis: Larcher, Fossati.
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Supervision: Montorsi, Mottrie.
Other: None.

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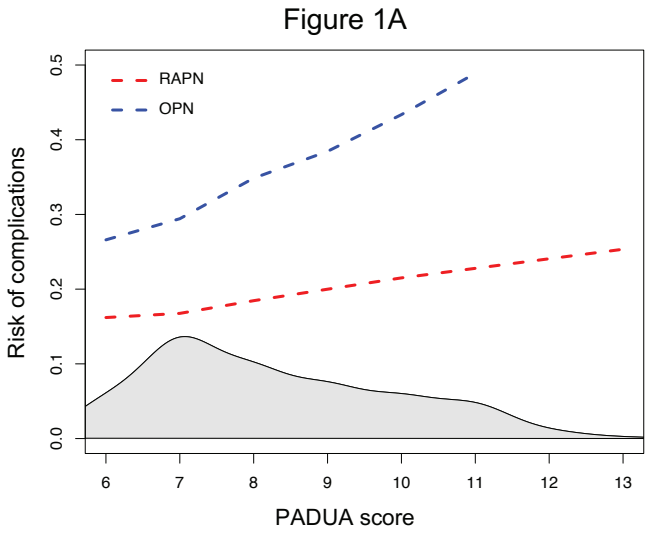
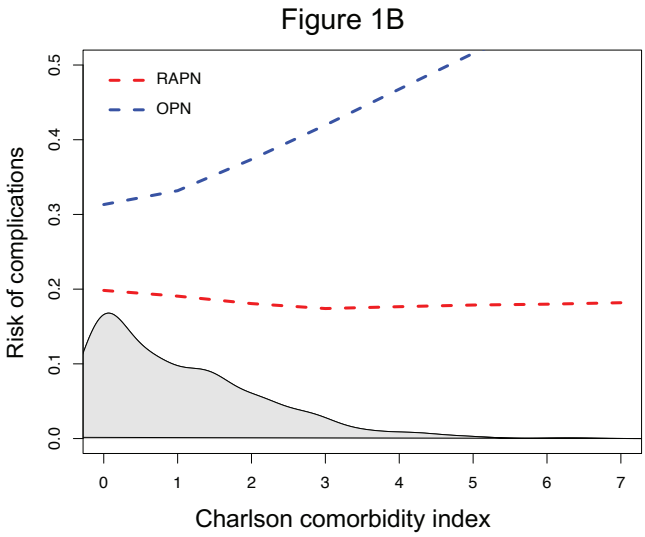
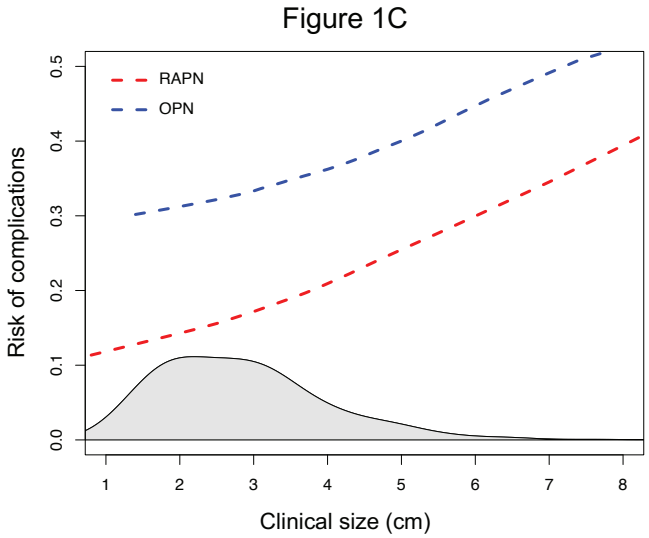
Figure 1

Overall risk of complications after robot-assisted partial nephrectomy (RAPN) or open partial nephrectomy (OPN) stratified according to (A) preoperative PADUA score, (B) Charlson comorbidity index, (C) clinical size, and (D) preoperative estimated glomerular filtration rate (ml/min/1.73 m2). Grey areas represent the distribution for the respective parameter. The risk of complications according to each individual characteristic was computed for 472 patients treated with RAPN or OPN for a cT1–2 renal mass at two European institutions during 2005–2016, using an interaction term between the characteristic of interest and the surgical approach included in a multivariable regression model adjusted for age, PADUA score, clinical size, Charlson comorbidity index, and preoperative estimated glomerular filtration rate.







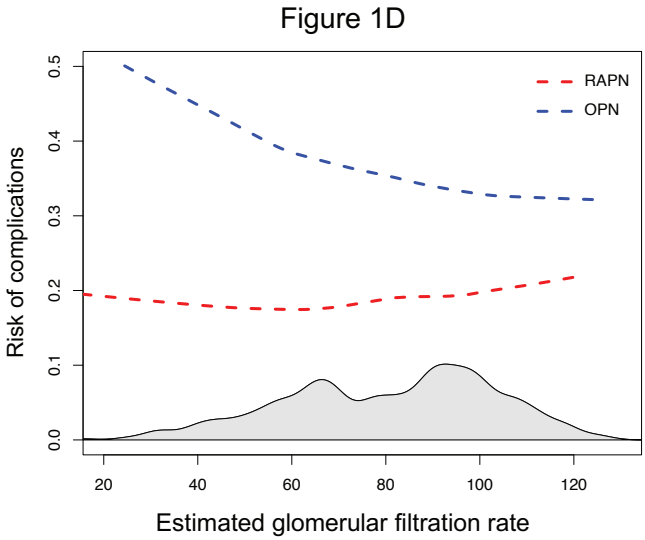


Table 1 - Descriptive characteristics for 472 patients treated with RAPN or OPN for a cT1–2 renal mass at two European institutions during 2005–2016

Variable	Cohort before PSM			Cohort after PSM		
	OPN (*n* = 170)	RAPN (*n* = 302)	*p* value	OPN (*n* = 170)	RAPN (*n* = 170)	*p* value
Age (yr)			0.2			1
Median	65	61		65	63	
IQR	54–72	51–71		54–72	53–72	
Gender			0.3			0.8
Male	116 (68)	191 (63)		116 (68)	119 (70)	
Female	54 (32)	111 (37)		54 (32)	51 (30)	
Charlson comorbidity index, *n* (%)			0.4			0.3
0	73 (43)	111 (36)		73 (43)	68 (40)	
1	31 (18)	66 (22)		31 (18)	32 (19)	
2	35 (21)	53 (18)		35 (21)	33 (19)	
≥3	31 (18)	72 (24)		31 (18)	37 (22)	
eGFR (ml/min/1.73 m^2)			0.4			0.8
Median	87	83		87	85	
IQR	65–98	64–97		65–98	65–98	
Single kidney, *n* (%)			0.1			0.5
No	164 (96)	299 (99)		164 (96)	167 (98)	
Yes	6 (4)	3 (1)		6 (4)	3 (2)	
Clinical size (cm)			0.01			0.3
Median	3.5	3		3.5	3.4	
IQR	2.5–4.2	2.2–4		2.5–4.2	2.4–4	
Clinical stage, *n* (%)			0.3			0.4
cT1a	123 (72)	235 (77)		123 (72)	130 (76)	
cT1b	44 (26)	62 (21)		44 (26)	36 (21)	
cT2a–b	3 (2)	5 (2)		3 (2)	4 (2)	
Tumour side, *n* (%)			1			0.9
Left	78 (46)	140 (46)		78 (46)	76 (45)	
Right	92 (54)	162 (54)		92 (54)	94 (55)	
PADUA score			0.8			0.4
Median	8	8		8	8	
IQR	7–9	7–9		7–9	7–9	
Longitudinal location, *n* (%)			0.6			0.9
Superior/inferior	88 (52)	166 (55)		88 (52)	90 (53)	
Middle	82 (48)	136 (45)		82 (48)	80 (47)	
Rim location, *n* (%)			0.2			0.5
Lateral	118 (69)	191 (63)		118 (69)	111 (65)	
Medial	52 (31)	111 (37)		52 (31)	59 (35)	
Renal sinus, *n* (%)			0.1			0.8
Not involved	132 (78)	210 (70)		132 (78)	135 (79)	
Involved	38 (22)	92 (30)		38 (22)	35 (21)	
Urinary collecting system, *n* (%)			0.8			0.6
Not involved	113 (66)	205 (68)		113 (66)	119 (70)	
Dislocated/infiltrated	57 (34)	97 (32)		57 (34)	51 (30)	
Exophytic rate, *n* (%)			0.5			0.8
≥50%	81 (48)	155 (51)		81 (48)	87 (51)	
<50%	71 (42)	110 (36)		71 (42)	67 (39)	
Endophytic	18 (11)	37 (12)		18 (11)	16 (9)	
Tumour size, *n* (%)			0.4			0.6
≤4 cm	123 (72)	235 (78)		123 (72)	130 (76)	
4–7 cm	44 (26)	62 (21)		44 (26)	36 (21)	
>7 cm	3 (2)	5 (2)		3 (2)	4 (2)	
Year of surgery, *n* (%) [a]			0.3			0.7
2005–2007	7 (4)	11 (4)		7 (4)	8 (5)	
2008–2010	59 (35)	98 (32)		59 (35)	63 (37)	
2011–2013	73 (43)	116 (38)		73 (43)	63 (37)	
2014–2016	31 (18)	77 (26)		31 (18)	36 (21)	

RAPN = robot-assisted partial nephrectomy; OPN = open partial nephrectomy; PSM = propensity score matching; eGFR = estimated glomerular filtration rate; IQR = interquartile range.

[a] Grouped in categories in the table for clarity, but computed as a continuous variable in propensity score matching.

Table 2 – Clinical outcomes for 170 patients treated with RAPN and 170 patients treated with OPN for a cT1–2 renal mass at two European institutions during 2005–2016 after propensity score matching for clinical characteristics

	OPN (*n* = 170)	RAPN (*n* = 170)	RAPN vs OPN	*p* value
Morbidity and complications			**OR or EST (95% CI)**	
Overall complications	61 (36)	35 (21)	0.46 (0.28–0.75)	0.002
Clavien-Dindo complication ≥2	42 (25)	14 (8)	0.27 (0.14–0.52)	<0.0001
Clavien-Dindo complication ≥3	15 (9)	5 (3)	0.31 (0.11–0.88)	0.03
Estimated blood loss (ml)	400 (250–600)	100 (60–200)	−381 (−469 to −293)	<0.0001
Operative time (min)	151(123–190)	150 (120–180)	−6 (−18 to 6)	0.3
Length of stay (d)	6 (5–8)	5 (4–6)	−2 (−3 to −1)	<0.0001
Functional outcomes			**OR or EST (95% CI)**	
Ischaemia time (min)	15 (0–21)	15 (11–19)	1 (−1 to 3)	0.2
Postoperative eGFR (ml/min/1.73 m^2)	73 (59–94)	79 (59– 97)	3 (−3 to 8)	0.4
1-yr eGFR (ml/min/1.73 m^2) [a]	77	71	−5 (−11 to 1)	0.1
Pathologic outcomes			**OR or EST (95% CI)**	
Pathologic size (cm)	3 (2.4–4)	3 (2.2–4)	−0.1 (−0.45 to 0.25)	0.6
Malignancy	135 (79)	136 (80)	1.04 (0.61–1.76)	0.9
Positive surgical margins	11 (6)	11 (6)	1 (0.42–2.37)	1
5-yr oncologic outcomes			**HR or EST (95% CI)**	
Local recurrence-free survival	4 (96)	4 (94)	1.76 (0.56–5.49)	0.3
Systemic progression-free survival	3 (98)	3 (95)	2.08 (0.46–9.32)	0.3
Disease-free survival	7 (94)	6 (91)	1.7 (0.67–4.03)	0.3

RAPN = robot-assisted partial nephrectomy; OPN = open partial nephrectomy; eGFR = estimated glomerular filtration rate; OR = odds ratio; EST = estimate; CI = confidence interval; HR = hazard ratio.

Data are presented as median (interquartile range) and EST for continuous variables, and as frequency (percentage) and OR or HR for categorical variables.

[a] Available for 204 patients.

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