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Management of Biochemical Recurrence After Primary Treatment of Prostate Cancer: A Systematic Review of the Literature

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Abstract

Context: Despite excellent cancer control with the treatment of localized prostate cancer (PCa), some men will experience a recurrence of disease. The optimal management of recurrent disease remains uncertain.
Objective: To systematically review recent literature regarding management of biochemical recurrence after primary treatment for localized PCa.
Evidence acquisition: A comprehensive systematic review of the literature was performed from 2000 to 2012 to identify articles pertaining to management after recurrent PCa. Search terms included *prostate cancer recurrence, salvage therapy, radiorecurrent prostate cancer, post HIFU, post cryoablation, postradiation*, and *postprostatectomy salvage.* Studies were selected according to Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines and required to provide a comprehensive description of primary and secondary treatments along with outcomes.
Evidence synthesis: The data from 32 original publications were reviewed. The most common option for local salvage therapy after radical prostatectomy (RP) was radiation. Options for local salvage therapy after primary radiation included RP, brachytherapy, and cryotherapy. Different definitions of *recurrence* and risk profiles among patients make comparative assessment among salvage treatment modalities difficult. Triggers for intervention and factors predicting response to salvage therapy vary.
Conclusions: Radiation therapy (RT) after RP can provide durable prostate-specific antigen (PSA) responses in a sizeable percentage of men, especially when given early (ie, PSA <1 ng/ml). Though a few studies suggest improvements in mortality, prospective randomized trials are needed and underway. The role of salvage treatment after RT is less clear.

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1. Introduction

Prostate cancer (PCa) accounted for an estimated 899 000 cases and 258 000 deaths worldwide in 2008, with 72% of cases and 53% of deaths occurring in developed countries [1]. Among men in the Surveillance, Epidemiology, and End Results database in the United States, 80% had localized disease, 12% had regional disease, and only 4% had distant

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disease [2]. A recent analysis of 11 892 men in the Cancer of the Prostate Strategic Urologic Research Endeavor registry, a national, largely community-based PCa registry, revealed that 6.8% elected active surveillance, 49.9% chose radical prostatectomy (RP), 11.6% underwent external-beam radiation therapy (EBRT), 13.3% had brachytherapy, 4.0% chose cryoablation, and 11.6% underwent primary androgen-deprivation therapy (ADT) as the primary treatment for PCa [3].

Despite primary treatment of localized PCa, 20–30% of patients experience a recurrence, typically detected by a rise in serum prostate-specific antigen (PSA) levels [4,5]. For these men, options for salvage local therapy are still available. No randomized trials have yet compared different modalities of salvage treatment, and most of the data come from retrospective series, small prospective studies, and extrapolation from clinical trials involving primary management. This review discusses the contemporary management of biochemical recurrence (BCR) after definitive primary therapy.

2. Evidence acquisition

A systematic review of the literature was conducted using the Medline and Embase electronic databases. Search terms included *prostate cancer recurrence, prostate salvage therapy, radiorecurrent prostate cancer, post HIFU, post cryoablation, postradiation*, and *postprostatectomy salvage*. The search was restricted to English-language articles from 2000 to 2012. Citations from original articles and review articles were assessed for important manuscripts not identified in the initial search. One article identified in this manner was outside the study window (1999) but was included because it was the largest series in its area.

Eligibility criteria for selecting studies included original articles with (1) a diagnosis of recurrent PCa after primary therapy, (2) a comprehensive description of primary and secondary treatments received with oncologic outcomes, (3) an adequate sample size, and (4) sufficient follow-up relative to the existing literature in the field. For articles regarding salvage radiation after RP and salvage RP after radiation, a minimum sample size of 100 men and a minimum follow-up of 36 mo were required. One exception to this rule was the largest series on salvage robot-assisted RP (RARP) after radiation failure, which included only 18 men with a median follow-up of 18 mo; this study was included because of the novelty of salvage RARP. For articles assessing salvage brachytherapy after radiation, because of the smaller number of available studies, a minimum sample size of 15 men and a minimum follow-up of 18 mo were required, while studies assessing salvage cryotherapy after radiation required a minimum sample size of 50 men and minimum follow-up of 18 mo. Articles were screened for relevance to the topic and adherence to inclusion criteria. The authors selected 32 articles according to our search strategy based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria [6]. The authors acknowledge that many studies were not included in this review because of the criteria enforced for selection.

Figure 1 displays a flow diagram of the search strategy and study selection for articles that were included in this review.

3. Evidence synthesis

3.1. Definitions of biochemical recurrence

Several different terminologies have been applied to men with an elevated post-treatment PSA, including *recurrence, progression*, and *persistence*. In theory, for a tumor to "recur," the primary treatment must not have been curative, and some persistence of tumor below biochemical or clinical detection must occur. For those tumors that do have significant declines in PSA levels, for the PSA level to reach the *recurrence* definition, the tumor must have progressed. Therefore, depending on how it is viewed, the terms *persistence, recurrence*, and *progression* are certainly overlapping and often synonymous.

Serum PSA is a valuable tool, used as a surrogate to define recurrence. However, definitions of *BCR* vary by treatment and study because of inherent differences in various treatments on PSA levels [7]. Given that the prostate produces PSA, after complete removal of the prostate (ie, RP), serum PSA should be undetectable, and any measurable PSA may suggest recurrence [4]. The availability of ultrasensitive PSA assays has allowed us to predict PSA relapse at an earlier point than most conventional assays [8]; however, not all patients with a detectable PSA level will manifest clinical progression [9]. For instance, although several studies have suggested that benign prostate glands at the margin are not associated with BCR [10], they may be associated with low levels of PSA that would only be detectable on an ultrasensitive assay. Treatment for such PSA elevations are unlikely to provide any benefit in preventing cancer progression. For this reason, the European Consensus Group recommended that an ultrasensitive assay be used in monitoring for PCa recurrence but not for treatment decision making [11]. In 2007, the American Urological Association Prostate Guideline Update Panel reviewed 53 different definitions of *BCR* after RP and recommended using a serum PSA level >0.2 ng/ml, with a second confirmatory level above 0.2 ng/ml to define recurrence [12]. This recommendation is similar to the definition proposed by a European Consensus committee in 2004 [13].

Defining an ideal cut point for radiation failure is more challenging, because the PSA level does not often drop to undetectable levels after treatment and takes longer to reach its nadir. The American Society for Therapeutic Radiology and Oncology (ASTRO) met in 1997 and suggested three consecutive rises in PSA level above the nadir to define recurrence following radiation [14]. However, the ASTRO definition has been criticized for being poorly linked to clinical progression, being heavily dependent on the length of follow-up, and not performing well in men on concomitant androgen-deprivation therapy (ADT). To address these and other shortcomings of the definition, a second consensus panel suggested an increase in the PSA level by $\geq$2 ng/ml