REVIEW PAPER

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Salvage local therapy for radiation-recurrent prostate cancer – where are we?

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Introduction Prostate cancer is the most frequent cancer among males in Europe and a leading cause of cancer deaths, with similar proportion in other developed countries. For more than twenty years, external-beam radiation therapy, alongside with radical prostatectomy, has been used as a primary radical therapeutic approach for localized prostate cancer. Yet, EBRT failures relate to 22–69% following curative radiotherapy (± androgen deprivation therapy). Additionally, a proportion of these men will have a biopsy-proven local recurrence.

Material and methods The Medline and Web of Science databases were searched without a time limit during March 2016 using the terms 'prostate cancer' in conjunction with 'radiotherapy', 'recurrence', 'biochemical', 'salvage', 'brachytherapy', 'prostatectomy', 'HIFU', 'cryotherapy' and 'focal'. The search was limited to the English, Polish, German and Spanish literature.

Results Currently, salvage treatment after failed radiotherapy includes radical prostatectomy, brachytherapy and ablative whole-gland therapies, such as cryotherapy and high intensity focused ultrasound. New approaches, so called focal salvage therapy, involve ablation of only the zone of recurrence in order to decrease tissue injury and therefore to diminish morbidity.

Conclusions At present no authoritative recommendations can be concluded because of the absence of randomized data with standardized definitions and protocols. Nevertheless, we believe that local salvage treatment should be at least considered in patients after biochemical relapse following radiotherapy.

Key Words: salvage ‹› prostate cancer ‹› biochemical recurrence ‹› radiotherapy

INTRODUCTION

Prostate cancer (PCa) is the most frequent cancer among males in Europe and a leading cause of cancer deaths with similar proportion in other developed countries.

For more than twenty years, external-beam radiation therapy (EBRT), along with radical prostatectomy (RP), was being used as a primary radical therapeutic approach for localized prostate cancer. Approximately one third of PCa patients choose EBRT as a primary treatment. Despite progressive increases in prescribed and delivered radiation and the introduction of many technological advances like three-dimensional conformal radiation therapy (3DCRT), intensity-modulated radiation therapy (IMRT) or image-guided radiation therapy (IGRT), EBRT failures relate to 22–69% of cases after curative radiotherapy (RT) (± androgen deprivation therapy (ADT)). Additionally, a proportion of these men will have a biopsy-proven local recurrence [1, 2, 3]. Biochemical recurrence (BCR) rates depend on the PCa risk in the D'Amico classification. The five-year BCR-free survival percent amounts to 75–80%, 58–65% and 35–38% for low, medium and high risk cancers, respectively [4].

20–30% of all recurrent cases are local recurrence patients, which could benefit from local salvage therapy (LST) [5, 6]. However, only a small percentage of local recurrence cases are managed with a local

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salvage approach, with the majority of patients ending up in observation protocols or receiving ADT. It is caused by concerns of high LST toxicity [7, 8]. Nevertheless, in these patients, the median time from BCR to metastases development is about 3 years if watchful waiting is adopted [9]. Also ADT therapy is associated with significant side effects, such as weight gain, osteoporosis with fracture risk, or metabolic syndrome and additionally, with high therapy cost. Since only a small amount of good quality data is available, there is no consensus regarding the most appropriate management of PCa recurrence after EBRT. In this paper, we review the current therapeutic options for patients with radiation-recurrent PCa.

MATERIAL AND METHODS

The Medline, and Web of Science databases were searched without a time limit during March 2016 using the terms 'prostate cancer' in conjunction with 'radiotherapy', 'recurrence', 'biochemical', 'salvage', 'brachytherapy', 'prostatectomy', 'HIFU', 'cryotherapy' and 'focal'. Boolean operators (NOT, AND, OR) were also used in succession to narrow and broaden the search. Auto alerts in Medline were also run, and reference lists of original articles, review articles, and book chapters were searched for further eligible articles. The search was limited to the English, Polish, German and Spanish literature. Articles that did not address the topics were excluded, and the full text of the remaining articles was reviewed.

Recurrence definition

Recurrence definition differs between men who have undergone RP and those who have received RT. It is generally acknowledged that in patients who undergone RP, BCR is defined by two consecutive PSA values of >0.2 ng/mL and rising [10]. After RT, the RTOG-ASTRO Phoenix Consensus Conference definition of BCR is any PSA increase above 2 ng/mL higher than the PSA nadir value, regardless of the serum concentration of the nadir [11]. However, it should be noted that, a PSA rise after RT may also be associated with a 'PSA bounce' phenomenon. This occurs due to the remaining areas of viable normal glandular tissue inside the prostate that produces PSA after RT [12].

Diagnosis

Determining the site of recurrence is crucial in BCR patients. Generally, patients with high-risk of metastases development present with a PSA – Doubling Time (PSA-DT) <3 months, time to biochemical progression below 3 years, biopsy Gleason score from 8 to 10 or clinical stage cT3b-T4. Contrariwise, patients with low risk of metastases are those with a PSA- DT more than 15 months, biopsy Gleason score below 7, clinical stage lower than cT3a and time to biochemical progression above 3 years [13, 14].

Local recurrence may be initially diagnosed by a digital rectal examination (DRE) or transrectal ultrasound (TRUS). However, DRE and TRUS are not reliable in revealing local recurrences. Multiparametric MRI (mpMRI) has shown good results in the local recurrence diagnosis, and additionally can be used for biopsy targeting and for LST guiding [15, 16]. Other technologies such as choline PET/CT can be also used, yet, PET/CT has a lower resolution than mpMRI [17, 18]. Among other examination options, histological assessment of biopsy specimens is the most important diagnostic tool. However, imaging and/or biopsy should be performed only in patients who are considered candidates for LST. Yet, it is necessary to obtain histological proof of the local recurrence before treating the patient [15]. Post-RT prostate specimens ought to be assessed by a pathologist who is experienced in this field. False-positive results can be observed due to difficulties in distinguishing radiation-induced atypia of benign glands from malignancy. Additionally, tumor resolution after RT has no identifiable glandular morphology, and these remnants can be given a high Gleason score [3, 19, 20]. Furthermore, the timing of biopsies has become a subject of debate. Cancer clearance after RT may last up to 30 months, therefore, early biopsy is associated with an overestimation bias. On the other hand, early diagnosis seems to be an important positive prognostic factor. Consequently, biopsies should be performed at least 24–36 months after RT [7, 19].

In determining distant or lymph node metastasis, imaging modalities such as bone scintigraphy or computed tomography (CT) have low diagnostic value, unless PSA level is higher than 10 ng/mL, or with the presence of adverse PSA kinetics (PSA-DT <6 months, PSA velocity >0.5 ng/mL/month) [21]. Generally, choline PET/CT is recommended to determine metastasis, however, some new techniques, such as whole body MRI (WB-MRI), PET with radiolabelled PSMA, bombesin or uPAR and PET/MRI, have been recently introduced [22, 23, 24]. In comparison with choline PET/CT, the effectiveness of newer methods is promising, yet, due to the lack of evidence, their value is to be established.

Indications for local salvage therapy

The EAU guidelines recommend consideration of LST for patients with low comorbidity index,

a life-expectancy of more than 10 years, an organ-confined prostate cancer (T1–T2), Gleason score ≤7 and a lower than 10 ng/mL. The NCCN recommends LST in patients with an original clinical stage of T1–T2, Nx or N0, life-expectancy of more than 10 years and a preoperative PSA level lower than 10 ng/mL. The NICE prostate cancer guidelines mention the option of salvage treatment without exact patient criteria. In summary, recent oncological guidelines recommend consideration of LST in patients with positive prostate biopsy who presented with initial T1/T2 disease, currently have less than 10 ng/mL PSA, have low or no suspicion of metastases and have at least a 10 year life expectancy [25, 26, 27].

Salvage treatment

Currently, salvage treatment after failed RT includes radical prostatectomy (sRP), brachytherapy (sBT) and ablative whole-gland therapies, such as cryotherapy (sCT) and high intensity focused ultrasound (sHIFU). New approaches, so called focal salvage therapy, involve ablation of only the zone of recurrence in order to decrease tissue injury and therefore diminish morbidity [19].

Salvage prostatectomy

Salvage prostatectomy yields a satisfactory oncological control with biochemical disease-free survival (b-DFS) of 31–82% at 5 years and at 30–53% at 10 years [7, 28]. Clinical disease-free survival (c-DFS) applies to 71–83% at 5 years and 61% at 10 years. Overall survival (OS) varied from 54% to 89% at 10 yrs. [7]. Patient selection is essential when considering sRP. When stratifying patients according to the EAU criteria, patients who met the guideline criteria showed a significantly better b-DFS survival and a strong trend towards a better metastasis-free survival (MFS) and cancer specific survival (CSS) [29].

SRP can be performed by an open, laparoscopic or robot-assisted approach. In patients who present with locally advanced disease (bladder neck and/or rectum infiltration), cystoprostatectomy, pelvic exenteration, or prostatectomy with permanent umbilical cystostomy may be an option. Lymph node dissection is a subject of debate, there is not enough data to give authoritative guidelines.

SRP is a procedure associated with a high risk of complications, such as incontinence, urethral stricture formation, rectal injuries and impotence in those men who still have erections. This could be explained by fact that RT results in extensive fibrosis, tissue planes merging and poor wound healing. Depending on the study group, incontinence applies to 10–80% patients, anastomotic stricture to 17–32% and rectal injuries to 3.3–50% [30–34]. In some small studies, urinary incontinence reached 100% of patients [35]. Other complications include ureter damages, urinary fistulae, lymphocoeles and obturator nerve injury. SRP is also associated with a higher rate of complications when compared to primary RP. Total complication rates apply to 23% and 60%, 30-days mortality to 0% and 6%, anastomosis stricture to 12% and 55% and 5 year CSS to 99% and 86% for primary and SRP, respectively. SRP is additionally a more expensive procedure than primary RP [36]. Thanks to the improvements in surgical experience and the emergence of technical advances, such as laparoscopic and robotic surgery, complications are less common in more recent studies [7, 29]. In some papers on laparoscopic sRP, major complications (Clavien 3–5) occurred in 0–11% of patients with no rectal injury or anastomotic strictures. In series on robotic sRP, 0–9% of patients had rectal injury, and 9–33% of patients developed anastomotic stricture after surgery [31, 34, 43, 49, 50]. Major complications (Clavien 3–5) occurred in 9–33% of patients [7, 34, 37, 38].

Salvage brachytherapy

Majority of older studies concerning sBT are based on low-dose rate (LDR). More recently, there have also been reports with high-dose rate (HDR) brachytherapy. Although most of HDR series have short follow-up time, all present good failure-free survival rates [39–44].

Generally, sBT have proved good CSS and b-DFS. In various studies b-DSF varied from 48–89.5% for 3 years follow-up, 70–75% for 4 years to 20–65% for 5 years [45–50]. However, the number of patients enrolled in these studies is often limited, and median follow-up rarely exceeds 60 months. Frequent complications comprise LUTS, nocturia, and gastrointestinal complications. Late genitourinary Radiation Therapy Oncology Group (RTOG) G1 and G2 toxicities were found in 38% and 48% of patients. The occurrence of G3–G4 genitourinary and gastrointestinal complications ranges from 0% to 47% and from 2.7% to 24%, respectively [51, 52]. In conclusion, sBT appears to be a potentially useful salvage therapy that needs further evaluation.

Salvage cryotherapy

Cryotherapy ablation is based on freezing and thawing prostatic tissue, which causes direct damage to prostate cells as well as secondary injury from the inflammatory response. The freezing is obtained by introducing liquid nitrogen or argon circulating

through hollow needles. Adjacent tissues (urethra) are protected by a warming catheter and thermocouplers. Nevertheless, this creates a risk of excluding cancer foci in the regions such as the apex or peri-urethral tissue.
In some studies, sCT has proven 40–58% b-DFS, which can be up to 73% in patients with primary low-risk disease. Yet, different criteria were used to establish efficacy [53–60]. When compared to sRP, sCT resulted in inferior b-DFS by both definitions of biochemical failure and an inferior OS [61].
SCT, as other methods, is not free from complications. Rates of urinary incontinence, obstructive symptoms, sexual impotence and severe perineal pain, rectal injuries (fistula) refer to 73%, 67%, 72%, 8% and 3%, respectively.
Furthermore , a single course of cryoablation is often not sufficient and multiple sessions are needed, provoking a significant growth in morbidity [51, 52]. In conclusion, at present there is no robust evidence in favor of cryotherapy in the salvage setting after RT failure.

Whole-gland salvage HIFU

High-intensity focused ultrasound is a local prostate ablation using focused intense ultrasound waves that heat the targeted region. In the largest published experience, Crouzet et al. described 290 patients, with the longest follow-up of 48 months achieving 7-year cancer-specific and MFS rates of 80% and 79.6%, respectively [62]. In other studies, rates of b-DFS ranged from 25% to 75%, yet, majority of the studies present short follow-up periods, ranging from 6 months to 5 years [63–67]. Frequent complications after HIFU include incontinence (10–50%), bladder neck stenosis (17%), retention due to urethral stricture (17%), and rectal injury (fistula) (3–16%) [19, 52]. In one study, 11% of patients required the implantation of an artificial urinary sphincter [66]. It is also proved, that HIFU in the salvage setting led to local complications much more frequently than when used as a primary treatment [66, 68]. To diminish acute urinary retention and bladder outlet obstruction after HIFU, some authors advocate performing a bladder-neck incision before an HIFU procedure [66].
It has to be remembered that an HIFU series, similarly to other local salvage modalities, are heterogenic in the definition of PSA failure, and present a short follow-up time. It is possible that with longer follow-up recurrence rates would be different.

Focal treatment

Whole-gland ablative methods are applied to the entire prostate. Due to surrounding tissue damage they are associated with significant toxicity, such as incontinence, urethral stricture formation, rectal injuries and impotence in those who still have erections. In theory, improved disease localization can allow the use of focal salvage treatment with significantly lower complication rates. However, this requires precise localization of intraprostatic recurrence and accurately targeted ablation, which are often challenging. In studies on focal salvage therapy, localization is performed by mpMRI, transperineal template prostate mapping biopsy (TPM) or by TRUS-biopsies. The definition of success and failure of focal therapy presents another issue that needs to be resolved.
In recent meta-analysis, focal salvage treatment b-DFS rates were reported at 70%, and 54% at 4 and 5 years [69]. Authors of Cryotherapy Online Data registry (COLD) showed b-DFS rates of 95.3%, 72.4%, and 46.5% at 1, 3, and 5 years, respectively [70]. However, it should be remembered that very small numbers of cases limit the generalizability of these findings considerably. The aforementioned analysis showed that continence was achieved in 87.2–100% of cases, potency was preserved in 29–40% of previously potent patients, and the rate of rectourethral fistula applied to 0–12% cases. The total complication rate was significantly higher than in the primary cases.

CONCLUSIONS

The rate of BCR after primary curative EBRT for PCa is not negligible. For BCR patients, LSTs, such as sRP sCT, HIFU, sBT and their focal modalities, are the only available options that offer potential for cure. Generally, b-DFS rates between different methods are comparable, oscillating between 52% and 57% at 5 years. The theoretical superiority of sRP over other salvage methods may be attributed not only to a desirable positive effect of the associated LND on micrometastases (as previously shown, the data are insufficient to defend this theory), but rather to the peculiar pattern of tumor recurrence after RT [71], i.e. in the peri-urethral zone, which is generally spared during these approaches to minimize side effects [72].
However, it should be remembered that available studies are heterogenic in patient selection criteria, definition of PSA failure, follow-up time limit and ADT usage. Moreover, majority of studies are retrospective in nature and include a small number of patients.
At present no authoritative recommendations can be concluded because of the absence of randomized data with standardized definitions and protocols. Nevertheless, we believe that LST should be at least considered in patients after biochemical relapse follow-

ing RT. Some of mentioned studies have identified factors associated with good response to LST. These factors include a long PSA-DT, a low pre-salvage PSA, and a lower Gleason score at the recurrence time. Patients with these factors, who had initial low-risk disease and present long enough life expectancy, are most likely to respond to LST.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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