

Emerging treatments for recurrent prostate cancer

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Abstract

Despite radical treatment, many men with prostate cancer will develop recurrence of their disease. In an exciting era of new therapies for prostate cancer in general, we focus on how these will specifically benefit those men with recurrent disease. We consider salvage treatments aimed at those with local recurrence confined to the prostate gland, therapies for those presenting with metastatic recurrence and the approach to men presenting with a rising PSA but no demonstrable disease (M0). In general, men with recurrent disease are often under-represented in randomised clinical trials.

Subsequently, evidence to guide treatment for these men is often lacking and this needs to be addressed in order to improve and better define our approach to this problem in the future.

Key terms: Prostate, Cancer, Relapse, Recurrent, Salvage, Cryotherapy, Prostatectomy, Radiotherapy, Docetaxel, Immunotherapy,

Current word count:

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Observational studies have shown that in 30% of men radically treated for localised prostate cancer with, for example, radical prostatectomy or external beam radiotherapy, this primary therapeutic modality will fail.[1] The most suitable treatment will depend on the type of recurrence and the nature of prior interventions.

Patterns of recurrence

Biochemical recurrence

For many men the first indication of recurrence will be a rising serum prostate specific antigen (PSA) referred to as 'biochemical recurrence' (BCR). BCR following radical prostatectomy (RP) is defined as any detectable PSA level following surgery and has been reported to occur in up to 35% of patients [2]. The exact cut-off level used to define failure for trial purposes has varied from $>0.4\text{ng/mL}$, $>0.2\text{ng/mL}$ or even lower levels with the use of contemporary high-sensitivity PSA assays.

PSA levels after EBRT may never become undetectable and may "bounce" in the months following radiation. 'Bounce' is a benign phenomenon that occurs as a result of PSA production by recovering normal tissue in the prostate gland. In 2006 the American Society for Therapeutic Radiology and Oncology (ASTRO) re-defined criteria for BCR following EBRT as a rise by 2ng/mL or more above the nadir PSA.[3] This definition replaced the previous ASTRO

definition of a rising PSA over three measurements.[4] BCR rates of up to 63% have been reported following EBRT with mean time to recurrence of 34 months.[1]

Metastatic recurrence

This refers to demonstrable distant metastases outside the prostate gland on imaging studies, with or without a PSA rise.

Investigation of recurrent disease

Ultrasound and biopsy is the standard tool to diagnose local recurrence. However, this is an invasive procedure, with risks of infection and sampling error. Furthermore, results are often indeterminate in the recurrent prostate cancer setting, particularly in the initial 36 months following radiotherapy.[5] Multiparametric MRI (MP-MRI) combines anatomical and biological information and is a general term that covers the use of techniques such as dynamic contrast enhancement (DCE), diffusion weighted imaging and spectroscopy. Roy and colleagues retrospectively compared the effectiveness of all three of these modalities in diagnosing recurrent disease (confirmed on biopsy) in the post RP (28 patients) and post EBRT (32 patients) settings. Post RP the sensitivity was highest for T2 weighted MRI imaging with DCE (97%) followed by DCE alone (94%) and it was highest for T2WI plus DWI and DCEI (100%) in the post-EBRT setting. [6] [7] MR/ultrasound fusion guided biopsy has been shown to be superior in picking up high grade

prostate cancers compared to standard sextant biopsy with ultrasound [6], but its utility in detecting recurrent disease remains uncertain.

Metastatic disease can also be difficult to demonstrate using conventional imaging. CT and technetium-99m bone scanning are often not sensitive enough to pick up low volume disease at the time of BCR.[7] Conventional PET-CT using fluorodeoxyglucose is suboptimal in this context due to modest glucose consumption by prostate cancer cells, the fact that uptake in recurrent tumour is similar to that in postoperative scarring or benign tissue and its excretion via the bladder obscuring the view of the prostate / prostatic bed. PET-CT using 11C-choline, a tracer which targets components of the phospholipids in the prostate cell membrane, has shown better results [8][9] and novel PET radiotracers such as those that target prostate-specific membrane antigen (PSMA) are being investigated in the hope that these will show greater sensitivity and specificity for the detection of prostate cancer recurrences. [10, 11] [12] Sodium fluoride F-18 imaging has also shown promising results, specifically for the identification of bone metastases.[13]

Local salvage therapy

Although deferred ADT is the most commonly used therapy for BCR, local treatment options that are increasingly employed (up to 72% of those with BCR following EBRT).[14] These can offer a second chance of cure to such men. They include salvage prostatectomy (SRP), cryotherapy (CA), high

intensity focused ultrasound (HIFU) and photodynamic therapy (PDT).

Predictors that may help to select patients who will derive most benefit from these therapies include low risk disease at time of original diagnosis, time to PSA failure and longer PSA doubling times (PSADT) at the time of BCR.[15]

Lack of consistency in trials with regards to the use of ADT and in the definition of failure following salvage treatment means that indirect comparison of the efficacy of these novel therapies is challenging.

Salvage radical prostatectomy (SRP) following EBRT

Only a small proportion of men with BCR following EBRT will have SRP (0.9-2%) [16] and good quality prospective trials assessing outcomes are lacking.

A retrospective, multi-centre cohort analysis of 404 men with recurrent prostate cancer after EBRT who underwent SRP between 1985-2009 reported ten year biochemical disease free (bDFS) and cancer-specific survival (CSS) rates of 37% and 83% respectively. [17] The median age of patients was 65 and the median pre-SRP PSA was 4.5 (IQR 2.5-7.4).

Multivariate analysis identified a more favourable group (93 men; approximately 30% of the cohort) who had pre-SRP Gleason score less than or equal to 7 and pre-SRP PSA less than or equal to 4ng/mL and showed that they had a BCR free probability of 64% (95% CI 52-74%) at 5 years and 51% (95% CI 35-64%) at 10 years. However, these were uncontrolled data in a likely highly selected population, so their applicability to the clinical setting remains uncertain. More recently, a systematic review [18] showed that pre-SRP PSA and prostate biopsy Gleason score were the strongest prognostic factors for progression free survival and CSS following SRP. A recent

systematic review highlighted that BCR-free survival rates are significantly lower in trials that had longer follow up times (>40 months) indicating the time-dependent nature of BCR-free survival as an outcome measure. [16] Case series have described the use of laparoscopic and robotic surgery and overall trends suggest that newer surgical techniques are helping to decrease the morbidity associated with SRP.[19] However morbidity following salvage surgery remains significantly higher compared to primary prostatectomy. In one report, the 90-day major surgical complication rate was 47% versus 5% in the primary prostatectomy population. [20]

Minimally invasive salvage therapy following EBRT

These treatments have been reported only in case series, it having proven difficult to recruit patients to trials with a placebo or ADT-only control arm. [21] A retrospective, non-randomised comparison of salvage CA (56 patients) with SRP (42 patients) showed that SRP was associated with significantly better rates of biochemical disease free survival (bDFC) and overall survival (OS) (at 5 years OS 85% for salvage cryotherapy versus 95% for SRP, $p=0.001$) but there was no difference in disease specific survival (DSS).[22] Variations in baseline characteristics between the two groups in this study may explain at least some of the differences in outcome. Retrospective analysis shows that patients with low risk disease at initial diagnosis or pre-salvage PSA less than 5ng/mL had 3-year and 10-year bDFS rates of 73% and 64% respectively but those with high risk disease or pre-salvage PSA over 5ng/mL had rates of 11% and 6.7%.[23, 24] Focal cryotherapy has been explored in the COLD database which reports 5-year bDFS of 46.5% with similar toxicity to whole

gland CA.[25] Complication rates for CA include urinary retention (6.6-12%), incontinence (5.5-13%), recto-urethral fistula (1-3.3%) and erectile dysfunction (ED) in up to 80-90% of men.[23, 25, 26]

Case series describing the use of HIFU in the salvage setting have included heterogeneous populations with short follow up times.[27] A single institution review of 290 patients treated with HIFU for biopsy proven local relapse following EBRT reported 80% CSS rate at 7 years. As with CA, it is evident that HIFU should be used with caution in men with high risk features. In this study, 5-year progression free survival (PFS) rate was inversely related to pre-EBRT d'Amico risk score and was 45% (95% CI 32-63%) in the low risk and 21% (95% CI 13.6-32%) in the high risk group.[28] Murat and colleagues showed a similar difference in three-year survival rates between high and low risk groups.[29] Complications included rectal fistula in 2-16% [28, 30], urinary incontinence in up to 50% [29], pubic bone osteitis in 2.8% [28] and bladder neck obstruction requiring TURP in up to 38% of patients.[27]

Finally, PDT uses intravenous photosensitising drugs followed by a focal light treatment given via optical fibres into the prostate gland. Phase I/II trials are on going to find the optimal doses of both drug and light required to give the best anti-tumour effect.[31] There are no trials reporting efficacy data.

These newer techniques may be suitable for men with low risk disease who do not want or are not suitable for major salvage surgery however, toxicity profiles of these treatments are not clearly superior to SRP.

Salvage EBRT following primary RP

Retrospective multivariate analyses have shown that salvage EBRT was associated with decreased cancer specific mortality [32] and all cause mortality [33] for patients who have BCR following primary treatment with RP. Trock and colleagues [32] found that the increase in prostate cancer specific survival (HR 0.32 (CI 0.91-0.54; $p < 0.001$) was limited to those men with a PSADT of less than 6 months, those who received SRT within 2 years of BCR and those patients whose PSA had become undetectable at some stage post RP. For men who underwent SRT their median age was 58.3 years, average PSA pre-op was 8.3 and PSA pre-SRT was 0.7. There was a difference in prognostic factors between SRT, SRT plus HT and no SRT groups but no group overall had a worse prognostic profile. Fewer men undergoing SRT had lymph node involvement compared to those not undergoing SRT but CSS was still significant after analysis was repeated to exclude those with LN metastases. Choueiri and colleagues [33] reported that those in their cohort who underwent salvage therapies were more likely to have Gleason 8-10 disease, T3b and above and PSADT < 6 months. Details of patient comorbidities were not reported and may be an important confounder for all cause mortality in this group. A larger study ($n = 2657$) that retrospectively looked at the benefits of SRT for 865 men who had BCR following RP found that they had lower risk of local recurrence and metastatic progression but there was no effect on overall survival compared to ADT alone. Specifically, improved survival was not apparent among patients with PSADT < 6 months. Stephenson and colleagues have constructed a nomogram to predict which

men will benefit most from salvage EBRT [34]. They show that factors such as pre-treatment PSA, positive surgical margins and seminal vesicle involvement adversely affected 6-year bDFS after SRT [35].

Importantly, it has also been reported that using a different approach and giving radiotherapy adjuvantly for high-risk patients following RP improves biochemical progression free survival compared to observation.[36-38]

Debate is on going surrounding which approach is better and head to head comparison trials to investigate this are under way (GETUG 17 (NCT00667069), RAVES (NCT00860652) and RADICALS (NCT00541047)).

Salvage EBRT plus hormone therapy

Recently, the results of a phase III randomised trial have reported a significant improvement in 5-year PFS (72% versus 62%) for patients with BCR following RP treated with radiotherapy plus ADT versus radiotherapy alone.[39] There was no OS benefit but there were only 11 deaths in the whole group indicating that longer follow up times are needed to assess OS. RTOG 96-01 compared salvage RT to salvage RT plus two years of bicalutamide 150mg and reported improved failure free survival. RTOG 0534 (NCT00567580) will assess the benefit of adding short term ADT to SRT with or without extended radiotherapy fields to include lymph node beds. STREAM NCT02057939 will investigate if adding enzalutamide to ADT can improve outcomes further.

Systemic therapy in recurrent prostate cancer

Non-castrate M0 disease

For many men with BCR but M0 disease, local salvage therapy is inappropriate because of a high clinical suspicion of distant micro-metastases. In this situation the standard of care is ADT. It is not clear if ADT should be used at the time of BCR or deferred until a “threshold” PSA or M1 disease is reached. Retrospective analysis of 1352 patients with PSA rise after RP showed no significant difference in OS or CSS for either approach.[40] The TROG 03.6 (TOAD) trial, which compared immediate (n= 142) with deferred ADT (n=151) in men with rising PSA with or without prior radical treatment or in those with asymptomatic disease at diagnosis who are unsuitable for curative treatment. 89 (58.9%) patients in the delayed arm were eventually treated with ADT at a median time of 18.7 months. It closed without full accrual but early results have shown that there was a non-statistically significant decrease in death from all causes (HR 0.54, (95% confidence interval (CI) 0.27,1.06, p = 0.07) and prostate specific death (HR 0.50 CI 0.17,1.51, p = 0.22) in patients undergoing early ADT. Not surprisingly, in this trial there was a greater burden of toxicity among those patients randomized to receive early ADT.[41]

Combining chemotherapy with initial ADT in patients with BCR but M0 disease has been investigated in an uncontrolled phase II trial (n=62) which suggested this might improve outcomes. [42] The STAMPEDE trial has recently reported statistically and clinically significant improvements when docetaxel was added at the time of initiation of ADT in men with high risk locally advanced or metastatic hormone sensitive prostate cancer. At the first

analysis however there was no significant survival benefit for the subgroup of patients without metastatic disease (39% of the total group), although there was a significant delay in time to recurrence. Men with BCR following radical treatment were included in this trial, but constituted less than 6% of the total group and so the use early use of docetaxel in this specific setting remains uncertain.[43]

Non-castrate metastatic (M1) recurrence following local therapy

The standard of care for treatment of metastatic disease is ADT. A recent Cochrane review reported significantly poorer OS when non-steroidal anti-androgens were used alone compared with castration (HR 1.34, 95% CI 1.14–1.57, 2103 participants), and so castration therapy remains the treatment of choice in this setting.[44]

There has been increasing interest in additional therapies to ADT at this point of hormone sensitive disease rather than waiting for the disease to become castrate refractory. The “CHAARTED” trial reported a 13.6 month median OS benefit using upfront docetaxel with ADT compared to ADT alone in men with hormone naïve metastatic prostate cancer. In a pre-planned subgroup analysis, patients with high volume metastatic disease (visceral disease and/or 4 or more bone metastases including at least one extra-axial metastasis) had a 17 month improvement in median OS (40% reduction in risk of death). With a median follow up of 29 months there were insufficient events to demonstrate a significant benefit in the subgroup with low volume disease. 27% of patients had prior radical treatment and the overall benefits

of the trial were maintained in this subgroup although the confidence intervals remain wide at the first analysis. [45] These data were tempered by contradictory results from the GETUG-15 trial which did not show a significant difference in OS (median 58.9 months in ADT plus docetaxel group (n=193, CI 50.8-69.1) and 54.2 months (n=192, CI 42.2-not reached) in the ADT alone group (HR 1.01, CI 0.75-1.36, p=0.955)). This trial included 272 patients with metastatic disease at diagnosis and 108 who had received prior radical treatment.[46] Most recently, the STAMPEDE trial reported a significant OS benefit for the addition of docetaxel to initial ADT (median survival 77 months versus 67 months for ADT alone; hazard ratio 0.76 (95% CI 0.63, 0.91;p=0.003)) in men with metastatic or locally advanced disease.[43]

In summary, despite some conflicting results, it seems clear that the addition of docetaxel at the point of initial ADT results in improved OS for men presenting with metastatic disease at diagnosis. These trials only included small numbers of patients failing with metastatic disease after previous radical treatment, and so there remains uncertainty about the value of adding chemotherapy for these patients.

Recurrent disease when on adjuvant hormones (Castrate Resistant Prostate Cancer) (M1 and M0)

M1 versus M0 disease

There have recently been several significant advances in the treatment of mCRPC and these have been reviewed elsewhere. [47] However, for the

subgroup of men with M0 castration resistant disease there remains high unmet need. These men are at high risk of developing metastases and subsequent death from prostate cancer, but there are currently no licensed treatments which prevent or delay stage progression. In particular these patients were not included in the pivotal trials of docetaxel, abiraterone or enzalutamide and there are no data to support their use in this setting. There are two on-going trials of note: The PROSPER trial (NCT02003924) is a placebo-controlled trial of enzalutamide and the SPARTAN trial (NCT01946204) explores the role of the novel, highly potent androgen receptor antagonist ARN-509. Both trials have a primary endpoint of distant metastasis free survival and continue to accrue patients.

Bone therapies for recurrent CRPC (M1 and M0)

Zoledronic acid (ZA) and denosumab have established roles in preventing skeletal related complications in men with CRPC and bone metastases.[46-48] Neither agent has provided survival benefit. The STAMPEDE trial failed to show a survival benefit from adding ZA to ADT alone (HR 0.93, 95% CI 0.79,1.11; p=0.437) or to ADT plus docetaxel in men with locally advanced or metastatic prostate cancer. Radioisotope treatment using radium-223 has shown improvement in median OS in men with mCRPC. The specific role of all of these therapies in recurrent disease remains the subject of investigation. [48]

The role of bone targeted therapy in M0 disease remains controversial. A large randomized phase III trial of denosumab did show a 4.2 month delay in time

to bone metastasis in men with high risk M0 CRPC, but there was no improvement in OS and the drug is not licensed in this setting.[49]

Immunotherapy for CRPC (M1 and M0)

Sipuleucel-T has been reported to extend median and 3-year survival in men with mCRPC. [50] A retrospective, unplanned subgroup analysis suggested that men with low PSA at trial entry had a much greater survival gain than those with high PSA suggesting that it could be useful at the time of early metastatic disease relapse after radical treatment. The phase III PROTECT trial showed that Sipuleucel-T immunotherapy prolonged PSADT when added to ADT to treat men with BCR after primary prostatectomy (M0). The study did not meet its primary objective of extending time to biochemical failure or the secondary objective of improving OS although extended follow up may yet prove clinical benefit in this setting. [51]

Other immune therapies including the vaccine therapy PROSTVAC-TRICOM and the immune checkpoint inhibitor ipilimumab have shown early signs of clinical benefit in CRPC and remain in clinical development in mCRPC. [52] [53]

Overall, immunotherapies may be more effective if given relatively early in the course of the disease [53] rather than after exhausting all other therapies. Hence they may be a promising approach in men with recurrent prostate cancer after failure of radical treatment.

Future considerations

Finally, Robinson and colleagues have recently described abnormalities at the genetic level in bone or soft tissue tumour biopsies from 150 men with CRPC. [55] 89% had a potentially “actionable” genetic mutation such as an alteration in the androgen receptor gene (62.7%). The treatments available to take advantage of this genetic testing are sparse and this personalised approach is still very much in its infancy and in the realm of clinical trials for prostate cancer. The aim for the future will be to offer targeted treatment against aberrations in the genetic profile of a man’s prostate cancer in the hope of increasing efficacy and specificity of therapeutic agents and decreasing the side effects from futile therapies.

Future perspective

The pattern and distribution of prostate cancer is changing. At present, a significant proportion of the men who die from prostate cancer do so having presented with advanced disease and, thus, have not received prior radical treatment. Through improved diagnosis and screening, more men are presenting with organ-confined disease and undergoing radical treatments. In addition, as life expectancy continues to increase, we can expect more of these men to develop problems associated with recurrent disease. Thus it is

likely that, in the future, the problem of recurrent prostate cancer will become a significant burden. Although the concept of local salvage therapy is well established, conventional salvage therapies can be associated with significant morbidity and evidence to support novel interventions is still relatively poor. Despite major steps forwards in our understanding of systemic therapies in advanced prostate cancer, most of the trials which have been undertaken have failed to specifically address the needs of men with recurrent cancers and there is a need to better understand their application to this group of men.

Executive summary (Not included in word count)

Patterns of recurrence
- Biochemical: Any rise in PSA after prostatectomy and rise of 2ng/dL over nadir after EBRT. Metastatic refers to demonstrable distant disease.
Local salvage treatments
- CA, HIFU and PDT are emerging treatments to rival salvage prostatectomy. – Salvage radiotherapy can benefit men with local relapse after RP but choosing which men will actually be cured by this approach and how it compares to adjuvant RT with or without concurrent ADT is still under investigation.
Systemic therapy in recurrent prostate cancer
- Recent evidence suggests that immediate ADT may be superior to delayed treatment but further trials to look specifically at this group of patients are needed.

- A paradigm shift with regards to the use of upfront docetaxel with ADT in those with metastatic disease has recently occurred. Patient presenting with relapse of previous disease were under-represented in the pivotal trials that showed this survival benefit.

- There are now multiple treatments for metastatic CRPC that prolong survival such as docetaxel, carbazitaxel, enzalutamide, abiraterone, radium 223 and immunotherapy. The evidence for treatment of those with recurrent M0 CRPC disease is sparse.

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Financial disclosures

RJJ receives research funding, speaker honoraria and consultancy payments from Astellas, AstraZeneca, CureVac, Dendreon, GSK, Janssen, Novartis, Pfizer, Roche, Steba.

CH has no disclosures.