ELSEVIER

Seminars in
RADIATION
ONCOLOGY

Options for Salvage of Radiation Failures for Prostate Cancer

Audrey Tetreault-Laflamme, MD, FRCPC, and Juanita Crook, MD, FRCPC

Biochemical failure after primary external beam radiotherapy for prostate cancer is common, and a significant proportion of these failures are due to local residual or recurrent disease. Early or delayed palliation using androgen deprivation therapy is the most common approach. Although a conservative approach is appropriate for many individuals, selected patients would benefit from retreatment with curative intent. We review the pertinent literature on salvage of locally recurrent prostate cancer after primary radiotherapy, including the modalities of surgery, cryotherapy, high-intensity focused ultrasound, or reirradiation with brachytherapy or stereotactic body radiotherapy. We discuss patient selection, outcomes, and toxicities. Patients with local recurrence and sufficient life expectancy, in the absence of metastatic disease, could be considered for local salvage. Although highly dependent on patient selection, the efficacy of the various salvage options seems comparable, with biochemical-recurrence-free survivals ranging approximately 50% at 5 years. The toxicity profiles differ, but all salvage treatments are more toxic than primary treatment. Management of isolated local failure after radiotherapy remains challenging. However, with the recent progress in salvage techniques, and more sensitive functional imaging for tumor localization and staging, salvage treatments are likely to play an increasingly important role.
Semin Radiat Oncol 27:67-78

Introduction

External beam radiotherapy (EBRT) is one of the standard options for definitive treatment of clinically localized prostate cancer. However, even with contemporary conformal techniques, including image-guidance and dose-escalation, 20%-50% of patients would develop biochemical failure within 10 years.[1-3] Post-EBRT prostate biopsies show that a significant proportion of these failures are due to local residual or recurrent disease. Without further treatment, progression to clinical symptoms with urinary obstruction, hematuria, or chronic pelvic or rectal pain would negatively affect the quality of life. Moreover, the untreated recurrence is a potential source of tumor de-differentiation and systemic dissemination.[4-6]

Department of Radiation Oncology, Center for the Southern Interior, British Columbia Cancer Agency, Kelowna, BC, Canada.

Conflict of interest: none.

Address reprint requests to Juanita Crook, MD, FRCPC, Department of Radiation Oncology, Cancer Centre for the Southern Interior, British Columbia Cancer Agency, 399 Royal Ave, Kelowna, BC, Canada V1Y 5L3. E-mail: jcrook@bccancer.bc.ca

Despite the potential benefits, local salvage is infrequently offered. Patients with a rising prostate-specific antigen (PSA) after radiotherapy in the absence of metastatic disease are most frequently managed with palliative intent, with either observation or androgen-deprivation therapy (ADT) given in either a continuous or intermittent approach.[7] This is largely because of advanced patient age, existing comorbidities, and concerns about potential toxicity from local salvage procedures. Both the American national dataset (CaPSURE) and the British Columbia Tumour Registry show marked underuse of salvage options: 25% of patients with biochemical failure are managed with observation, whereas 70% are offered ADT. Fewer than 5% undergo potentially curative local salvage.[8,9] Although a conservative approach may well be appropriate for many individuals, selected patients could benefit from retreatment with curative intent. The local salvage options include salvage prostatectomy, focal or whole-gland brachytherapy, cryotherapy, high-intensity focused ultrasound (HIFU), and stereotactic body radiotherapy (SBRT).

We present a review of the pertinent literature on the salvage of locally recurrent prostate cancer after primary radiotherapy with discussion of the procedures, oncologic outcomes, and potential toxicity.

http://dx.doi.org/10.1016/j.semradonc.2016.08.007
1053-4296/

Patient Selection

Selection of appropriate patients for consideration of salvage depends on many factors including patient age and life expectancy, the presence of comorbidities, and perhaps most importantly, the determination of whether the patient is still potentially curable. Differentiation of an isolated local recurrence from one with coexisting systemic spread is key. And finally, if all the above factors favor salvage, one must evaluate the risks of potential harm from retreatment against the risk of progression to clinically important symptoms within that patient's lifetime. Approximately 25% of biochemical failures would become clinical failures within 7-8 years.[10]

Implications of the Timing of Biochemical Failure

A rising PSA within 18-24months of definitive radiotherapy should not be considered indicative of isolated local failure.[11-14] Even if there is an apparent local component, there is almost certainly coexisting metastatic disease, whether clinically evident or subclinical. Such patients usually also have a higher PSA nadir after radiotherapy and a more rapid PSA doubling time, all of which are predictors of the likely futility of local salvage. PSA nadir ≥ 2 ng/mL, PSA doubling time (DT) ≤ 6 months, and an interval to biochemical failure ≤ 18 months are all strongly associated with occurrence of distant metastasis.[1,11,12,14]

Investigation of Rising PSA After 24 Months

Once the standard metastatic work-up has proven to be clear, transrectal ultrasound (TRUS), and TRUS-guided biopsies have been traditionally the first step to evaluate the prostate for local recurrence. Recurrence is rarely visualized with TRUS; systematic biopsies may well miss foci of recurrent disease, especially if the PSA is still low (< 3 ng/mL). Salvage prostatectomy series have shown that up to 26% of local relapses can be missed, mainly at the mid and anterior gland.[15] In current practice, multiparametric prostate magnetic resonance imaging (mpMRI) is becoming the imaging modality of choice and should precede TRUS. In the postradiotherapy scenario, the standard anatomical T2 sequences are not often helpful because of changes in prostate composition and vascularity resulting in generalized hypointensity of the peripheral zone.[16] Similarly, diffusion-weighted imaging is altered throughout the irradiated gland. On the contrary, dynamic contrast enhancement, with a bolus infusion of gadolinium, is especially useful in demonstrating areas of recurrent disease because of the neovascularity of the tumor seen against the background of a relatively avascular irradiated prostate.[17] Use of an endorectal coil is advised, especially when using a 1.5 T scanner. The use of mpMRI or (dynamic contrast enhancement)-MRI have shown better (90%) accuracy in identifying recurrent disease.[18,19] TRUS-guided biopsies should follow for confirmation of the MR-findings, using either cognitive fusion or a computer-based fusion program. MRI-targeted biopsies are feasible and increase the disease-detection rates.[20-22]

Biopsy Interpretation

Histopathologic resolution of prostate cancer after radiotherapy takes 24-30 months. It has been demonstrated that one-third of biopsies showing tumor at 12 months after radiation would become negative by 24-30 months.[23,24] Biopsies performed before this time are not helpful in determining the success or failure of local treatment, and as discussed earlier, a rising PSA earlier than this interval is generally indicative of systemic disease. Biopsy review by an expert genitourinary (GU) pathologist is essential as postradiotherapy prostate biopsies can be very difficult to interpret.[25] Radiation change alters the gland morphology such that cellular drop out often leaves isolated cells or nests of cells with no residual recognizable gland formation. This mimics high-grade disease when indeed it represents severe radiation effect. The hallmarks of radiation change have been classified by Crook et al and include nuclear and cytoplasmic changes such as smudged and distorted chromatin, large bizarre or pyknotic nuclei, microvesicular or macrovesicular changes, ruptured cytoplasm, and scarce or no glandular formation. Such biopsies cannot be assigned a Gleason grade. On the contrary, residual apparently viable tumor, showing scarce or no radiation effect, can and should be graded. Before considering any local salvage option, residual tumor with minimal or no radiation change must be demonstrated on histopathology.

Distant Staging

Once local recurrence has been proven, further effort should be made to rule out regional or distant metastases (DM), beyond the standard pelvic computed tomography (CT) scan or magnetic resonance imaging (MRI) and bone scan, if possible. Whole-body MRI (WB-MRI) has been used to assess both regional and boney metastases. LeCouvet et al[26] compared WB-MRI with a combination of bone scan, plain x-rays, and CT scan in 100 patients. The sensitivity for detecting bone lesions was higher with the WB-MRI (98% vs 86%, $P < 0.04$), but was similar in detecting enlarged lymph nodes. The use of WB-MRI is currently undergoing furthermore evaluation in clinical trials such as the FORECAST study (NCT01883128).[27]

Perhaps the most promising imaging tool for evaluation of biochemical recurrence (BCR) after definitive treatment is functional imaging using a small molecule ligand of prostate membrane-specific antigen (PSMA). PSMA is a type II membrane glycoprotein with an extracellular, transmembrane, and intracellular component. It is expressed on the cell surface, is not released into the circulation, and is over expressed in 90%-100% of localized prostate cancer. It was first explored in Prostascint as an Indium[111] Capromab-labeled anti-PSA monoclonal antibody, but poor tumor penetration, a long half-life, and lack of sensitivity at a low PSA level made it of limited use in the investigation of patients with an early rising PSA after definitive therapy or for detection of nodal disease.[28] In contrast, Ga^{68} PSMA PET/CT has excellent tumor penetration, a high tumor to normal tissue ratio and ideal pharmacokinetics. Eiber et al[29] reported on 248 patients with a rising PSA after RP and found disease detection rates of 58%