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Original article

Stereotactic body radiotherapy for localized prostate cancer: Pooled analysis from a multi-institutional consortium of prospective phase II trials ☆

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ABSTRACT

Purpose: The effectiveness of stereotactic body radiotherapy (SBRT) for localized prostate cancer is tested.
Methods and materials: A total of 1100 patients with clinically localized prostate cancer were enrolled in separate prospective phase 2 clinical trials of SBRT from 8 institutions during 2003–11 and pooled for analysis. SBRT using the CyberKnife delivered a median dose of 36.25 Gy in 4–5 fractions. Patients were low-risk (58%), intermediate-risk (30%) and high-risk (11%). A short-course of androgen deprivation therapy (ADT) was given to 14%. PSA relapse defined as a rise >2 ng/ml above nadir was analyzed with the Kaplan Meier method.
Results: With a median follow-up of 36 months there were 49 patients with PSA failure (4.5%), 9 of whom were subsequently determined to be benign PSA bounces. The 5-year biochemical relapse free survival (bRFS) rate was 93% for all patients; 95%, 83% and 78% for GS $\leqslant$6, 7 and $\geqslant$8, respectively ($p = 0.001$), and 95%, 84% and 81% for low-, intermediate- and high-risk patients, respectively ($p < 0.001$). No differences were observed with ADT ($p = 0.71$) or as a function of total dose ($p = 0.17$). A PSA bounce of >0.2 ng/ml was noted among 16% of patients. For 135 patients possessing a minimum of 5 years follow-up, the 5-year bRFS rate for low- and intermediate-risk patients was 99% and 93%, respectively.
Conclusion: PSA relapse-free survival rates after SBRT compare favorably with other definitive treatments for low and intermediate risk patients. The current evidence supports consideration of SBRT among the therapeutic options for these patients.
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The long term effectiveness and safety of hypofractionated external beam radiotherapy in the definitive treatment of prostate cancer was first suggested by a landmark program which ran in the UK during the 1980s that delivered 6 fractions of 6 Gy each over a two week period [1]. Over the ensuing two decades the evolution of radiotherapy technology to integrate 3D anatomy, conformal dose coverage and image guidance combined with a deeper understanding of the radiobiology of prostate cancer led to the proliferation of various fractionated radiotherapy schedules. Consequently, substantial clinical data now exist from several studies including randomized trials using various moderately hypofractionated regimens, with dose-per-fraction ranging from 2.5 Gy per fraction to 70 and 3.1 Gy per fraction to 62 Gy [2–10] and more recently, extreme hypofractionation schemes of 7.25 Gy per fraction for 36.25–10 Gy for 50 Gy [11–18] using stereotactic body radiotherapy (SBRT) approaches.

The basis for the successful clinical results from these hypofractionation schemes stems from the unique radiobiology of prostate cancer that favors large dose per fraction over conventionally fractionated schedules. Indeed, a recent systematic review and analysis [19] combining the clinical outcomes after various hypofractionated schedules for prostate cancer involving over 2800 patients compared to conventionally fractionated regimens among over 11,000 patients confirmed that prostate cancer has a very high sensitivity to dose per fraction (i.e., quantified by the linear quadratic radiobiologic relationship as a low α/β ratio of 1.0–1.7). Consequently, hypofractionation for prostate results in a means of radiobiological dose-escalation and probably represents a therapeutic gain. It also affords a more economical course of definitive radiotherapy, improves patient access to care, and enhances patient convenience.

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In 2011 we formed a consortium for prostate SBRT with a two-fold purpose: first, to analyze all of the currently available clinical data and second, to establish a centralized center for prospective data acquisition and analysis accessible to all current and future eligible centers. At present only a handful of smaller studies using SBRT for prostate cancer have been published which have shown successful outcomes with low toxicity profiles [11–18]. The merits of the current study are to pool all of the available published, as well as unpublished data, into a sufficiently large dataset to provide benchmark conclusions regarding overall effectiveness and to also allow for hypothesis-testing with regard to the impact of risk-groups, total dose, or concurrent use of ADT. Given its size and follow-up it also serves as a more convincing basis for comparison with other approaches for the definitive treatment of prostate cancer.

In this report we present the consortium data collected thus far and the clinical outcomes. Nearly half of the patients reported herein represent new data, having either not been included in prior studies or who now have updated follow-up. Early and late toxicity data acquisition and analysis is ongoing and will be reported separately.

Methods and materials

Study design

A separate IRB was for centralized data collection and analysis was obtained at this academic institution. In the present study, patients enrolled in separate IRB-approved prospective phase II clinical trials of prostate SBRT from 8 centers were pooled, yielding a total of 1100 patients treated between years 2003 and 11. It is noted that nearly half of the patients reported upon in this study represent new data not previously published. Eligible patients had biopsy-proven newly diagnosed, non-metastatic and untreated prostate cancer. For each trial the endpoints included early and late urinary and rectal toxicities, questionnaire-based quality of life measures and PSA response. Prostate cancer risk stratification followed the standard D'Amico risk stratification (low risk: PSA <10 and Gleason sum of 6 and clinical stage T1c–T2a, intermediate risk: PSA 10–20 or Gleason sum of 7 or clinical stage T2b, and high-risk: PSA >20 or Gleason sum 8–10 or clinical stage T2c/T3). Patient characteristics are summarized in Table 1. Median patient age was 70 (range 44–91 years old).

Treatment specifics

The CyberKnife (Accuray Inc., Sunnyvale CA) was used to deliver fiducial-based image-guided SBRT. The treatment specifics from individual centers have been published previously [11–17]. Differences among the eight centers are primarily related to dose while the remainder of the technical treatment specifications remained remarkably uniform. The most common general principles are only briefly outlined here. Three to four gold fiducials were placed in the prostate via trans-rectal ultrasound (some used a trans-perineal approach), followed by a non-contrast CT scan in the supine position and in an alpha cradle. Anatomical contours of the prostate, seminal vesicles, rectum, bladder, penile bulb, femoral heads and testes were generated. For homogeneous planning, dose was prescribed to the planning target volume (PTV) that consisted of a volumetric expansion of the prostate by 5 mm, reduced to 3 mm in the posterior direction. For heterogeneous planning (i.e., HDR-like dosimetry) the PTV expansion was 2 mm, reduced to 0 mm posteriorly. The course of radiotherapy consisted of a median of 36.25 Gy (range 35–40 Gy) over 5 fractions (given daily among >95% of patients, every other day for the remainder). The overwhelming majority of patients (89%) received a dose of 35–36.25 Gy in 5 fractions. Homogeneous dose planning was used in >90% of patients (heterogenous HDR-like DVHs were given to the remainder). For the homogenous planning, dose was normalized to the 90% isodose line in order for the prescription dose to cover at least 95% of the PTV. Generally speaking, dose volume histogram (DVH) goals for the rectum were such that the V50% <50% (i.e., the volume receiving 50% of the prescribed dose was <50%), V80% <20%, V90% <10% and V100% <5%. The bladder DVH goals were V50% <40% and V100% <10%. The femoral head DVH goal was V40% <5%.

A short course (median 4 months) of neoadjuvant and concurrent androgen deprivation therapy (ADT) was allowed at the discretion of the treating physician and given to 8%, 15% and 38% of patients within the low-, intermediate- and high-risk groups, respectively.

Follow-up and analysis

In general, PSAs were obtained at baseline, and prospectively at 3 months post-treatment intervals during the first 2 years and at 6 month intervals thereafter. The PSA relapse definition used was the currently adopted standard of care Phoenix definition (i.e., nadir +2). Biochemical relapse free survival (bRFS or PSA RFS) was calculated with the Kaplan Meier method and differences between groups determined by the logrank test. A benign PSA bounce was called when PSA rose by >0.2 ng/mL above the post-treatment nadir and subsequently returned to nadir levels or below.

Results

With a median follow-up of 36 months there were 49 patients with a strictly defined PSA failure (4.5%) 9 of whom were however determined to be benign PSA bounces since they subsequently fell to below nadir levels. The 5-year biochemical relapse free survival (bRFS) rate was 93% for all patients. It was 95%, 83% and 78% for GS $\leqslant$6, 7 and $\geqslant$8, respectively ($p = 0.001$), and 95%, 84% and 81% for low-, intermediate- and high-risk patients, respectively ($p < 0.001$) (Fig. 1). The 5-year bRFS rates as a function of total dose or ADT use are summarized in Table 2. No differences in bRFS were observed as a function of total dose ($p = 0.17$), or related to the use of ADT ($p = 0.71$). Even when substratified within each individual risk group, neither the addition of ADT nor the total dose resulted in significant differences in bRFS rates (Table 3).

PSA decline after SBRT gradually fell to an overall median of 0.20 ng/mL at 3-years. While the post-treatment PSA at 3-years was progressively lower as a function of total dose, with a mean and median PSA of 0.51 and 0.3 for 35 Gy, 0.35 and 0.20 for 36.25 Gy and 0.29 and 0.20 for 38–40 Gy, this did not translate into any significant differences in bRFS rates as a function of dose (Table 2). A PSA bounce of >0.2 ng/ml was noted among 16% of patients at a median of 36 months, with median bounce height of 0.50 ng/ml (range 0.2–5.29).

There were 135 patients possessing a minimum of 5 years follow-up (range 60–72 months) 77% of whom were low-risk, 21% intermediate-risk and only 2% high-risk. The 5-year bRFS was 97% for this entire cohort, 99% for patients with low-risk and 93% for patients with intermediate-risk ($p = 0.11$). Neither the total dose nor the use of ADT was significantly associated with bRFS. Although not significant, the 5-year bRFS was 93% for patients receiving a dose 35 Gy vs. 100% for those receiving $\geqslant$36.25 Gy.

Discussion

This consortium project has demonstrated the feasibility of a centralized multi-institutional data collection and analysis of

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