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Original article

Underutilization of local salvage therapy after radiation therapy for prostate cancer[1]

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Abstract

Objective: To evaluate the rates at which patients are offered and receive local salvage therapy (LST) after failure of primary radiotherapy for localized prostate cancer, as it is the only potentially curative treatment for localized recurrence but appears to be underutilized when compared with androgen-deprivation therapy (ADT) or observation.

Materials and methods: Patients with localized prostate cancer who received primary radiotherapy with curative intent between 1999 and 2000 were identified in the British Columbia Tumour Registry. Exclusion criteria included patient age >72 years, prostate-specific antigen >40 ng/ml, and clinical stage T4 at diagnosis. Data on clinicopathologic features, primary therapy, prostate-specific antigen kinetics, and salvage therapy were collected retrospectively. Radiation failure was defined as biochemical recurrence according to the Phoenix criteria or by initiation of salvage therapy.

Results: Of 1,782 patients treated in the study period, 1,067 met inclusion criteria. Of these, 257 failed radiation therapy. Radiation therapy failure was managed with observation (>12 mo) in 126 patients and ADT in 119. Of the observed patients, 66 subsequently received ADT. Five patients (1.8%) received LST (3 radical prostatectomy and 2 brachytherapy).

Conclusions: Only 2% of patients relapsing after radiation therapy for localized prostate cancer received LST. Although the benefits of LST are unproven, these findings reveal a possible underutilization of LST and indicate a need for enhanced collaboration between specialties to optimize care of this challenging cohort.

Keywords: Prostatic neoplasms; Radiotherapy; Brachytherapy; Salvage therapy; Cryotherapy; Salvage radical prostatectomy; Salvage brachytherapy

1. Introduction

External beam radiation therapy (EBRT) and brachytherapy (BT) are commonly used treatment modalities for localized prostate cancer. Although highly efficacious, some patients do have disease recurrence, and management of these patients has traditionally been challenging. Several clinical questions arise in any patient, including whether a rise in prostate-specific antigen (PSA) is reflective of disease recurrence, whether treatment of the biochemical recurrence (BCR) is necessary, and whether the recurrence is localized to the prostate or metastatic. If one is convinced that the recurrence warrants therapy and is localized to the prostate, a number of local therapy options are available. Treatment options include salvage cryotherapy (SCT) [1,2], high-intensity focused ultrasound (HIFU) ablation [3], salvage BT (SBT) [4], and salvage radical prostatectomy (SRP) [2,5,6]. Further alternatives include observation for presumed indolent recurrence and androgen-deprivation therapy (ADT).

Despite these many alternatives, our impression is that most patients are not offered local salvage therapy (LST) after failure of EBRT or BT. For example, the number of patients treated with SRP in Vancouver has been minimal (21 cases over 15 y) [6]. Observation and ADT appear to be the mainstays of therapy. LSTs, however, are the only potentially curative options. There is risk of underutilizing LST and missing opportunity for cure. SRP is the most established and definitive local salvage option, but it may be

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avoided in many cases owing to technical difficulty and high risk of subsequent incontinence and impotence [5,7]. SCT, HIFU, and SBT are newer salvage options associated with less patient morbidity but also less certain efficacy [8]. Nevertheless, the likelihood of cure is difficult to predict in any individual patient for any given salvage therapy modality.

In this study, we aimed to ascertain rates at which patients receive LST after failure of radiation therapy in British Columbia (B.C.).

2. Materials and methods

All patients with localized prostate cancer (T1-3N0M0) who received primary radiation treatment (EBRT or BT) with curative intent in B.C. from January 1999 until December 2000 were identified from the prospectively maintained B.C. Cancer Agency database. These cases were linked to ADT records captured in a province-wide pharmacy database. The study was approved by the Research Ethics Board of University of British Columbia (protocol H12-01180).

The medical records of the identified patients were retrospectively reviewed to acquire variables not included in the prospective database. Patients older than 72 years and those with high-risk disease defined by a PSA >40 ng/ml and clinical T4 disease at diagnosis were excluded. These arbitrary criteria were set based on the consensus of the authors that these patients were unlikely to be eligible for LST in the event of BCR. Gleason score was not used as exclusion criteria. Patients who had combined primary orchiectomy and radiotherapy were also excluded.

Data regarding patient characteristics, clinical and pathologic cancer features (pretreatment PSA, clinical tumor stage, and Gleason score), primary radiotherapy modality (dose, fractions, start/end dates, and concomitant ADT), and subsequent PSA kinetics (PSA nadir and date/time to recurrence) were collected. A PSA nadir was not recorded for 26 patients who had no PSA follow-up within 3 years after primary EBRT or before secondary intervention. We determined from the patient charts which physician was performing the follow-up of the patient′s prostate cancer at the time of radiation therapy failure.

Failure of radiation therapy was defined as BCR meeting the Phoenix definition [9] or initiation of salvage therapy regardless of PSA kinetics. Relapsed patients were assigned to low-, intermediate-, or high-risk groups according to D′Amico classification [10].

Patient characteristics, including age, Charlson score, PSA, digital rectal examination, biopsy, bone scan, and computed tomography scan results, at time of radiation failure were collected and analyzed for salvage eligibility. In an exploratory analysis, medical charts were reviewed to assess the salvage options offered to patients, recognizing that options may have been discussed but not documented. Reasons for not offering SRP specifically were also recorded. When no explicit reason was provided for patients older than 75 years at time of radiation failure, we attributed this to age. Observation after BCR was defined as no secondary treatment within 1 year of BCR.

3. Results

A total of 1,782 patients received curative radiotherapy for prostate cancer treatment between January 1999 and December 2000 in B.C. Of these patients, 715 were excluded: 624 for age >72 years at diagnosis, 63 for PSA >40 ng/ml, 19 for stage $\geq$T4, and 9 had primary orchiectomy at time of primary radiotherapy. Of the remaining 1,067 patients included in the study, 796 patients (75%) received EBRT and 271 (25%) received BT (Fig.). Radiation failure was observed in 257 patients (24%) based on either BCR (85%) or initiation of secondary intervention for presumed relapse (15%). Only 19 of these patients (7%) had undergone BT, and the other 238 (93%) received EBRT.

Of the 257 patients who failed primary radiotherapy, the median age at the time of first diagnosis was 67 years. The clinical tumor stage and Gleason scores are summarized in Table 1. The median time from primary therapy to radiation failure was 53 months. Table 2 provides a demographic and clinical breakdown of the study patients based on primary radiotherapy modality.

At time of radiation failure, 126 patients (49%) were observed for >1 year without intervention. Of these, treatment beyond 1 year consisted of further observation in 61 and ADT in 65 patients. ADT was continuous in 15 (including 3 with bilateral orchiectomy), intermittent in 44, and not clearly defined in 6 patients. One patient receiving intermittent ADT eventually underwent secondary SBT 4 years after BCR. The median time to any intervention after BCR was 6 months.

Another 119 patients (46%) received ADT within 1 year of radiation failure after radiotherapy. ADT was continuous in 46 (including 7 with bilateral orchiectomy), intermittent in 66, and not clearly defined in 7 patients.

Of these patients, 3 were involved in a clinical trial comparing intermittent to continuous ADT [11]. Of note, 13 other patients were offered enrollment in this trial but declined or were found ineligible as per trial protocol. One patient was enrolled in a clinical trial with a vascular endothelial growth factor pathway inhibitor and subsequently received ADT.

A total of 5 patients (1.9%) underwent LST. Two patients, including the one mentioned previously, received SBT and 3 patients received SRP. Two patients undergoing SRP also received ADT (Table 3).

A discussion of LST was documented in the chart of 44 patients (17%), absent in 157 patients (61%), and could not be determined in 56 cases (22%). A discussion about SRP was specifically documented in 35 instances, whereas SBT, SCT, and HIFU were considered in 12, 15 and 5 instances, respectively (Table 4). The role of these latter interventions has evolved over the study period with varying