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Salvage Therapies for Radiorecurrent Prostate Cancer

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Abstract

Introduction: We report available salvage options in patients with biochemical recurrence after radiation therapy for prostate cancer.
Methods: We performed MEDLINE® searches for various salvage options and reviewed the most recent publications on each modality.
Results: Salvage radical prostatectomy, brachytherapy, cryotherapy and high intensity focused ultrasound are the main therapeutic options available for men with biochemical recurrence after radiation therapy. These modalities have different side effect profiles. There is also wide variability in followup and reporting of oncologic outcomes. Androgen deprivation therapy remains the most common form of therapy after biochemical recurrence.
Conclusions: No standard salvage therapy exists. Treatments are best administered at specialist centers where there is expertise with managing potential complications.

Key Words: prostatic neoplasms; radiotherapy; neoplasm recurrence, local; salvage therapy; prostate-specific antigen

Abbreviations and Acronyms

ADT = androgen deprivation therapy

ASTRO = American Society for Radiation Oncology

BCR = biochemical recurrence

EBRT = external beam radiation therapy

HIFU = high intensity focused ultrasound

mMRI = multiparametric magnetic resonance imaging

PCa = prostate cancer

PET/CT = positron emission tomography/computerized tomography

PSA = prostate specific antigen

RP = radical prostatectomy

RT = radiotherapy

SRP = salvage RP

SV = seminal vesicle

Various options are available for the primary treatment of PCa, although not every modality is suitable in all patients. Success is dictated by clinical and pathological variables, and disease eventually recurs in certain patients. A proportion of these patients may be candidates for salvage therapy.

Method

We reviewed the current status of salvage options available for BCR after radiation therapy for PCa (see figure). This is not a systematic review of this topic. MEDLINE searches were performed for the terms surgery, radiation therapy, brachytherapy, cryotherapy and high intensity focused ultrasound combined with "key word and salvage and prostate." Emphasis was placed on the most recent review articles and studies done in the last 10 years. Subsequently we also searched the reference lists of these publications for other relevant articles.

Diagnosis

Recurrence can be classified based on clinical sign, symptoms or location (local or systemic). However, after RT with curative intent BCR is often the first sign of disease relapse. The ASTRO Phoenix definition of BCR following RT is PSA greater than 2 ng/ml above the post-RT nadir with or without neoadjuvant ADT.[1] The same definition is also often used after cryotherapy, although no standardized definition exists in this setting. After BCR is suspected histological confirmation is essential in patients who are candidates for local salvage therapy.

Relevant Investigations

Confirmation of local recurrence and absent metastatic disease is the first step when

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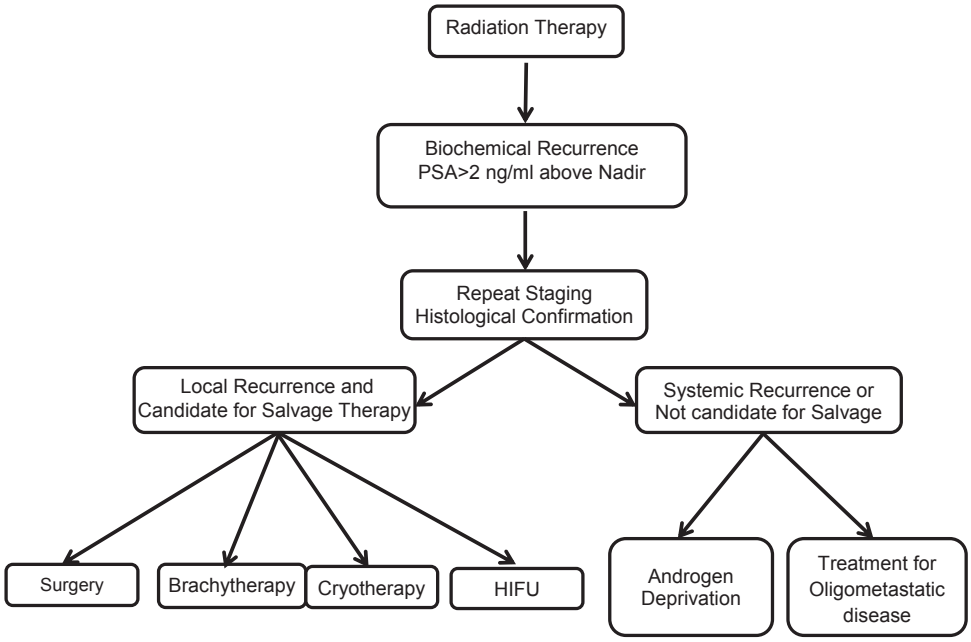

Figure. Study outline

planning salvage therapy. Men with widely disseminated disease are best treated with systemic therapies. Clinical and laboratory variables can be used to stratify patients who may benefit from further investigations and staging information. After failed treatment with EBRT or brachytherapy PET/CT and mMRI may be helpful to differentiate local vs systemic recurrence. The detection rate depends on the PSA value and on kinetics, although imaging, including ^{11}C choline PET/CT, is not sensitive for detecting micrometastatic disease. mMRI with an endorectal coil is highly sensitive to detect recurrent PCa after RT. It can be used for accurate local staging and guiding biopsy but it cannot replace confirmatory tissue diagnosis. While mMRI is operator dependent, after RT biopsy confirmed recurrence the sensitivity of mMRI was reported to be 80% to 94% in the PSA range of 0.4 to 6 ng/ml.[2] At a median PSA of 3.2 ng/ml ^{11}C choline PET/CT has 93% sensitivity and can alter management in up to a third of patients.[3,4] Bone scan may be considered in cases of post-RT recurrence. Although ^{18}F-fluoride PET/CT has higher sensitivity than traditional technetium bone scintigraphy (93% vs 51%), it is less specific (52% vs 82%) and can be positive when there is benign bone disease.[5]

Biopsy after RT has an important role in planning salvage treatment. However, histological changes following RT usually require an 18 to 24-month delay before biopsy. False-negative and false-positive results were observed in 19% and 30% of cases, respectively, when early biopsy was performed at 12 months.[6,7]

Patients with SV involvement and more locally advanced disease have a higher likelihood of harboring occult metastatic disease. Some clinicians consider these men unsuitable candidates for local salvage therapy because the efficacy of a number of local salvage options is decreased in the presence of SV infiltration. SV biopsy can be considered in cases in which the confirmation of SV involvement could impact management. This may be based on mMRI findings or on clinical examination.

A 70% to 80% disease-free survival rate was reported in patients with localized disease compared to 40% to 60% in those with more advanced disease.[8,9] Therefore a proportion of men with clinically nonmetastatic disease who show features of high risk disease such as high PSA, brief PSA doubling time, cT3 or greater, high volume and high Gleason scores on biopsy, may not benefit from salvage therapy. Careful patient consultation and selection should be essential parts of the treatment algorithm.

Recurrence after RT

Salvage Radical Prostatectomy

SRP after RT has an extended history as a treatment alternative but the morbidity associated with SRP has limited widespread use. Earlier detection, improved surgical technique and better patient selection have led to SRP being considered a viable option at specialized centers.

When considering SRP after RT, metastatic disease should be ruled out. Bone assessment for metastatic disease and abdominopelvic computerized tomography or magnetic resonance imaging are recommended. Additionally, biopsy should be done to confirm disease recurrence. Ideal candidates are those with biopsy proven local recurrence, T1-T2 disease before initial radiation, PSA less than 10 ng/ml and no evidence of metastatic disease. PSA at salvage surgery is a strong predictor of BCR-free and overall survival. Patients should also have adequately long life expectancy to benefit from salvage therapy. A review of SRP data showed a decreased positive surgical margin rate in more contemporary studies (0% to