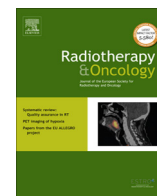




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Original article

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 ≤6, 7 and ≥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 (heterogeneous HDR-like DVHs were given to the remainder). For the homogeneous 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 ≤6, 7 and ≥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 ≥36.25 Gy.

Discussion

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

Table 1
Patient and treatment characteristics (n = 1100[†]).

Risk group	N (%)	35 Gy	36.25 Gy	38–40 Gy	ADT use	FU [*]
Low	641 (58%)	254 (40% [‡])	319 (50%)	68 (11%)	50 (8%)	36
Intermediate	334 (30%)	108 (32%)	188 (56%)	38 (11%)	49 (15%)	30.5
High	125 (11%)	23 (18%)	82 (66%)	20 (16%)	48 (38%)	23
Total	1100	385 (35%)	589 (54%)	126 (11%)	147 (14%)	

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Dept. of Radiation Oncology, Stanford, CA.

Dept. of Radiation Oncology, Georgetown University, Washington DC.

Dept. of Radiation Oncology, Swedish Medical Center, Seattle, WA.

[‡] % calculated with respect to the total number of patients within each respective risk-group.

^{*} Median follow-up in months.

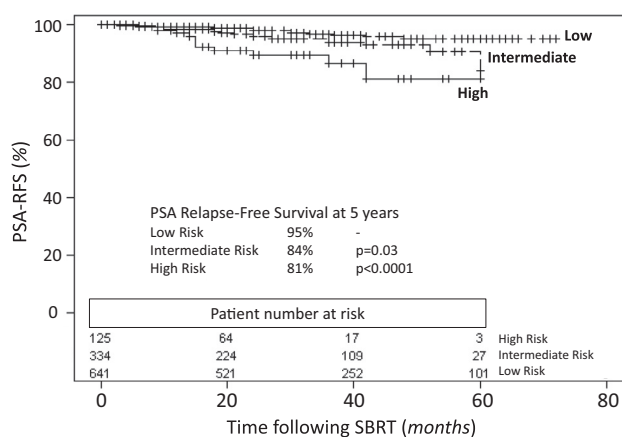


Fig. 1. PSA relapse-free survival Kaplan–Meier curves stratified by risk group. The 5-year actuarial PSA relapse-free survival rates are 95%, 84% and 81% for low-, intermediate- and high-risk patients, respectively ($p < 0.0001$). Censoring is indicated by tick marks on the curves and the number of patients at risk is given for the time intervals indicated.

Table 2
5-year Kaplan–Meier PSA relapse-free survival rates as a function of risk group, use of ADT and dose.

	5-yr bRFS	p-Value
Low Risk	95.2%	*
Intermediate Risk	84.1%	$p = 0.03$
High Risk	81.2%	$p < 0.0001$
ADT use	92.6%	*
No ADT	91.3%	$p = 0.71$
Dose 35 Gy	92.5%	*
Dose 36.25 Gy	90.7%	$p = 0.08$
Dose 38–40 Gy	95.8%	$p = 0.83$

* Reference group.

prospective clinical trials for prostate SBRT. Data thus far accumulated on 1100 patients from eight independent centers allow for the reporting of the long term clinical outcomes as well as testing the effect of ADT with SBRT and the effect of total dose. The three principal conclusions were: (1) the overall long term bRFS were excellent, 93% for all patients, and 95%, 84% and 81% for low-, intermediate- and high-risk patients, respectively ($p < 0.001$); (2) no differences in bRFS were observed with or without the use of ADT ($p = 0.71$); and (3) no differences were observed as a function of total dose ($p = 0.17$).

A comparison between all definitive therapies for localized prostate cancer (i.e., radical prostatectomy, conventional external beam radiotherapy, permanent low dose-rate brachytherapy, and high dose-rate brachytherapy) is well beyond the possible scope of this study. However, as a surrogate for any such necessary comparison, we chose a validated nomogram [20] that in essence comprises a synthesis of all modern surgical and radiotherapy outcome studies. Using patient characteristics as upper and lower bounds based on the D’Amico risk groups we calculate using the nomogram the following 5-year range in predicted biochemical RFS rates after radical prostatectomy as 95–98%, after 78 Gy external beam radiotherapy as 91–94%, and after permanent brachytherapy as 80–90%. Nomograms are of course susceptible to all of the caveats of retrospective studies, therefore we consider outcomes of >90% among all of the therapeutic options for low-risk prostate cancer to be essentially equivalent. Similar conclusions are drawn from such comparisons within the intermediate- and high-risk groups. We note however that while our data for the high-risk group is very encouraging, given the relatively low number of patients and shorter follow-up available, that one should remain cautious at the present time. There are two notable multi-institutional randomized clinical trials that have recently opened comparing SBRT to conventionally fractionated IMRT: the PACE trial (Prostate Advances in Comparative Evidence) will examine outcomes between radical prostatectomy, IMRT (78 Gy in 39 fractions) or CyberKnife SBRT (36.25 Gy in 5 fractions or 38 Gy in 4 fractions) for low and intermediate risk prostate cancer, and the other a Swedish trial HYPO-RT-PC (Hypofractionated radiotherapy of intermediate risk localized prostate cancer) will compare 78 Gy in 39 fractions with IMRT vs. SBRT 42.7 Gy in 7 fractions of 6.1 Gy.

It is interesting to note that our data did not reveal a dose response for SBRT within the range of 35–40 Gy with respect to bRFS rates. This is not altogether surprising when one considers that these extreme hypofractionated doses likely correspond biologically to 90 Gy or higher at conventional fractionation (i.e., 1.8–2 Gy per fraction) if our radiobiological assumption of prostate cancer is correct. These high doses are considered to lie near the plateau of the known sigmoidal dose–response for prostate cancer where the 5-year bRFS rates lie above the 90% level. Given this observation, we feel further escalation of SBRT doses above 40 Gy is not warranted at this time and would not be prudent given the potential for higher rates of grade 3 GI and GU toxicities shown for SBRT to 50 Gy [18]. Higher doses could hypothetically be necessary for SBRT among patients with high-risk localized prostate cancers, and this is the subject of investigation. The excellent bRFS rates with SBRT are further support of the consistent radiobiological

Table 3
Comparisons of 5-year PSA relapse-free survival rates by risk group and stratified by use of ADT or total dose.

	Low risk		Intermediate risk		High risk	
	5-yr bRFS	p-Value	5-yr bRFS	p-Value	5-yr bRFS	p-Value
ADT use	96.8%	*	97.2%	*	82.5%	*
No ADT	95.1%	0.46	79.7%	0.17	80.2%	0.50
Dose 35 Gy	95.8%	*	72.3%	*	NE	*
Dose 36.25 Gy	95.0%	0.77	87.2%	0.73	74.1%	0.99
Dose 38–40 Gy	94.4%	0.41	96.7%	0.58	NE	1.0

NE, no events.

* Reference group.

picture of prostate cancer as being inherently highly sensitive to large dose per fraction.

Our data did not reveal any benefit for a short-course of ADT when given with SBRT, even within the intermediate- and high-risk groups. We suspect that this is a consequence of the high biological doses that SBRT corresponds to. The evidence for improved outcomes with the addition of ADT originates from clinical trials where the external beam dose was 70 Gy. Indeed, there is current retrospective evidence that with conventionally fractionated dose-escalation to 78 Gy or higher there may be little to gain from ADT. However, only a randomized trial will be able to settle this question.

When considering toxicities, it is challenging to separate differences resulting from technique alone, i.e., 3D vs. IMRT vs. IGRT, from that of dose-escalation itself. Caution should therefore be made when comparing SBRT, which inherently adopts rather small PTV margins and provides intra-fraction IGRT, to dose-escalation IMRT. Data comparing the early and late GI and GU toxicities of moderately hypofractionated dose regimens have been reported among randomized trials and have shown no significant differences when compared to conventionally fractionated dose-escalated courses [2–10]. So far, data from published prostate SBRT trials have shown late grade 3 GI and GU toxicities within the 1–3% range [11–17] with the exception of one SBRT trial giving 50 Gy in 5 fractions resulting in a 7% grade 3 toxicity for both late GI and GU [18]. The toxicity counterpart of this consortium data will be presented separately [21]. That study examined patients with a median follow-up of 3 years and evaluable patients out to more than 5 years using patient self-reported QOL using the EPIC validated tool (expanded prostate cancer index composite). A transient decline in the urinary and bowel domains was observed within the first 3 months after SBRT which returned to baseline status or better within 6 months and remained so beyond 5 years. The same pattern was observed among patients with good vs. poor baseline function and was independent of the degree of early toxicities.

Conclusion

PSA relapse-free survival rates after SBRT compare very favorably with other definitive treatments for low and intermediate risk groups. The data for high risk patients is very encouraging but requires longer follow-up at this time. The added benefit of ADT for any risk group has not yet been demonstrated. A dose–response within the range of 35–40 Gy in 5 fractions has not been observed and therefore escalation beyond 40 Gy is not warranted at this time, especially for low- and intermediate-risk patients. The current evidence supports consideration of SBRT among the definitive therapeutic options for localized prostate cancer with low and intermediate risk.

Conflict of interest

Several physicians have received speaker honoraria for presentations at conferences, otherwise none of the authors have any conflict of interest regarding the content, treatment, drugs or technology associated with this report.

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