Original Research Article

A prospective phase II study of prostate-specific antigen-guided salvage radiotherapy and $^{68}$Ga-PSMA-PET for biochemical relapse after radical prostatectomy – The PROPER 1 trial

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ABSTRACT

Background and purpose: The treatment of biochemical recurrence (BCR) after prostatectomy is challenging as the site of the recurrence is often undetectable. Our aim was to test a personalised treatment concept for BCR based on PSA kinetics during salvage radiotherapy (SRT) combined with prostate-specific membrane antigen positron emission tomography ($^{68}$Ga-PSMA-PET).

Materials and methods: This phase II trial included 100 patients with BCR. PSMA-PET was performed at baseline. PSA was measured weekly during SRT. Initially, 70 Gy in 35 fractions was prescribed to the prostate bed. Radiotherapy was adapted after 50 Gy. Non-responders (PSA still $\geq 0.15$ ng/mL) received sequential lymph node irradiation with a boost to PSMA-PET positive lesions, while responders (PSA $< 0.15$ ng/mL) continued SRT as planned. PET-findings were only taken into consideration for treatment planning in case of PSA non-response after 50 Gy.

Results: Data from 97 patients were eligible for analysis. Thirty-four patients were classified as responders and 63 as non-responders. PSMA-PET was positive in 3 patients (9%) in the responder group and in 22 (35%) in the non-responder group ($p = 0.007$). The three-year failure-free survival was 94% for responders and 68% for non-responders (median follow-up 38 months). There were no significant differences in physician-reported urinary and bowel toxicity. Patient-reported diarrhoea at end of SRT was more common among non-responders.

Conclusion: This new personalised treatment concept with intensified SRT based on PSA response demonstrated a high tumour control rate in both responders and non-responders. These results suggest a clinically significant effect with moderate side effects in a patient group with otherwise poor prognosis. PSMA-PET added limited value. The treatment approach is now being evaluated in a phase III trial.

Clinical trial registration numbers: NCT02699424 & ISRCTN45905321.

Introduction

Patients who experience biochemical recurrence (BCR) after radical prostatectomy with rising prostate-specific antigen (PSA) levels are most often treated with salvage radiotherapy (SRT) to the prostate bed, sometimes in combination with androgen deprivation therapy (ADT) [1,2]. For patients with BCR at low PSA values, contemporary imaging methods rarely identify the site of recurrence. Therefore, the decision to treat the prostate bed with SRT is instead most often based on the probability that the BCR is the result of a local recurrence only. Tumour control probability after SRT can be predicted, for example, by the Stephenson nomogram, which is based on pre-treatment clinical factors [3]. The clinical value of including lymph node irradiation (LNI) in SRT is unknown, but studies are ongoing [4].

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Novel imaging methods are emerging to improve the detection of the site of early prostate cancer recurrences. 68Ga-prostate-specific membrane antigen positron emission tomography (PSMA-PET) with computed tomography has shown encouraging results in detecting tumour recurrence at low PSA levels [5–8]. Several studies have demonstrated that it is important to start SRT at as low PSA levels as possible. It is therefore vital to improve the detection rate to optimise treatment planning [9–11]. According to a recent systematic review, the detection rate of PSMA-PET is estimated to be about 33% for patients with PSA < 0.2 ng/mL, and 45% for PSA levels of 0.2–0.5 ng/mL [12], which are the ranges within which patients are most often prescribed SRT. The identification of the site of recurrence enables more personalised planning of SRT. Although these new imaging methods are promising, in most cases it is still not possible to identify the site of recurrence. In addition, a detectable local recurrence does not exclude the presence of concurrent microscopic spread to pelvic lymph nodes or other locations. Furthermore, the reported specificity and sensitivity of PSMA-PET are high in the primary treatment setting, the corresponding values are more seldom histologically confirmed in the early salvage setting, making them less precise [12].

Instead of relying only on pre-treatment factors for the prediction of outcome after SRT, it is desirable to have a reliable biomarker that reflects treatment response during SRT, which could be used to adapt the SRT according to each patient’s response to treatment. Such a biomarker could be used in combination with PSMA-PET imaging to identify patients with increased risk of failing SRT to the prostate bed only and guide the use of more extended therapies for high-risk patients. We have previously shown that PSA kinetics in the early phase of SRT is strongly correlated to long-term treatment outcome in this setting, supporting its potential as a predictive biomarker [13]. The local tumour burden in the early BCR setting could be the prerequisite for the sharp PSA response observed during SRT to the prostate bed only in patients with isolated local recurrence. The opposite applies to patients with disease spread beyond the prostate fossa, with a less pronounced PSA decrease as all sites of recurrence are not receiving an adequate radiation dose. It is therefore appealing to use the change in PSA during SRT as a biomarker to guide the adaptation of SRT and to aid in the interpretation of PSMA-PET findings in the early tumour recurrence setting.

The aim of this open-label prospective phase II trial was to evaluate a new adaptive treatment strategy involving sequential LNI and radiation boost to PSMA-PET-positive lesions guided by PSA kinetics as a biomarker during SRT.

Materials and methods

Trial information

The PROPER I trial is an open-label, prospective, phase II study (NCT02699424 and ISRCTN45905321) conducted at Skåne University Hospital in Sweden. The study was approved by the Ethics Committee in Lund (reference number 2015/431). Trial data were collected and stored at the Clinical Trial Office in Lund.

Eligibility criteria

Patients ≥ 18 years of age with histologically confirmed prostate cancer in the prostatectomy specimen and any pT, pN0/Nx, M0 with a confirmatory PSA level ≥ 0.15 ng/mL, WHO performance status 0–1, and with adequate laboratory findings according to the study protocol were eligible for inclusion.

Evidence of metastases on pre-operative imaging or in the surgical specimen (e.g., N1 at lymph-node dissection) was an exclusion criterion. Patients who were undergoing or had undergone previous ADT, or who had a history of previous pelvic radiotherapy or malignancies other than prostate cancer or basal cell carcinoma in the past five years were also excluded. Patients with clinically significant disease other than prostate cancer (e.g., heart, pulmonary, gastrointestinal or urogenital), which in the opinion of the investigator made inclusion undesirable, were not included in the trial.

PSMA-PET

Prior to radiation treatment, all patients underwent a PSMA-PET (68Ga-PSMA-11) examination with low-dose CT. One hour after the injection of 2.5 MBq/kg bodyweight, with a maximum of 300 MBq, patients were scanned from the mid-thigh level to the base of the skull using a GE Discovery 690 PET-CT scanner (GE HealthCare, Milwaukee, WI, USA). The scan was analysed by two experienced readers, one a specialist in nuclear medicine and the other an oncologist, blinded to the PSA response. Uptakes not typical of a normal physiological pattern or unspecific uptake patterns were regarded as suspicious for malignancy. The treatment planning CT was available for correlation in the reading situation.

Response evaluation and adaptive salvage radiotherapy

The adaptive sequential radiotherapy treatment techniques used in PROPER I trial have been described in detail previously [14]. Initially, all patients were prescribed 70 Gy to the prostate bed in 35 fractions. PSA was measured on the day on which SRT started, and thereafter once weekly during SRT. After five weeks of SRT (i.e., after 50 Gy), patients were defined as responders if their PSA level had decreased below 0.15 ng/mL, or non-responders if their PSA level was still ≥ 0.15 ng/mL.

The treatment of patients classified as responders continued according to the initial prescription (70 Gy to the prostate bed) regardless of PSMA-PET findings. The treatment of patients classified as non-responders was adapted with a new prescription including the initial 70 Gy to the prostate bed and an additional 50 Gy in 25 fractions to adjuvant lymph nodes. In addition, non-responders showing lymph node metastases on the pre-therapy PSMA-PET examination received a simultaneously integrated boost of 60 Gy in 25 fractions, corresponding to EQD2 \( α/β=3 \) Gy of 64. Gy. Local recurrence was treated with a dose corresponding to EQD2 \( α/β=3 \) Gy of 74–78 Gy. In cases of distant metastases, or more than three lymph node metastases on PSMA-PET (verified histologically or by another imaging method if a biopsy was not considered feasible), the patients were considered ineligible, and were excluded from further SRT. They were then referred for standard of care treatment for metastatic disease (Fig. 1). All target volumes were treated with 1 fraction/day and 5 fractions/week. To be able to adapt the SRT for non-responders, and to add LNI and boost doses during SRT, we developed the biologically adaptive plan-on-plan volumetric-modulated-arc-therapy method, which has been described elsewhere [14].

Outcomes

PSA was measured during SRT as described above, and thereafter at 3, 6, 9 and 12 months post-SRT, and every six months thereafter. Treatment failure was defined as either BCR (PSA increase of 0.2 ng/mL above post-SRT nadir, confirmed by a second measurement with the date of the prior measurement registered as the time of BCR) or as a clinical recurrence (identified clinically or with imaging methods).

Physician evaluated urinary and bowel toxicity were evaluated according to the RTOG toxicity scale at baseline, at the end of SRT, 3 and 12 months after the end of SRT, and thereafter according to local clinical routine. Patient-reported quality of life was evaluated with the EORTC QLC-C30 questionnaire, and urinary and bowel symptoms as well as sexual function with the EORTC QLC-PR25 at baseline, at the end of SRT, and 12 months after the end of SRT.
Statistics

The primary outcome was analysed in the per-protocol population. The Kaplan-Meier method was used to illustrate failure-free survival (FFS). The QLQ-C30 and QLQ-PR25 functional and symptom raw scores were linearly transformed to a 0–100 scale according to the EORTC scoring manuals. Results are presented as mean values with standard errors (SE), and the Wilcoxon rank sum test, adjusted for ties, was used to compare treatment groups. Fisher’s exact test or the chi-squared test for trend was used to compare proportions between responders and non-responders. Analyses were based on the study database as of 22/09/2021. Statistical calculations were performed with MedCalc Statistical Software, version 20.014.

Results

Between March 2016 and December 2019, 100 patients were included in the trial. Two patients withdrew their consent. One patient had more than 3 lymph node metastases and was excluded from further study treatment and follow-up according to protocol, leaving data from 97 patients for further analysis. The median follow-up time was 38 months (interquartile range (IQR) 29–48). Baseline clinical characteristics are presented in Table 1.

Clinical outcomes

Of the 97 patients completing the study, 34 (35%) were classified as responders (PSA < 0.15 ng/mL after 50 Gy) and 63 (65%) as non-responders (PSA ≥ 0.15 ng/mL after 50 Gy). The estimated overall three-year FFS for the whole cohort (N = 97) was 76% (95% CI 67–86). The corresponding values for the group of responders and the group of non-responders were 94% (95% CI 86–100) and 68% (95% CI 56–81), respectively (Fig. 2).

PSMA-PET findings

The overall PSMA-PET detection rate was 26% (25/97). Further specification of the sites of recurrence according to PSMA-PET is given in Table 3.

Table 1

| Baseline clinical characteristics (N=97) | IQR=inter-quartile range. |
|----------------------------------------|---------------------------|
| PSA at start of SRT (ng/mL)            | 0.25 (0.19–0.37)          |
| Time between surgery and SRT (months)  | 38 (24–59)                |
| Gleason score in prostatectomy specimen|                            |
| 5                                      | 1 (1%)                    |
| 6                                      | 7 (7%)                    |
| 7                                      | 78 (80%)                  |
| 8                                      | 5 (5%)                    |
| 9                                      | 6 (6%)                    |
| Gleason score in prostatectomy specimen|                            |
| ≤3+4                                   | 52 (54%)                  |
| ≥4+3*                                  | 45 (46%)                  |
| Surgical margins                       |                            |
| Negative                               | 52 (54%)                  |
| Positive                               | 45 (46%)                  |
| pT stage                               |                            |
| T2                                     | 50 (52%)                  |
| T3a                                    | 32 (33%)                  |
| T3b                                    | 15 (15%)                  |

*Gleason 3+5 included in the ≥4+3 group.

Table 3. Three patients (9%) in the responder group had findings on PSMA-PET classified as a probable site of recurrence, compared to 22 (35%) in the non-responder group. This difference in detection rate between the groups was statistically significant (p = 0.007).

One patient in the responder group had a local recurrence which we considered to be a true finding, even though histological confirmation was not possible. As we did not consider findings in the responder group other than in the prostate fossa as potentially true positives, we could monitor the two patients where the PET findings were outside the prostate bed (one in pelvic lymph nodes and one in bone). We were later able to confirm that these in both cases were false positive.

During the five weeks of SRT before response evaluation we were able to evaluate suspected sites of distant metastases with both further imaging and histological evaluation. In all cases, we were able to confirm that they were false positive findings, through metastatic work-up during the first five weeks of SRT, and with further confirmation through follow-up.
Discussion

To the best of our knowledge, this is the first prospective trial to report the efficacy and tolerability of PSA-response-guided SRT for prostate cancer BCR. Our results show that SRT responders receiving local SRT only experienced a very low rate of treatment failure, confirming our results from a previous prospective observational study [13]. Comparison with a matched cohort of 152 patients from that study (applying the same definition of responder/non-responder, and the same median follow-up time) showed 37% FFS at three years among non-responders without LNI, compared to the 68% observed in the non-responder group treated with LNI in the present study (Supplementary Fig. 1). The benefit of including regional lymph nodes in the SRT setting is a subject of debate [4,15–19], but our results suggest that PSA non-response during SRT of the prostate bed is often associated with lymph-node metastases, and that these metastases can be effectively treated with radiotherapy.

The overall PSMA-PET detection rate (26%) in the study cohort was slightly lower than expected considering the PSA levels [12]. We found a significant difference in detection rate between the responder (9%) and the non-responder groups (35%). In this study, we scanned the first ever patient in Sweden with PSMA-PET. Since PSMA was a new PET tracer at the time of the start of the study, the PROPER 1 trial was also a feasibility study for this imaging method, as well as for the PSA-response-adapted...
SRT. Therefore, we chose not to include the PSMA-PET findings in the initial work-up of the radiotherapy treatment planning and not to exclude patients from curative treatment based on PSMA-PET findings alone. Furthermore, we considered PET-positive findings outside the prostate bed in treatment responders as false positive. This assumption was based on our earlier findings showing excellent treatment outcome for PSA responders at 5 weeks with SRT to the prostate bed only [13]. Only three patients in the responder group had positive PSMA-PET scans, two of which were assumed to be false positive in accordance with the discussion above. The third patient had PSMA uptake in the prostate bed receiving 70 Gy, probably reflecting local recurrence, however, this could not be histologically confirmed. Our findings show that PSMA-PET was of no clinical value in the group of responders in the present study. It is often difficult to confirm pathology from observations made on PSMA-PET, especially when the uptake is not clearly elevated. Therefore, we chose not to take PSMA-PET into account before starting SRT. Instead, our adaptive treatment strategy could be used as a tool to guide the initial work-up of the radiotherapy treatment planning and not to exclude patients from curative treatment based on PSMA-PET findings alone. Furthermore, we considered PET-positive findings outside the prostate bed in treatment responders as false positive. This assumption was based on our earlier findings showing excellent treatment outcome for PSA responders at 5 weeks with SRT to the prostate bed only [13]. Only three patients in the responder group had positive PSMA-PET scans, two of which were assumed to be false positive in accordance with the discussion above. The third patient had PSMA uptake in the prostate bed receiving 70 Gy, probably reflecting local recurrence, however, this could not be histologically confirmed. Our findings show that PSMA-PET was of no clinical value in the group of responders in the present study.

It is often difficult to confirm pathology from observations made on PSMA-PET, especially when the uptake is not clearly elevated. Therefore, we chose not to take PSMA-PET into account before starting SRT. Instead, our adaptive treatment strategy could be used as a tool to guide which PSMA-PET findings warrant further work-up and treatment, and which could be excluded to avoid over-treatment. For example, in patients with PSMA-PET findings in lymph nodes of unknown significance and a distinct decrease in PSA during SRT (involving only the prostate bed), lymph node involvement is unlikely. In contrast, the risk of lymph node involvement in non-responders is more probable, and hence they have a higher probability of benefiting from LNI.

The five weeks of treatment before deciding whether to add LNI made it possible to confirm or exclude possible metastatic spread through biopsy and/or further imaging without delaying the start of treatment. In seven cases, six of whom were non-responders, PSMA-PET showed suspicion of disease spread outside the pelvic region. All suspected distant metastases (n = 7) were confirmed as false positives, either through biopsy or follow-up. As distant metastases, detectable on PSMA-PET, should most likely occur at higher PSA levels than the baseline levels in this study, we deem it important not to exclude these patients from curative treatment, if spread of disease is not confirmed by further investigation, optimally histologically. If distant metastases are confirmed, the decision can be made to stop SRT after five weeks i.e., 50 Gy, a dose that can be considered plausible in the palliative setting, and to change to systemic therapy. Unspecific bone uptake (UBU) is an issue for 68 Ga-PSMA-11 (and even more so for the now more widely used 18F-PSMA-1007). The experience gained in interpreting this new imaging method during the course of the PROPER I study resulted in fewer non-specific foci. However, our method with PET-results subordinated to the PSA response can be valuable for future patients with UBUs on PSMA-PET. This was demonstrated with the several cases mentioned above where biopsies confirmed false positive findings.

Another unique factor in our study is the sequential plan-on-plan VMAT optimisation method that we developed to adapt the SRT according to PSA response. When implementing new radiotherapy techniques, it is important to verify their robustness with thorough QA procedures (as reported previously [14]) and to prospectively study the clinical feasibility, as described in the present paper. We did not observe any statistically significant increase in long-term toxicity between responders and non-responders. Acute bowel toxicity was higher in patients receiving additional LNI, which does not preclude the use of LNI, but motivates the selective approach used in this study. The PROPER I trial is not powered to rule out the possibility of any significant differences in long-term tolerability between the groups. However, we feel confident about the safety profile shown in the LNI arm as it is both in line with what has been shown in other studies using LNI in the salvage setting [4], and consistent regarding physician-reported toxicity as well as patient-reported outcomes and quality of life.

This phase II study has some weaknesses. The sample size was rather small and the follow-up time short. The single-centre design may also limit the generalisability of the results. Another weakness is the definition of PSA response. A cut-off level of 0.15 ng/mL was the strongest predictor of short-term outcome (PSA < 0.1 ng/mL one-year post-SRT) according to early data from our previous prospective trial at the time of initiating the present study, and was therefore used to differentiate responders from non-responders. This analysis did not take into account other known predictive factors (e.g., PSA at baseline, Gleason score, surgical margins, time between surgery and SRT). Therefore, we developed a multivariable model based on the slope of the PSA curve during the first weeks of treatment (rather than a fixed PSA value at 5 weeks) and predictive clinical factors, as mentioned above. This updated model has been implemented in our ongoing phase III trial (see below).

In conclusion, we have evaluated a PSA-guided personalised treatment concept for intensified SRT with LNI. The high FPS rate among non-responders after the intensified SRT suggests a clinically significant effect with moderate side effects in a patient group with otherwise poor prognosis. Furthermore, we showed that the PSA response during SRT accurately discriminates patients with a very favourable outcome after local SRT (responders) from those with a high risk of treatment failure (non-responders). These results of PSA-guided SRT compare favourably with our earlier findings and motivate further investigations of the

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**Table 3**

| Site of recurrence (PSMA-PET) | All patients (N=97) | Responders (n=34) | Non-responders (n=63) |
|-----------------------------|-------------------|------------------|----------------------|
| Pelvic lymph nodes          | 10 (10%)          | 1 (3%)           | 9 (14%)              |
| Bone                        | 5 (5%)            | 1 (3%)           | 4 (6%)               |
| Bone and liver              | 1 (1%)            | 0 (0%)           | 1 (2%)               |
| All signs of recurrence (detection rate) | 25 (26%) | 3 (9%) | 22 (35%) |

**Fig. 3.** Patient-reported A) urinary and B) bowel symptoms from the EORTC QLQ-PR25 questionnaire (transformed to a 0–100 scale according to the EORTC scoring manual) for responders vs. non-responders at baseline, and 3 and 12 months post-SRT.
benefit of LNI for non-responders. In 2021, we launched a prospective phase III trial for this purpose (NCT04858880).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctradon.2022.07.001.

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