INTRODUCTION

Globally, prostate cancer (PCa) has the second highest incidence to lung cancer among males and is the second leading cause of cancer, with an estimated 358,989 deaths in 2018. [1]

Options for the primary management of localized PCa most commonly include radical prostatectomy (RP) and radiotherapy (RT) with or without androgen deprivation therapy, or a combination of both. Patients over the age of 65 are more likely to receive RT than surgery [2,3] Thanks to the development of advanced radiation treatment technologies, is it now possible to achieve dose escalation limited to the gland while avoiding the surrounding structures [4]. However, biochemical recurrence (BCR) occurs within 5 years after treatment in nearly one-third of patients treated with radical RT for localized disease [5].

Biochemical failure after radiation therapy was initially defined by the American Society for Therapeutic Radiology and Oncology (ASTRO) and then revised at a Consensus Conference with the Radiation Therapy Oncology Group of Phoenix, Arizona in 2005. The current ASTRO-Phoenix criteria define biochemical failure after external beam radiotherapy (EBRT) as a PSA rise equal to or greater than 2 ng/mL above the nadir PSA regardless of hormonal therapy administration [6].

However, especially in the first 2 years after RT, PSA fluctuations are common. Therefore, a post-RT PSA increase could be expression from either malignant or benign prostate tissue [7]. Prostate biopsies and diagnostic imaging are helpful in identifying true local recurrence. Despite its limitations in the setting of previously irradiated tissues, the correlation between histologic findings and PSA could help in recognition of truly localized recurrence, which would most likely benefit from local treatment, and unrecognized metastatic disease.[8] While the detection rate of conventional anatomic magnetic resonance imaging (MRI) has traditionally been limited by the glandular atrophy and fibrosis induced by RT, evidence regarding the role of multiparametric MRI (mpMRI) in the detection of radiorecurrent disease is growing [9]. Choline positron emission tomography (PET)/computed tomography (CT), fluciclovine PET and 68Ga-labeled PSMA ligand PET/CT were found to be more efficient than conventional imaging in restaging patients with BCR [10].

Therapeutic strategies adopted for local relapses include salvage prostatectomy, re-irradiation (with brachytherapy [BT] or external beam RT [EBRT]), high-intensity focused ultrasound (HIFU) and cryotherapy (CRYO). However observation currently represent the most commonly chosen option for therapeutic

management of these patients, with only a small proportion of patients with radiorecurrent prostate cancer (between 15% and 20%) undergoing local salvage therapy [11].

Unfortunately, ADT is not curative and there is a well-known association of ADT with diabetes, coronary heart disease, myocardial infarction, and sudden cardiac death. In patients with comorbidities, ADT is associated with increased mortality and should be used cautiously. In fact, ADT therapy is most beneficial in settings of subclinical metastasis outside of the radiation field rather than as a tool to control local disease in the setting of failed RT [12]. Use of ADT in salvage settings is most warranted in men with high-risk disease features such as pT3b/4 and grade group ≥ 4 or those with features of pT3b/4 and early salvage RT PSA ≥ 0.4 ng/ml (12). However, the majority of radiorecurrent prostate cancers are localized to the prostate [13], making patients potential candidates to local curative treatment options.

The aim of this review was to conduct a comprehensive analysis of the role of minimally invasive salvage modalities in radiorecurrent prostate cancer and the associated clinical outcomes and toxicity profiles.

EVIDENCE ACQUISITION

Literature search strategy

A review of the current literature was conducted through the Medline and NCBI PubMed, Scopus databases in January 2020. The updated PRISMA guidelines [14] were followed for this systematic review.

Keywords used were “salvage radiotherapy”, “salvage hifu”, “salvage high-intensity focused ultrasound”, “salvage brachytherapy”, “salvage cryotherapy”, “salvage prostatectomy”, “recurrent prostate cancer”, “radio-recurrent prostate cancer”. We used the previous keywords as our primary search string, which combine established MeSH terms for prostate cancer, diagnosis, and treatment combined with the highly sensitive Cochrane search strategy. [15] Reference list of the retrieved reviews were also checked and cross-referenced. Following literature search, all duplicates were manually excluded.

The searches were performed independently by two researchers (GM and FC), and any disagreement resolved by a third independent researcher (NS). The initial screening was done on the base of titles and abstracts.

Inclusion and exclusion criteria

All papers published after 2000, concerning studies conducted on humans for radio-recurrent prostate cancer were considered for the review. Only original articles (randomized controlled trials, cohort studies, case-control studies) regarding a series of more than 5 patients were included. Other publications such as reviews, commentaries, editorials and letters to the editor were excluded. The most recent publication was considered if more studies evaluating the same patient cohort. Only studies published in English and about minimally-invasive treatment for radio-recurrent PCa were considered.

Data extraction design

To assess the overall risk of bias and Levels of Evidence (LoE) was assessed by the three reviewers using theROBINS-1 tool recommended by Cochrane and the OCEBM criteria. [16,17] Variables that were recorded, when possible, include: variables related to the publication (year, country, design of the study); primary radiotherapy data (age, PSA, D'Amico Class Risk), time from radiotherapy to salvage therapy, biochemical recurrence definition, pre-salvage therapy data (PSA, staging method, biopsy), salvage therapy data (type of salvage therapy, adjuvant ADT, Follow-up, oncologic outcomes, toxicity data with the complications/toxicity classification used).

Statistical analysis

Data were entered into a Microsoft Excel (Version 14.0) database and then transferred to Sofastat TM 1.4.6 for Windows. Descriptive statistics were calculated for all demographic, treatment, clinical and follow-up variables, and reported as median (first to third quartile) or as a proportion with percentage.

EVIDENCE SYNTHESIS

Overall, 545 studies were identified. After duplicate exclusion, initial screening, and eligibility evaluation, a total of 80 studies, 68 retrospective and 12 prospective, were included in the qualitative analysis, corresponding to a cohort of 6681 patients. A flowchart of the systematic review is presented in Fig. 1. The data are summarized in Table.1-5. Overall, studies were of poor to moderate quality based on the risk of bias assessment. (Figure 2).

The median age at initial diagnosis ranged from 59 to 75.5. Pre-treatment PSA ranged from 6.2 to 27.4 ng/ml. All patients underwent primary RT for localized prostate cancer, and EBRT was the modality most widely used. Biochemical recurrence after primary treatment was assessed using Phoenix definition in the majority of cases, but some also used ASTRO or Stuttgart definitions. To assess local relapse, patients underwent different imaging modalities including MRI, choline PET and ultrasound. Diagnosis of local recurrence was confirmed by biopsy in the majority of the studies. Pre-salvage treatment PSA ranged from 3.1 to 14.4 ng/ml. Overall, ADT was used before primary treatment, between primary and salvage treatment, and during or after salvage treatment in 35 studies. Toxicity was mainly reported using Common Terminology Criteria for Adverse Events (CTCAE) and Clavien-Dindo scales [98,99]. Oncologic outcomes were reported as biochemical recurrence free survival (bRFS), biochemichemical progression free survival (bPFS), cancer specific survival (CSS), overall survival (OS), metastasis free survival (MFS) and ADT-free survival (ADT-FS). The median follow-up after salvage therapy ranged from 9 to 61 months.

Salvage radiotherapy

Few studies are available on salvage radiotherapy (Table 1). In the majority of them, the technique used was Stereotactic body RT (SBRT), which is similar to EBRT except that the treatment dose is typically delivered in 2 to 5 total fractions. To our knowledge, the largest study (29 patients) is by Fuller et al. [24], who reported a bRFS of 82% at 2 years, with GU toxicity of grade ≥2 in 18% of patients and no patients with GI toxicity above Grade 1. In another small series, Mbeutcha et al. [19] reported 1-year bPFS of 70% among their 18 patients. They reported a low rate of toxicity, with only one patient experiencing transient CTCAE v4.0.3 urinary complication and no grade 3-4 GI toxicities. We also found a study evaluating salvage CyberKnife-based ablative radiotherapy (SABR) [18]. In this study, Miszczyk et al. reported 1-y bPFS of 68% among their 38

patients, with CTCAE v4.0 acute GI toxicity in 3% of patients, acute GU toxicities in 21%, late GI toxicities in 11% and late GU in 37%. Data suggests that salvage EBRT is a promising approach for recurrent PCa control, with acceptable toxicities.

Salvage brachytherapy

We included 24 studies on salvage brachytherapy (SBT), published from 2003 and 2019 (Table 2). Oldest studies include a patient population that was largely treated with variable rates of ADT prior to salvage BT, resulting in a wide range of biochemical control outcomes. However, in more recent studies, salvage BT appear to be able to achieve bPFS in more than half of all local failures in patients who are candidates for the procedures. The largest reported case series of patients receiving salvage BT was published by Henriquez-Lopez et al. [26]. In this study of 119 patients with biopsy-proven, locally-recurrent PCa the 5-year prostate-specific antigen (PSA) RFS rate was 71% and the 5-year CSS was higher than 90%, with only 32% developing biochemical progression after salvage BT. The toxicity was acceptable and comparable to older studies, with RTOG toxicity ≥grade 3 observed in 23.5% of patients. In patients previously treated with EBRT, brachytherapy (BT) can be an appealing option due to the ability to deliver a very conformal high dose to the target lesion while reducing toxicity to the surrounding healthy tissue.

Salvage high-intensity focused ultrasound (HIFU)

Originally developed in the 1940s, high-intensity focused ultrasound (HIFU) technology has advanced to become a viable option for minimally invasive treatment of cancer. Delivering heat generated by a beam of focused ultrasound using a transrectal probe, HIFU works to cause coagulation necrosis of tumor tissue. HIFU was first employed for the treatment of PCa in the 1990s. HIFU devices have led to durable oncologic control with acceptable toxicity outcomes.

We analyzed 17 studies for a total of 1520 patients (Table 3). The latest prospective study, published in 2018, was conducted on 150 patients, with a median follow up of 35 months. Results showed a median bRFS of 33

months, with a total of 77 (51.3%) of patients experiencing biochemical failure after salvage treatment during the rate comparable to other methods of salvage therapy. Unfortunately, complications where not recorded. [51]

Crouzet et al. [52] published the largest series of 418 patients undergoing HIFU from 1995 to 2009 in an international, multi-institutional analysis. They reported 37% of patients were free from initiation of ADT at 5 years but also report a bRFS of 49% overall at 5 years. For what concerns complications, they reported incontinence of any grade in 42% of patients, need of artificial urinary sphincter in 7%, bladder outlet obstruction or stenosis in 18%, fistula in 2.3% and pubic bone osteitis in 2%.

HIFU has also been explored as a feasible salvage therapy option with reduced adverse events. However, there is a need for larger, prospective investigations, with a standardized classification of complications.

Salvage cryotherapy

Cryotherapy, also known as cryosurgery and cryoablation therapy, involves placement of probes within the prostate that undergo extreme cooling using argon gas. Prostate tissue is consumed by an expanding ball of ice that is monitored by transrectal ultrasound. Rapid freezing of the tissue results in ice crystal formation that leads to cell death. A urethral warming catheter is used to prevent urethral tissue damage.

Cryotherapy was the most widely analyzed treatment in our systematic review, with 25 studies evaluated (Table 4). In the largest retrospective study on salvage cryotherapy, including 898 patients, Ginsburg et al. reported biochemical recurrence in 213 (23.7%) patients, with a median time to biochemical recurrence of 13.4 months. Unfortunately, complications were not adequately recorded. [70]

The largest study to record complications after salvage HIFU was published by Kongnyuy et al. [69] In this study on 65 patients, bRFS survival at 1- and 3-year of 48.1%. A total of eight (12.3%) patients experienced minor complications (Clavien–Dindo Grade I). Two (3.1%) patients experienced transient haematuria. Three (4.1%) patients had urethral strictures, none of which required surgical intervention. No patients were hospitalised. Three patients (4.1%) had prolonged (>4 d) catheterization. Four (6.1%) patients reported having incontinence and 14 (21.5%) patients reported erectile dysfunction (ED) following the procedure. Cryotherapy has also been explored as a feasible salvage therapy option with relatively low adverse events.

Salvage robotic and laparoscopic prostatectomy

Salvage radical prostatectomy (SRP) after external beam RT (EBRT) is more technically difficult and is associated with higher potential for morbidity than primary radical prostatectomy (RP) due to effects of primary radiation on normal tissues in the pelvis. For these reasons SRP should be performed by an experienced physician at a high-volume center and patients should also be counseled regarding the increased risk of side effects with this procedure. Removal of the prostate gland is achieved by open approach or minimally invasive robotic or laparoscopic technique. Nerve sparing techniques attempt to preserve erectile function by leaving the neurovascular bundles intact but are only appropriate when tumor control will not be compromised. Pelvic lymph node dissection is often performed at the discretion of the surgeon and may be especially appropriate in the setting of oligometastatic disease confined to pelvic lymph nodes[100].

To our knowledge, the largest and most recent study was published by Onol et al. in 2019 on evaluated 126 patients who underwent salvage RALP between 2008 and 2018. Of these, 94 (74.6%) received radiation and 32 focal ablation (25.4%) as primary therapy. The results of this study show a 5-year bRFS of 59%. Postoperative 1-year full (no pads/day) and social (0–1 pad/day) continence rates 39.2%, and 51.3%, respectively. Erectile function was preserved in 13% of preoperatively potent patients. Postoperative complications of grade IIIa or higher according to Clavien-Dindo classification were 4.4%. [91]

The only study on salvage laparoscopic prostatectomy respecting our selection criteria was published by Nunez-Mora et al in 2009, reporting a median follow up of 26.8 months and a bRFS of 87.8%. However, only 9 patients were included in the study, so the evidence is quite weak. [96]

The high surgical difficulty, not supported by an evident benefit in terms of oncological outcomes and reduced complications, does not seem to make minimally-invasive SRP an ideal option for treating patients with radio-recurrent PCa.

Salvage electroporation

Irreversible electroporation (IRE) is a novel focal therapy treatment which involves delivering high-voltage electrical pulses between needle electrodes. The obtained direct electrical current destabilizes the targeted cellular membrane, inducing nanopores that cause irreversible permeability and subsequent cell death. Preclinical studies have shown that the ablative effect of IRE harbours tissue selectivity and is able to preserve blood vessel patency and spare nerves. In a study published in 2017, Scheltema et al. evaluated the role of salvage focal IRE in radio-recurrent prostate cancer. They included 18 patients in the studied and followed them up for a median of 21 months. No high-grade adverse events (CTCAE >2) or recto-urethral fistulae occurred. Three and four patients experienced biochemical failure using the Phoenix and Stuttgart definitions of biochemical failure, respectively. The results suggest that focal IRE could be a feasible salvage option for localized radio-recurrent PCa [97]. Further insight into the ability of focal IRE to obtain oncological control in radio-recurrent PCa will be provided by the ongoing prospective multicenter study FIRE trial.

Comparison of Minimally Invasive Treatment Strategies for Radio-Recurrent Prostate Cancer

Most relevant data for each treatment strategy are summarized in Table 6. Of note, patients undergoing non-surgical salvage treatments appear to be somewhat older in comparison with patients undergoing salvage surgery. For what oncologic outcomes are concerned, EBRT seems to have worse 5-year bRFS in comparison with the other strategies analyzed. However, when 5-year CSS is taken into account, all strategies seem to have excellent results, ranging from 87% of BT to 100% of EBRT and cryotherapy. Regarding toxicity, HIFU seems to cause more acute GU and acute or chronic GI toxicity than other strategies, while EBRT seems to be more detrimental for GU tract in the chronic setting. While scarcely investigated, perineal pain appears to be more likely after cryotherapy.

It is important to underline that the scope of this table is purely informative, and it is not supported by statistical evidence. Moreover, the great heterogeneity in pre-treatment and outcome measures and the quite wide range of follow-up duration limit a comprehensive interpretation.

DISCUSSION

This systematic review suffers of some limitations. First of all, it is important to underline that the majority of the studies on which our work is based are retrospective case series; therefore, they lack a control group and some of them have a limited follow-up. Moreover, the heterogeneity in pre-treatment and outcome measures makes a comprehensive interpretation quite difficult. Another possible limitation of our review is the absence of a baseline evaluation, which, together with the limited information on primary EBRT characteristics and the relatively short follow-up of most studies, hampers our interpretation of salvage therapy–related toxicity. However, not only this comprehensive systematic review indicates that nonsurgical local therapies for radiorecurrent prostate cancer could be a valid treatment option because of their efficacy and good toxicity profile, but also it compares them with outcomes reported for patients treated with minimally invasive salvage radical prostatectomy, either laparoscopic or robotic.

While there is no high quality comparative data to guide the decision of which local salvage therapy is best, it is reasonable to offer local salvage based on institutional strengths.

It is evident that with the continuous improvement in imaging technology and staging methodology [101,102], the future of salvage therapy for locally recurring PCa will be focused on targeted and tissue-sparing focal therapies. Investigation into novel focal therapy techniques such as electroporation may offer a new method of therapy to further improve outcomes after failed radiation.

Even if not a subject of our review, other directions for future PCa treatment options include advancement in immunotherapy targeting checkpoint inhibitors, particularly for castration-resistant PCa. However, high-quality data from prospective trials are needed to validate the long-term outcomes for minimally invasive strategies for the treatment of intraprostatic recurrence after previous RT.

CONCLUSIONS

Overall, what seems to emerge from our systematic review is that minimally invasive therapeutic options offer promising results in terms of biochemical control in the local recurrence setting. Unfortunately, the absence of high quality and comparative studies makes it difficult to establish which method is the best in terms of

oncological and safety outcomes. Therefore, the level of experience of the team with one or more methods should guide the therapeutic choice.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin [Internet]. 2018;68(6):394–424.
2. Burt LM, Shrieve DC, Tward JD. Factors influencing prostate cancer patterns of care: An analysis of treatment variation using the SEER database. Adv Radiat Oncol. 2018 1;3(2):170–80.
3. Marra G, Dell'oglio P, Baghdadi M, Cathelineau X, Sanchez-Salas R. EvaluatioN of HIFU Hemiablation and short-term AndrogeN deprivation therapy Combination to Enhance prostate cancer control (ENHANCE) Study. Multimodal treatment in focal therapy for localized prostate cancer using concomitant short-term androgen deprivation therapy: the ENHANCE prospective pilot study. Minerva Urol Nefrol. 2019;71(5):544-548.
4. Antonelli A, Palumbo C, Noale M, et al. Overview of potential determinants of radical prostatectomy versus radiation therapy in management of clinically localized prostate cancer: results from an Italian, prospective, observational study (the Pros-IT CNR study). Minerva Urol Nefrol. 2020; 7.
5. Beckendorf V, Guerif S, Le Prisé E, et al. 70 Gy versus 80 Gy in localized prostate cancer: 5-year results of GETUG 06 randomized trial. Int J Radiat Oncol Biol Phys. 2011; 15;80(4):1056–63.
6. Roach M, Hanks G, Thames H, et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: Recommendations of the RTOG-ASTRO Phoenix Consensus Conference. Int J Radiat Oncol Biol Phys. 2006; 15;65(4):965–74.
7. Vance W, Tucker SL, de Crevoisier R, Kuban DA, Cheung MR. The predictive value of 2-year posttreatment biopsy after prostate cancer radiotherapy for eventual biochemical outcome. Int J Radiat Oncol Biol Phys. 2007; 1;67(3):828–33.
8. Jones JS. Radiorecurrent prostate cancer: An emerging and largely mismanaged epidemic. Vol. 60, European Urology. 2011. p. 411–2.

9. Abd-Alazeez M, Ramachandran N, Dikaios N, et al. Multiparametric MRI for detection of radiorecurrent prostate cancer: Added value of apparent diffusion coefficient maps and dynamic contrast-enhanced images. Prostate Cancer Prostatic Dis. 2015;14;18(2):128–36.

10. Evans JD, Jethwa KR, Ost P, et al. Prostate cancer–specific PET radiotracers: A review on the clinical utility in recurrent disease. Pract Radiat Oncol. 2018; 1;8(1):28–39.

11. Cooperberg MR, Vickers AJ, Broering JM, Carroll PR. Comparative risk-adjusted mortality outcomes after primary surgery, radiotherapy, or androgen-deprivation therapy for localized prostate cancer. Cancer [Internet]. 2010;116(22):5226–34.

12. Gandaglia G, Fossati N, Karnes RJ, et al. Use of Concomitant Androgen Deprivation Therapy in Patients Treated with Early Salvage Radiotherapy for Biochemical Recurrence After Radical Prostatectomy: Long-term Results from a Large, Multi-institutional Series. Eur Urol. 2018;1;73(4):512–8.

13. Zdrojowy R, Dembowski J, Małkiewicz B, Tupikowski K, Krajewski W. Salvage local therapy for radiation-recurrent prostate cancer-where are we? Vol. 69, Central European Journal of Urology. Polish Urological Association; 2016. p. 264–70.

14. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med [Internet]. 2009;6(7):e1000097.

15. Higgins JP, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions [Internet]. Chichester, UK: John Wiley & Sons, Ltd; 2008.

16. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016;12;355:i4919.

17. OCEBM Levels of Evidence Working Group. OCEBM Levels of Evidence [Internet]. CEBM. 2016. Available from: http://www.cebm.net/blog/2016/05/01/ocebm-levels-of-evidence/

18. Miszczyk L, Stąpór-Fudzińska M, Miszczyk M, Maciejewski B, Tukiendorf A. Salvage CyberKnife-Based Reirradiation of Patients With Recurrent Prostate Cancer: The Single-Center Experience. Technol Cancer Res Treat. 2018;17:1533033818785496.

19. Mbeutcha A, Chauveinc L, Bondiau PY, et al. Salvage prostate re-irradiation using high-dose-rate brachytherapy or focal stereotactic body radiotherapy for local recurrence after definitive radiation

therapy. Radiat Oncol. 2017; 9;12(1):49.

20. Leroy T, Lacornerie T, Bogart E, Nickers P, Lartigau E, Pasquier D. Salvage robotic SBRT for local prostate cancer recurrence after radiotherapy: preliminary results of the Oscar Lambret Center. Radiat Oncol. 2017;12(1):95.

21. Janoray G, Reynaud-Bougnoux A, Ruffier-Loubière A, Bernadou G, Pointreau Y, Calais G. Stereotactic body re-irradiation therapy for locally recurrent prostate cancer after external-beam radiation therapy: Initial report. Cancer Radiother. 2016;20(4):275-81.

22. Rutenberg MS, Meister M, Amin PP, Hussain A, Naslund MJ, Kwok Y. Salvage external beam radiotherapy for locally recurrent prostate cancer after definitive brachytherapy. Brachytherapy. 2016;15(6):722-729.

23. Zilli T, Benz E, Dipasquale G, Rouzaud M, Miralbell R. Reirradiation of Prostate Cancer Local Failures After Previous Curative Radiation Therapy: Long-Term Outcome and Tolerance. Int J Radiat Oncol Biol Phys. 2016;1;96(2):318-322.

24. Fuller DB, Wurzer J, Shirazi R, et al. High-dose-rate stereotactic body radiation therapy for postradiation therapy locally recurrent prostatic carcinoma: preliminary prostate-specific antigen response, disease-free survival, and toxicity assessment. Pract Radiat Oncol 2015;5:e615–23.

25. Jereczek-Fossa BA, Beltramo G, Fariselli L, et al. Robotic imageguided stereotactic radiotherapy, for isolated recurrent primary, lymph node or metastatic prostate cancer. Int J Radiat Oncol Biol Phys 2012;82:889–97.

26. Henríquez López I, González-San Segundo C, Vegas JO, et al. Salvage brachytherapy for locally-recurrent prostate cancer after radiation therapy: A comparison of efficacy and toxicity outcomes with high-dose rate and low-dose rate brachytherapy. Radiother Oncol. 2019;141:156-163.

27. Yamada Y, Okihara K, Masui K, et al. Focal salvage low-dose-rate brachytherapy for recurrent prostate cancer based on magnetic resonance imaging/transrectal ultrasound fusion biopsy technique. Int J Urol. 2019.

28. Maenhout M, Peters M, van Vulpen M, et al. Focal MRI-guided salvage high-dose-rate brachytherapy in patients with radiorecur- rent prostate cancer. Technol Cancer Res Treat 2017;16:1194–201.

29. Barbera F, Triggiani L, Buglione M, et al. Salvage low dose rate brachytherapy for recurrent prostate

cancer after external beam radiotherapy: results from a single institution with focus on toxicity and functional outcomes. Clin Med Insights Oncol 2017;11:1–6.

30. Kollmeier MA, McBride S, Taggar A, et al. Salvage brachytherapy for recurrent prostate cancer after definitive radiation therapy: a comparison of low-dose-rate and high-dose-rate brachytherapy and the importance of prostate-specific antigen doubling time. Brachytherapy 2017;16:1091–8.

31. Baumann BC, Baumann JC, Christodouleas JP, et al. Salvage of locally recurrent prostate cancer after external beam radiation using reduced-dose brachytherapy with neoadjuvant plus adjuvant androgen deprivation. Brachytherapy 2017;16:291–8.

32. Wojcieszek P, Szlag M, Głowacki G, et al. Salvage high-dose-rate brachytherapy for locally recurrent prostate cancer after primary radiotherapy failure. Radiother Oncol 2016;119:405–10.

33. Rose JN, Crook JM, Pickles T, et al. Salvage low-dose-rate permanent seed brachytherapy for locally recurrent prostate cancer: association between dose and late toxicity. Brachytherapy 2015;14:342–9.

34. Yamada Y, Kollmeier MA, Pei X, et al. A phase II study of salvage high-dose-rate brachytherapy for the treatment of locally recurrent prostate cancer after definitive external beam radiotherapy. Brachytherapy 2014;13:111–6.

35. Peters M, Maenhout M, van der Voort van Zyp JR, et al. Focal salvage iodine-125 brachytherapy for prostate cancer recurrences after primary radiotherapy: a retrospective study regarding toxicity, biochemical outcome and quality of life. Radiother Oncol 2014; 112:77–82.

36. Vargas C, Swartz D, Vashi A, et al. Salvage brachytherapy for recurrent prostate cancer. Brachytherapy 2014;13:53–8.

37. Shimbo M, Inoue K, Koike Y, et al. Salvage I seed implantation for prostate cancer with postradiation local recurrence. Urol Int 2013;90:294–300.

38. Lahmer G, Lotter M, Kreppner S, et al. Protocol-based image-guided salvage brachytherapy. Early results in patients with local failure of prostate cancer after radiation therapy. Strahlenther Onkol 2013;189:668–74.

39. Chen CP, Weinberg V, Shinohara K, et al. Salvage HDR brachytherapy for recurrent prostate cancer after previous definitive radiation therapy: 5-year outcomes. Int J Radiat Oncol Biol Phys 2013;86:324–9.

40. Jo Y, Fujii T, Hara R, et al. Salvage high-dose-rate brachytherapy for local prostate cancer recurrence after radiotherapy—preliminary results. BJU Int 2012;109:835–9.

41. Burri RJ, Stone NN, Unger P, et al. Long-term outcome and toxicity of salvage brachytherapy for local failure after initial radiotherapy for prostate cancer. Int J Radiat Oncol Biol Phys 2010;77:1338–44.

42. Moman MR, van der Poel HG, Battermann JJ, et al. Treatment outcome and toxicity after salvage 125-I implantation for prostate cancer recurrences after primary 125-I implantation and external beam radiotherapy. Brachytherapy 2010;9:119–25.

43. Aaronson DS, Yamasaki I, Gottschalk A, et al. Salvage permanent perineal radioactive-seed implantation for treating recurrence of localized prostate adenocarcinoma after external beam radiotherapy. BJU Int 2009;104:600–4.

44. Gawkowska-Suwinska M, Fijałkowski M, Białas B, et al. Salvage brachytherapy for local recurrences of prostate cancer treated previously with radiotherapy. J Contemp Brachyther 2009;1:211–5.

45. Lee HK, Adams MT, Motta J. Salvage prostate brachytherapy for localized prostate cancer failure after external beam radiation therapy. Brachytherapy 2008;7:17–21.

46. Nguyen PL, Chen MH, D'Amico AV, et al. Magnetic resonance image-guided salvage brachytherapy after radiation in select men who initially presented with favorable-risk prostate cancer: a prospec-tive phase 2 study. Cancer 2007;110:1485–92.

47. Lee B, Shinohara K, Weinberg V, et al. Feasibility of high-dose-rate brachytherapy salvage for local prostate cancer recurrence after radiotherapy: the University of California-San Francisco experience. Int J Radiat Oncol Biol Phys 2007;67:1106–12.

48. Koutrouvelis P, Hendricks F, Lailas N, et al. Salvage reimplantation in patient with local recurrent prostate carcinoma after brachytherapy with three dimensional computed tomography-guided permanent pararectal implant. Technol Cancer Res Treat 2003;2:339–44.

49. Hostiou T, Gelet A, Chapelon JY, et al. Salvage high-intensity focused ultrasound for locally recurrent prostate cancer after low-dose-rate brachytherapy: oncological and functional outcomes. BJU Int. 2019;124(5):746-757.

50. Devos B, Al Hajj Obeid W, Andrianne C, et al. Salvage high-intensity focused ultrasound versus salvage radical prostatectomy for radiation-recurrent prostate cancer: a comparative study of

oncological, functional, and toxicity outcomes. World J Urol. 2019;37(8):1507-1515.

51. Peters M, Kanthabalan A, Shah TT, et al. Development and internal validation of prediction models for biochemical failure and composite failure after focal salvage high intensity focused ultrasound for local radiorecurrent prostate cancer: Presentation of risk scores for individual patient prognoses. Urol Oncol. 2018;36(1):13.e1-13.e10.

52. Crouzet S, Blana A, Murat FJ, et al. Salvage high-intensity focused ultrasound (HIFU) for locally recurrent prostate cancer after failed radiation therapy: multi-institutional analysis of 418 patients. BJU Int 2017;119:896–904.

53. Dason S, Wong NC, Allard CB, et al. High-intensity focused ultra-sound (HIFU) as salvage therapy for radio-recurrent prostate can-cer: predictors of disease response. Int Braz J Urol 2018;44:248–57.

54. Jones TA, Chin J, Mcleod D, Barkin J, et al. High intensity focused ultrasound for radiorecurrent prostate cancer: a North American clinical trial. J Urol 2018;199:133–9.

55. Kanthabalan A, Peters M, Van Vulpen M, et al. Focal salvage high-intensity focused ultrasound in radiorecurrent prostate cancer. BJU Int 2017;120:246–56.

56. Siddiqui KM, Billia M, Arifin A, et al. Pathological, oncologic and functional outcomes of a prospective registry of salvage high in-tensity focused ultrasound ablation for radiorecurrent prostate cancer. J Urol 2017;197:97–102.

57. Shah TT, Peters M, Kanthabalan A, et al. PSA nadir as a predictive factor for biochemical disease-free survival and overall survival following whole-gland salvage HIFU following radiotherapy failure. Prostate Cancer Prostat Dis 2016;19:311–6.

58. Baco E, Gelet A, Crouzet S, et al. Hemi salvage high-intensity focused ultrasound (HIFU) in unilateral radiorecurrent prostate cancer: a prospective two-centre study. BJU Int. 2014;114(4):532-40.

59. Song W, Jung US, Suh YS, et al. High-intensity focused ultrasound as salvage therapy for patients with recurrent prostate cancer after radiotherapy. Korean J Urol 2014;55:91–6.

60. Yutkin V, Ahmed HU, Donaldson I, et al. Salvage high-intensity focused ultrasound for patients with recurrent prostate cancer after brachytherapy. Urology 2014;84:1157–62.

61. Ahmed HU, Cathcart P, Chalasani V, et al. Whole-gland salvage high- intensity focused ultrasound therapy for localized prostate cancer recur- rence after external beam radiation therapy. Cancer

2012;118:3071–8.

62. Uchida T, Shoji S, Nakano M, et al. High-intensity focused ultra-sound as salvage therapy for patients with recurrent prostate cancer after external beam radiation, brachytherapy or proton therapy. BJU Int 2011;107:378–82.

63. Berge V, Baco E, Dahl AA, et al. Health-related quality of life after salvage high-intensity focused ultrasound (HIFU) treatment for locally radiorecurrent prostate cancer. Int J Urol 2011;18:646–51.

64. Murat FJ, Poissonnier L, Rabilloud M, et al. Mid-term results dem-onstrate salvage high-intensity focused ultrasound (HIFU) as an effective and acceptably morbid salvage treatment option for local-ly radiorecurrent prostate cancer. Eur Urol 2009;55:640–7.

65. Gelet A, Chapelon JY, Poissonnier L, et al. Local recurrence of prostate cancer after external beam radiotherapy: early experience of salvage therapy using high-intensity focused ultrasonography. Urology 2004;63:625–9.

66. Tan WP, ElShafei A, Aminsharifi A, Khalifa AO, Polascik TJ. Salvage Focal Cryotherapy Offers Similar Short-term Oncologic Control and Improved Urinary Function Compared With Salvage Whole Gland Cryotherapy for Radiation-resistant or Recurrent Prostate Cancer. Clin Genitourin Cancer. 2019.

67. Safavy S, Jabaji RB, Lu SM, Slezak JM, Cosmatos HA, Williams SG, Finley DS. Salvage Cryoablation for Radiorecurrent Prostate Cancer: Initial Experience at a Regional Health Care System. Perm J. 2019;23.

68. Barat M, Colleter L, Mongiat-Artus P, Jolibois Z, Quero L, Hennequin C, Desgrandchamps F, de Kerviler E. Salvage cryoablation for local recurrence of prostatic cancer after curative therapy. Diagn Interv Imaging. 2019;100(11):679-687.

69. Kongnyuy M, Berg CJ, Kosinski KE, et al. Salvage focal cryosurgery may delay use of androgen deprivation therapy in cryotherapy and radiation recurrent prostate cancer patients. Int J Hyperthermia 2017;33:810–3.

70. Ginsburg KB, Elshafei A, Yu C, et al. Avoidance of androgen depri-vation therapy in radiorecurrent prostate cancer as a clinically meaningful endpoint for salvage cryoablation. Prostate 2017;77: 1446–1450.

71. Kovac E, ElShafei A, Tay KJ, et al. Five-year biochemical progression- free survival following salvage

whole-gland prostate cryoablation: defining success with nadir prostate-specific antigen. J Endourol 2016;30:624–31.

72. Lian H, Yang R, Lin T, et al. Salvage cryotherapy with third-genera- tion technology for locally recurrent prostate cancer after radiation therapy. Int Urol Nephrol 2016;48:1461–6.

73. Li YH, Elshafei A, Agarwal G, et al. Salvage focal prostate cryoabla- tion for locally recurrent prostate cancer after radiotherapy: initial results from the Cryo On-Line Data registry. Prostate 2015;75:1–7.

74. Ahmad I, Kalna G, Ismail M, et al. Prostate gland lengths and iceball dimensions predict micturition functional outcome following salvage prostate cryotherapy in men with radiation recurrent prostate cancer. PLoS One 2013;8:e69243.

75. de Castro Abreu AL, Bahn D, Leslie S, et al. Salvage focal and salvage total cryoablation for locally recurrent prostate cancer after primary radiation therapy. BJU Int 2013;112:298–307.

76. Spiess PE, Levy DA, Pisters LL, et al. Outcomes of salvage prostate cryotherapy stratified by pre-treatment PSA: update from the COLD registry. World J Urol 2013;31:1321–5.

77. Philippou P, Yap T, Chinegwundoh F. Third-generation salvage cryotherapy for radiorecurrent prostate cancer: a centre's experi- ence. Urol Int 2012;88:137–44.

78. Williams AK, Martínez CH, Lu C, et al. Disease-free survival follow- ing salvage cryotherapy for biopsy-proven radio-recurrent prostate cancer. Eur Urol 2011;60:405–10.

79. Spiess PE, Katz AE, Chin JL, et al. A pretreatment nomogram pre- dicting biochemical failure after salvage cryotherapy for locally recurrent prostate cancer. BJU Int 2010;106:194–8.

80. Pisters LL, Leibovici D, Blute M, et al. Locally recurrent prostate cancer after initial radiation therapy: a comparison of salvage radical prostatectomy versus cryotherapy. J Urol 2009;182:517–25.

81. Eisenberg ML, Shinohara K. Partial salvage cryoablation of the prostate for recurrent prostate cancer after radiotherapy failure. Urology 2008;72:1315–8.

82. Ismail M, Ahmed S, Kastner C, et al. Salvage cryotherapy for recur- rent prostate cancer after radiation failure: a prospective case series of the first 100 patients. BJU Int 2007;100:760–4.

83. Ng CK, Moussa M, Downey DB, et al. Salvage cryoablation of the prostate: followup and analysis of predictive factors for outcome. J Urol 2007;178:1253–7.

84. Spiess PE, Lee AK, Leibovici D, et al. Presalvage prostate-specific antigen (PSA) and PSA doubling

time as predictors of biochemical failure of salvage cryotherapy in patients with locally recurrent prostate cancer after radiotherapy. Cancer 2006;107:275–80.

85. Donnelly BJ, Saliken JC, Ernst DS, et al. Role of transrectal ultrasound guided salvage cryosurgery for recurrent prostate carcinoma after radiotherapy. Prostate Cancer Prostat Dis 2005;8:235–42.

86. Bahn DK, Lee F, Silverman P, et al. Salvage cryosurgery for recurrent prostate cancer after radiation therapy: a seven-year follow-up. Clin Prostate Cancer 2003;2:111–4.

87. Izawa JI, Morganstern N, Chan DM, et al. Incomplete glandular ablation after salvage cryotherapy for recurrent prostate cancer after radiotherapy. Int J Radiat Oncol Biol Phys 2003;56:468–72.

88. Ghafar MA, Johnson CW, De La Taille A, et al. Salvage cryotherapy using an argon based system for locally recurrent prostate cancer after radiation therapy: the Columbia experience. J Urol 2001;166: 1333–1337.

89. Chin JL, Pautler SE, Mouraviev V, et al. Results of salvage cryoabla- tion of the prostate after radiation: identifying predictors of treat-ment failure and complications. J Urol 2001;165:1937–41.

90. de la Taille A, Hayek O, Benson MC, et al. Salvage cryotherapy for recurrent prostate cancer after radiation therapy: the Columbia experience. Urology 2000;55:79–84.

91. Onol FF, Bhat S, Moschovas M, Rogers T, Ganapathi H, Roof S, Rocco B, Patel V. Comparison of outcomes of salvage robot-assisted laparoscopic prostatectomy for post-primary radiation vs focal therapy. BJU Int. 2020;125(1):103-111.

92. Orré M, Piéchaud T, Sargos P, Richaud P, Roubaud G, Thomas L. Oncological and functional results of robotic salvage radical prostatectomy after permanent brachytherapy implants. Cancer Radiother. 2017;21(2):119-123.

93. Zugor V, Labanaris AP, Porres D, Heidenreich A, Witt JH. Robot-assisted radical prostatectomy for the treatment of radiation-resistant prostate cancer: surgical, oncological and short-term functional outcomes. Urol Int. 2014;92(1):20-6.

94. Eandi JA, Link BA, Nelson RA, Josephson DY, Lau C, Kawachi MH, Wilson TG. Robotic assisted laparoscopic salvage prostatectomy for radiation resistant prostate cancer. J Urol. 2010;183(1):133-7.

95. Boris RS, Bhandari A, Krane LS, Eun D, Kaul S, Peabody JO. Salvage robotic-assisted radical prostatectomy: initial results and early report of outcomes. BJU Int. 2009;103(7):952-6.

96. Nuñez-Mora C, García-Mediero JM, Cabrera-Castillo PM. Radical laparoscopic salvage prostatectomy: medium-term functional and oncological results. J Endourol. 2009;23(8):1301-5.

97. Scheltema MJ, van den Bos W, Siriwardana AR, Kalsbeek AMF, Thompson JE, Ting F, Böhm M, Haynes AM, Shnier R, Delprado W, Stricker PD. Feasibility and safety of focal irreversible electroporation as salvage treatment for localized radio-recurrent prostate cancer. BJU Int. 2017;120 Suppl 3:51-58.

98. Common Terminology Criteria for Adverse Events (CTCAE). Consulted the 29/01/2020. Available at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

99. Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg. 2009;250(2):187-96.

100. Moschovas MC, Onol FF, Bhat S, et al. Salvage Robot-Assisted Laparoscopic Prostatectomy: Tips and Tricks for Challenges Caused by Different Primary Treatments. VideourologyVol. 33, No. 6,

101. Checcucci E, Autorino R, Cacciamani GE, et al; Uro-technology and SoMe Working Group of the Young Academic Urologists Working Party of the European Association of Urology. Artificial intelligence and neural networks in urology: current clinical applications. Minerva Urol Nefrol. 2019.

102. Antonelli A, Francavilla S, Gallotta A, et al. Current evidence and future perspectives about the role of iXip® in the diagnosis of prostate cancer. Minerva Urol Nefrol. 2019;71(3):201-204.

FIGURE LEGENDS

Figure 1 – PRISMA flowchart

Figure 2 – Risk of bias assessment

TABLES

Table 1 – Salvage treatment, study design, pre-primary treatment data, pre-salvage therapy features, oncologic outcomes and toxicity of patients treated with salvage external beam radiotherapy (EBRT)

Salvage Treatment	Author	Year	Design	LoE	Patients	Age	Pre-PT PSA	Class risk	Primary treatment	BCR definition	Pre-ST PSA	Time from PT to ST	Imaging	Biopsy	ADT	Oncologic outcomes	Follow-up	Toxicity
EBRT	Miszczyk (18)	2018	RS	III	38	71.6	12	N/A	EBRT, BT	Phoenix	4.3	101	C-PET, MRI	Yes	Yes (55%)	1 yr - bRFS 68%	14.4	CTCAE V4.0. Acute GI: 3%; Acute GU: 21%;

																	Late GI: 11%; Late GU: 37%
EBRT	Mbeutcha (19)	2017	RS	IV	18	62	6.6	L	EBRT, BT	Phoenix	4.5	77	C-PET, MRI	Yes	Yes (39%)	1 yr - bRFS 70%	14.5	N/A
EBRT	Leroy (20)	2017	RS	IV	23	65	10.3	N/A	EBRT, BT	Phoenix	2.5	65	C-PET, MRI	Yes	Yes (61%)	2 yr - bRFS 54%; 2 yr OFS 100%	22.6	CTCAE V4.0. Late GU 8.7%
EBRT	Janoray (21)	2016	RS	IV	11	75.5	7.28	H	EBRT	Phoenix	11	98	C-PET, MRI	No	Yes (9%)	1 yr - bRSF 85.7%	11.7	N/A
EBRT	Rutenberg (22)	2016	RS	IV	11	59	6.2	L	BT	Phoenix	4.7	81	US	Yes	Yes (45%)	3 yr - bRFS 69%; 3 yr - OS 77%	26.5	CTCAE V4.0. GU: 18%; GI: 9%

EBRT	Zilli (23)	2016	RS	IV	14	59	26.7	H	EBRT, BT	Phoenix	7.4	73	C-PET, MRI	Yes	Yes (78%)	5 yr - bRFS 35.7%; 5 yr - CSS 100%; 5 yr - OS 92.9%; 5 yr - MFS 85.7%	94	CTCAE V3.0. Acute GU: 14.2; Late GU: 7.1; GI: 28.5%; PP: 7.1%
EBRT	Fuller (24)	2015	PS	III	29	65.6	N/A	N/A	EBRT, BT	Phoenix	3.1	88	MRI	Yes	No	2 yr - bRFS 82%	24	CTCAE V3.0. Acute GU: 3.4%
EBRT	Jereczak-Fossa (25)	2012	RS	IV	15	62.8	9.8	N/A	EBRT, BT	Phoenix	3.5	66	C-PET, MRI	Yes	Yes (33%)	30 mo - PFS 42.6%	9.5	RTOG. Acute GU: 6%

Table 2 – Salvage treatment, study design, pre-primary treatment data, pre-salvage therapy features, oncologic outcomes and toxicity of patients treated with salvage brachytherapy (BT)

Salvage Treatment	Author	Year	Design	LoE	Patients	Age	Pre-PT PSA	Class risk	Primary treatment	BCR definition	Pre-ST PSA	Time from PT to ST	Imaging	Biopsy	ADT	Oncologic outcomes	Follow-up	Toxicity
BT	Henriquez-Lopez (26)	2019	RS	III	119	61.5	10.8	N/A	EBRT	Phoenix	3.9	N/A	CT, MRI, bone scan	Yes	Yes (25%)	bRSF 71%	52	RTOG. Acute GU: 29.4%; Late GU: 10.9%; Toxicity Grade >3: 23.5%
BT	Yamada (27)	2019	RS	III	13	68.1	27.4	H	EBRT	Phoenix	3.5	78.4	N/A	Yes	N/A	4 yr - bRFS 74%	40.6	CTCAE V4.0. Grade

																		>3: 0.
BT	Maenhout (28)	2017	RS	IV	17	N/A	13.2	I	EBRT, BT	Phoenix	4.8	96	MRI	Yes	N/A	1 yr - bRFS 91%	10	CTCAE V4.0. Late GU 6%
BT	Mbeutcha (19)	2017	RS	III	10	63	26	H	EBRT, BT	Phoenix	4.3	69	C-PET, MRI	Yes	Yes (20%)	1 yr - bRFS 75%	22.5	N/A
BT	Barbera (29)	2017	RS	IV	19	63	8.2	I	EBRT	Phoenix	3.4	70	MRI	No	Yes (10%)	3 yr - bRFS 85.2%	24	CTCAE V4.0. GI: 5%
BT	Kollmeier (30)	2017	RS	II	98	64.5	N/A	N/A	EBRT, BT	Phoenix	3.7	78.6	MRI	Yes	Yes (45%)	3 yr - bRFS 60.1%	31	CTCAE V4.0. Acute GU: 18%; Late GU: 7.1%;

																		GI: 3%
BT	Baumann (31)	2017	RS	IV	33	69	8.4	H	EBRT	Phoenix	5	56.1	MRI	Yes	Yes (100%)	7 yr - bRFS 67%	61	CTCAE V4.0. Acute GU: 3%; GI: 3%
BT	Wojcieszek (32)	2016	RS	IV	83	63	13.7	N/A	EBRT, BT	N/A	3.1	67	MRI	Yes	Yes (53%)	5 yr - CSS 87%	41	CTCAE V4.0. Acute GU: 14%
BT	Rose (33)	2015	RS	IV	18	67.2	11	N/A	EBRT	N/A	4.3	31.5	US	Yes	Yes (33%)	N/A	31.5	CTCAE V3.0. Acute GU: 11%; Late

																		GU: 16.6%; PP 11.1%
BT	Yamada (34)	2014	PS	II	42	65.5	N/A	N/A	EBRT	Phoenix	3.5	78	MRI	Yes	No	5 yr - OS 90.3%	36	CTCAE V3.0. Acute GU: 7%
BT	Peters (35)	2014	RS	IV	20	69	N/A	H	EBRT, BT	Phoenix	N/A	93	MRI	Yes	No	3 yr - bRFS 71%	36	CTCAE V4.0. Acute GU: 20%; Late GU: 5%
BT	Vargas (36)	2014	RS	IV	69	63.9	N/A	N/A	EBRT	Phoenix	N/A	81.6	N/A	Yes	Yes (90%)	5 yr - MFS 90%, 5 yr - OS 64%	60	N/A

BT	Shimbo (37)	2013	RS	IV	15	68.5	N/A	N/A	EBRT, BT	Phoenix	3	45.5	US	Yes	No	3 yr - bRFS 60.2%	33	CTCAE V3.0. PP 6.6%
BT	Lahmer (38)	2013	RS	IV	18	60.5	8.2	N/A	EBRT, BT	Phoenix	4.4	64.5	C-PET	Yes	Yes (11%)	3 yr - bRFS 57%; 3 yr - OS 89%	21	CTCAE V4.0. Acute GU: 27.7%
BT	Chen (39)	2013	RS	IV	52	63.2	9.3	N/A	EBRT, BT	Phoenix	5	51.6	CT	Yes	No	5 yr - bRFS 51%; 5 yr - OS 92%	59.6	N/A
BT	Jo (40)	2012	RS	IV	11	64.2	17.8	H	EBRT, BT	ASTRO	7.2	22	MRI, US	Yes	No	N/A	29	N/A
BT	Burri (41)	2010	RS	IV	37	65	10.9	I	EBRT, BT	Phoenix	5.6	62	US	Yes	Yes (84%)	5 yr - bRFS 65%; 5 yr - OS 94%	86	CTCAE V3.0. Acute GU:

																		29.7%; GI: 2.7%
BT	Moman (42)	2010	RS	III	31	64.3	24.3	N/A	EBRT, BT	ASTRO - Phoenix	11.4	60	N/A	Yes	N/A	5 yr - bRFS 51%; 5 yr - OS 72%	108	CTCAE V3.0. Acute GU: 19%; GI: 6.4%
BT	Aaronson (43)	2009	RS	IV	24	62	9.9	N/A	EBRT	Phoenix	3.3	49	MRI	Yes	Yes (29%)	3 yr - bRFS 89.5%	30	CTCAE V3.0. Acute GU: 8.2%
BT	Gawkowska-suwinska (44)	2009	RS	IV	15	67	N/A	N/A	EBRT	N/A	4	N/A	N/A	Yes	Yes (53%)	N/A	N/A	RTOG. Acute GU: 6.6%
BT	Lee (45)	20	RS	IV	21	65	N/A	N/A	EBRT	Phoenix	3.8	85	N/A	Yes	Yes(57%)	5 yr - bRF	36	N/A

		08														S 38%; 5 yr - OS 81%		
BT	Nguyen (46)	2007	PS	III	25	60	7.4	N/A	EBRT, BT	ASTRO	5.5	62.4	MRI	Yes	No	4 yr - bRFS 70%	47	RTOG. Late GU: 4%; GI: 12 %
BT	Lee (47)	2007	RS	IV	21	62.6	N/A	N/A	EBRT	N/A	5.9	63.6	MRI	Yes	No	2 yr - bRFS 89%	18.7	N/A
BT	Koutrouvelis (48)	2003	RS	IV	31	62.5	N/A	N/A	BT	N/A	N/A	49.5	N/A	Yes	No	5 yr - bRFS 87%	30	N/A

Table 3 – Salvage treatment, study design, pre-primary treatment data, pre-salvage therapy features, oncologic outcomes and toxicity of patients treated with high-intensity focused ultrasound (HIFU)

Salvage Treatment	Author	Year	Design	LoE	Patients	Age	Pre-PT PSA	Class risk	Primary treatment	BCR definition	Pre-ST PSA	Time from PT to ST	Imaging	Biopsy	ADT	Oncologic outcomes	Follow-up	Toxicity

HIFU	Hostiou (49)	2019	PS	II	50	61.8	7	L	BT	ASTRO	5.3	62	C-PET, MRI, bone scan	Yes	Yes (84%)	6 yr - bRFS 41%; 6 yr - OS 93%; 6 yr - CSS 98%; 6 yr - MFS 80%	54	CD. > IIIa: 24%
HIFU	Devos (50)	2019	RS	III	27	69.2	N/A	H	EBRT, BT	Phoenix	3.2	N/A	C-PET, MRI, bone scan	Yes	N/A	5 yr - CSS 84%; 5 yr - OS 80.9%; 5 yr - MFS 60.3%	45	CD. > IIIa: 28.2%
HIFU	Peters (51)	2018	PS	III	150	69.8	13.9	N/A	EBRT	Phoenix	5.8	N/A	C-PET, MRI	Yes	Yes (45.3%)	median bRFS 33 mo	35	N/A
HIFU	Crouzet (52)	2018	RS	III	418	63.9	N/A	H	EBRT	Phoenix	4.6	56.4	N/A	Yes	No	7 yr - CSS 82%; 7 yr - OS 72%; 7 yr -	39.6	N/A

															MFS 81%		
HIFU	Dason (53)	2018	PS	III	24	N/A	N/A	N/A	EBRT, BT	Phoenix	4.02	N/A	MRI	Yes	No	5 yr - bRFS 51.6%	31	CD. Late GU: 4.1%
HIFU	Jones (54)	2018	PS	III	100	N/A	4.9	N/A	EBRT	N/A	N/A	N/A	CT	Yes	No	N/A	12	CTCAE V4.0. Acute GU: 64%; Late GU: 13%; GI: 3%
HIFU	Kanthabalan (55)	2017	RS	IV	150	64	13.9	H	EBRT, BT	Phoenix	5.5	80	MRI	Yes	No	3 yr - bRFS 48%	35	CD. Late GU: 8%; GI 2%
HIFU	Siddiqui (56)	2017	PS	III	81	N/A	N/A	N/A	EBRT, BT	N/A	4.8	N/A	N/A	Yes	No	5 yr - CSS 94.4%; 5 yr - OS 88%	53.5	CD. Acute GU: 19.7%; GI 3.7%
HIFU	Shah (57)	2016	RS	IV	50	62	17	N/A	EBRT	Phoenix	5.9	80	MRI	Yes	No	5 yr - OS 87%	64	N/A

HIFU	Baco (58)	2014	PS	III	48	68.8	14.2	H	EBRT	Phoenix	N/A	N/A	MRI	Yes	N/A	2 yr - PFS 52%	N/A	N/A
HIFU	Song (59)	2014	RS	IV	13	66	21.1	I	EBRT	ASTRO	4.6	37.2	MRI	Yes	No	5 yr - bRFS 53.8%	44.5	CD. Acute GU: 68.4%
HIFU	Yutkin (60)	2014	PS	III	19	60	N/A	N/A	BT	Phoenix	5	72	N/A	Yes	No	4 yr - bRFS 73.8%	59.3	CD. Acute GU: 31.6%; GI: 15.7%
HIFU	Ahmed (61)	2012	RS	IV	84	N/A	N/A	N/A	EBRT	N/A	3.8	N/A	MRI	Yes	Yes (36%)	2 yr - PFS 43%	19.8	N/A
HIFU	Uchida (62)	2011	RS	IV	22	62	14.5	H	EBRT	N/A	4	36	MRI	Yes	No	5 yr - bRFS 52%	24	NCIC TCv2.0. Acute GU: 18.2%; Late GU: 18.2%; GI: 4.5%
HIFU	Berge (63)	2011	RS	IV	46	60.8	N/A	H	EBRT	N/A	5.5	68.1	MRI	Yes	Yes (17%)	N/A	9	N/A
HIFU	Murat (64)	2009	RS	IV	167	63	N/A	I	EBRT	ASTRO	4.5	55.6	MRI	Yes	No	5 yr - OS 84%	18.1	N/A
HIFU	Gelet (65)	2004	RS	IV	71	N/A	20.4	N/A	EBRT	N/A	5.7	N/A	N/A	Yes	No	30 mo -	14.8	N/A

																DFS 38%		

Table 4 – Salvage treatment, study design, pre-primary treatment data, pre-salvage therapy features, oncologic outcomes and toxicity of patients treated with salvage cryotherapy

Salvage Treatment	Author	Year	Design	LoE	Patients	Age	Pre-PT PSA	Class risk	Primary treatment	BCR definition	Pre-ST PSA	Time from PT to ST	Imaging	Biopsy	ADT	Oncologic outcomes	Follow-up	Toxicity
CRYO	Tan (66)	2019	RS	III	385	70	N/A	N/A	EBRT, BT	Phoenix	4	N/A	N/A	Yes	Yes (31%)	bRSF 78.1 %	24.4	N/A
CRYO	Safavy (67)	2019	RS	IV	75	69.3	N/A	I	EBRT, BT	Phoenix	5.5	N/A	N/A	Yes	Yes (25.9 %)	bRSF 50.7 %	45	N/A
CRYO	Barat (68)	2019	RS	IV	21	68	11.5	I	EBRT	Phoenix	6.3	95	C-PET, MRI	Yes	Yes (29%)	bRSF 67%	19	N/A
CRYO	Kongnyuy (69)	2017	RS	IV	65	65.5	N/A	N/A	EBRT, BT	Phoenix	4	66	N/A	Yes	N/A	N/A	26.6	CD. Acute GU: 25.6 %; Late GU: 4.1 %
CRYO	Ginsburg (70)	2017	RS	IV	898	69	N/A	I	EBRT, BT	Phoenix	5	13.4	N/A	Yes	Yes (19%)	5 yr - ADT FS	19	N/A

																71.3 %		
CRYO	Kovac (71)	2016	RS	IV	486	N/A	N/A	N/A	RT	Phoenix	4.7	N/A	N/A	Yes	No	5 yr - bRFS 75.5 %	18.2	N/A
CRYO	Lian (72)	2016	RS	IV	32	N/A	7.9	H	EBRT, BT	Phoenix	9.5	N/A	MRI	Yes	No	5 yr - OS 92.3 %; 5 yr - CSS 100%	63	CD. Acute GU: 28.1 %; PP: 31.3 %
CRYO	Li (73)	2015	RS	IV	91	N/A	N/A	N/A	EBRT, BT	Phoenix	4.8	N/A	N/A	Yes	Yes (35%)	5 yr - bRFS 46.5 %	15	N/A
CRYO	Ahmad (74)	2013	RS	IV	283	N/A	N/A	I	RT	Phoenix	N/A	N/A	MRI	Yes	No	5 yr - bRFS 56.5 %	23.9	N/A
CRYO	De Castro Abreu (75)	2013	RS	IV	25	66	6	N/A	EBRT, BT	Phoenix	3.9	75	US	Yes	Yes (28%)	5 yr - bRFS 86.5 %	53	N/A
CRYO	Spiess (76)	2013	PS	III	156	70	N/A	I	RT	Phoenix	N/A	30.3	N/A	Yes	No	3 yr - bRFS 66.7 %	44	N/A
CRYO	Philippou (77)	2012	RS	IV	19	62.1	8.6	H	RT	Phoenix	6.8	72.3	MRI	Yes	N/A	2 yr - bRFS 58%	33.3	N/A

CRYO	Williams (78)	2011	RS	IV	176	N/A	N/A	H	EBRT, BT	Phoenix	N/A	N/A	CT	Yes	Yes (39%)	10 yr - OS 87%	88	N/A
CRYO	Spiess (79)	2010	RS	IV	450	64.1	17.8	H	RT	N/A	7.8	N/A	MRI, CT	Yes	No	N/A	40	N/A
CRYO	Pisters (80)	2009	RS	IV	56	N/A	N/A	N/A	EBRT, BT	N/A	5.4	N/A	N/A	Yes	No	5 yr - bRFS 21%	60.5	N/A
CRYO	Eisenberg (81)	2008	RS	IV	19	64.6	N/A	N/A	EBRT, BT	ASTRO-Phoenix	3.3	N/A	US	Yes	N/A	3 yr - bRFS 79%	18	N/A
CRYO	Ismail (82)	2007	RS	IV	100	N/A	N/A	H	RT	ASTRO	5.4	N/A	MRI	Yes	N/A	5 yr - bRFS: L73%, I45%, H11%	33.5	N/A
CRYO	Ng (83)	2007	RS	IV	187	N/A	11	N/A	EBRT, BT	Houston	4.9	N/A	CT	Yes	No	5 yr - OS 97%	39	N/A
CRYO	Spiess (84)	2006	RS	IV	49	66	N/A	N/A	EBRT	Phoenix	5.9	N/A	MRI	Yes	Yes (53%)	N/A	60.7	N/A
CRYO	Donelly (85)	2005	PS	IV	46	63.9	19.2	N/A	EBRT	N/A	5.6	61	MRI	Yes	No	2 yr - bRFS 44%	20	CTCAE V3.0. Acute GU: 10.8%; Late

																		GU: 2.1 %; GI: 17.4 %
CRYO	Bahn (86)	2003	RS	IV	59	N/A	N/A	N/A	RT	N/A	5.6	N/A	US	Yes	N/A	N/A	82.3	N/A
CRYO	Izawa (87)	2003	RS	IV	113	N/A	N/A	N/A	RT	N/A	N/A	N/A	N/A	Yes	No	N/A	N/A	N/A
CRYO	Ghafar (88)	2001	RS	IV	38	65.8	N/A	N/A	EBRT	N/A	7.5	72.1	N/A	Yes	Yes (100%)	2 yr - bRFS 74%	20.7	N/A
CRYO	Chin (89)	2001	RS	IV	118	N/A	N/A	H	EBRT, BT	N/A	N/A	N/A	CT	Yes	No	N/A	18.6	N/A
CRYO	De La Taille (90)	2000	RS	IV	43	65.5	16.7	N/A	EBRT	N/A	7	43	US	Yes	N/A	1 yr - bRFS 66%	21.9	N/A

Table 5 – Salvage treatment, study design, pre-primary treatment data, pre-salvage therapy features, oncologic outcomes and toxicity of patients treated with salvage robotic or laparoscopic radical prostatectomy and irreversible electroporation

Salvage Treatment	Author	Year	Design	LoE	Patients	Age	Pre-PT PSA	Class risk	Primary treatment	BCR definition	Pre-ST PSA	Time from PT to ST	Imaging	Biopsy	ADT	Oncologic outcomes	Follow-up	Toxicity

RP (RARP)	Onol (91)	2019	RS	III	94	65.3	N/A	I-H	EBRT	Phoenix	4.5	82.5	N/A	Yes	Yes (25.5 %)	5 yr - bRFS 59%	32	CD. > IIIa: 4.4 % - 1 yr UI: 60.8%
RP (RARP)	Orré (92)	2016	RS	I V	7	66	7.1	L	BT	Phoenix	6.6	46	CT, MRI, bone scan	Yes	N/A	2 yr - bRFS 85.7 %	24	CD. Early UI: 100 %; 1 yr UI: 42.9%
RP (RARP)	Zugor (93)	2014	RS	I V	13	63.1	22.7	H	EBRT, BT	Phoenix	14.4	48.9	N/A	Yes	N/A	1 yr - bRFS 76.9 %	12	CD. > IIIa: 15.3%; 1 yr UI: 23.1%
RP (RARP)	Eandi (94)	2009	RS	I V	18	N/A	6.8	N/A	EBRT	N/A	N/A	N/A	N/A	Yes	Yes (22.2 %)	bRFS 67%	18	N/A
RP (RARP)	Boris (95)	2009	RS	I V	11	64.9	N/A	N/A	EBRT, BT	N/A	5.2	53.2	N/A	Yes	N/A	bRFS 80%	21	N/A

RP (Laparoscopic)	Nunez-Mora (96)	2009	RS	IV	9	59.3	N/A	N/A	EBRT, BT	Phoenix	9.1	N/A	N/A	No	N/A	bRFS 87.8%	26.8	N/A
IRREVERSIBLE ELECTROPORATION	Schelte ma (97)	2017	PS / RS	IV	18	71	8.6	N/A	EBRT, BT	Phoenix, Stuttgart	3.5	N/A	MRI	Yes	N/A	bRFS 72.7%	21	CTCAE V4.0. 6 mo UI: 72.7

Table 6 - Summary of minimally invasive treatments for radio-recurrent prostate cancer.

	EBRT	BT	HIFU	Cryotherapy	Robotic/Laparoscopic RP
Age	59-75.5	60,5-69	60-69.8	62.1-70	59.3-66
Time from PT to ST (months)	66-101	22-96	36-80	13.4-95	46-82.5
Follow-up (months)	11.7-94	10-108	9-64	15-88	12-32
Oncologic outcome					
bRFS					
1 year	68-85%	75-91%	-	-	76.9%
2 years	54-82%	89%	-	44-74%	85.7%
5 years	37.5%	38-90%	51.6-53.8%	21-86.5%	59%
CSS					
5 years	100%	87%	84-94.4%	100%	-
Toxicity					
Acute GU	3.4-21%	11-29.4%	19.7-68.4%	10.8-28.1%	CD > IIIa: 4.4-15.3% 1-year UI: 23.1-60.8%
Chronic GU	7.1-37%	5-16.6%	8-18.2%	2.1-4.1%	
GI (acute or chronic)	3-28.5%	2.7-12%	2-15.7%	17.4%	
PP	7.1%	6.6-11.1%	-	31.3%	

* All ranges are minimum to maximum.

Abbreviations: LoE = level of evidence; PT = primary treatment; BCR = biochemical recurrence; ST = salvage treatment; ADT = androgen deprivation therapy; EBRT = external beam radiotherapy; BT = brachytherapy; HIFU = high-intensity focused ultrasound; CRYO = cryotherapy; RP = radical prostatectomy; RARP = robot-assisted radical prostatectomy; RS =retrospective study ; PS=prospective study; N/A = not applicable; L = low; I= intermediate; H = high; ASTRO = American Society for the Therapeutic Radiology and Oncology; C-PET = Choline – positron emission thomography; MRI = magnetic resonance imaging; US = Ultrasound; yr = year; mo = months; bRFS = biochemical recurrence free survival; bPSF = biochemical progression free surval; OS = overall survival; CSS = cancer-specific survival; MFS = metastasis-free survival; PSF = progression free survival; ADT-FS: androgen deprivation therapy free survival; CTCAE = Common Terminology Criteria for Adverse Events; RTOG = Radiation Therapy Oncology Group; NCI-CTC= National Cancer Institute Common Toxicity Criteria; GU = genito-urinary; GI= gastro-intestinal; PP= Perineal Pain; UI = Urinary Incontinence

AUTHORS' CONTRIBUTION

G Mantica: Literature search, data extraction, data analysis, writing of the manuscript

F Chierigo: Literature search, data extraction, data analysis, writing of the manuscript

N Suardi: Literature search, supervision

J Gomez Rivas: Editing of the manuscript, critical review

V Kasivisvanathan: Editing of the manuscript, critical review

R Papalia: Editing of the manuscript, critical review

C Fiori: Editing of the manuscript, critical review

F Porpiglia: Editing of the manuscript, critical review

C Terrone: Editing of the manuscript, critical review

F Esperto: Writing and editing of the manuscript, critical review